AMP

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

ACTA MED PORT. ISSN 0870-399X e-ISSN 1646-0758

12 | 25

Número 12
Série II
Lisboa

Volume 38
Dezembro 2025
Publicação Mensal

FICHA TÉCNICA

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

Director: Bastonário da Ordem dos Médicos, **Carlos Cortes**

Director-Adjunto e Editor: **Tiago Villanueva**

Corpo Editorial

Propriedade: Ordem dos Médicos (NIPC 500 984 492)
Sede do Editor / Redação: Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com
ISSN:0870-399X | e-ISSN: 1646-0758

Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros.

AMP38(12) - Dezembro de 2025

Registo: Inscrito na Entidade Reguladora para a Comunicação Social com o Nº 106 369
Depósito legal: 20 957/88
Estatuto Editorial: http://www.actamedicaportuguesa.com/normas-de-publicacao

Conselho Científico

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Porque Rejeitamos Tantos Artigos na Acta Médica Portuguesa?

Why Do We Reject So Many Articles in Acta Médica Portuguesa?

Tiago VILLANUEVA [1,2], Helena DONATO [3,4,5]
Acta Med Port 2025 Dec;38(12):759-761 ▪ https://doi.org/10.20344/amp.24098

Palavras-chave: Políticas Editoriais; Publicação; Revisão por Pares; Revistas
Keywords: Editorial Policies; Peer Review, Research; Periodicals as Topic; Publishing

Prevalece um grande desconhecimento entre a comunidade médico-científica sobre qual é o papel de um editor de uma revista científica médica. As responsabilidades dos editores incluem a seleção de conteúdos que refletem os objetivos e âmbito da revista, analisar políticas editoriais da revista, práticas e métricas de desempenho com vista a melhorar a revista, avaliar o rigor científico e integridade dos artigos, gerir e assegurar a integridade do processo de revisão por pares, assegurar a confidencialidade do processo editorial, selecionar os artigos que seguem para revisão por pares, selecionar revisores (assegurando equidade, diversidade e inclusão nesse processo), assegurar a rapidez do processo editorial, bem como desenvolver um processo para responder a *appeals* e reclamações.

Ser editor, ou seja, ser responsável pelo conteúdo da publicação/revista implica também ter uma visão para tomar decisões editoriais imediatas ou quase 'sem medo ou favor' e que não podem, nem devem, agradar a toda a gente. As decisões editoriais devem, sobretudo, ser baseadas na relevância, originalidade e qualidade.

Assim, tomar decisões relativamente a artigos implica não só ser cortês, mas também aberto (*open*), justo (*fair*) e firme (COFF).

Uma das tarefas mais difíceis do editor é a rejeição de manuscritos. O editor deseja, naturalmente, agradar aos autores e que todos os artigos percorram o processo editorial de forma célere e construtiva; no entanto, é frequentemente obrigado a rejeitar trabalhos por diversas razões, que vão desde limitações técnicas ou metodológicas até questões de adequação editorial ou de política da revista.

Entre as razões técnicas para rejeição incluem-se: dados incompletos, como um tamanho de amostra demasiado pequeno ou a ausência de controlos adequados; análise deficiente, por exemplo, a utilização de testes estatísticos inadequados ou a ausência total de análise estatística; metodologia inadequada para responder à hipótese formulada, ou utilização de métodos ultrapassados por técnicas mais recentes e robustas; motivação científica fraca, quando a hipótese não é clara ou cientificamente válida, ou quando os dados não respondem à questão colocada; conclusões imprecisas, baseadas em pressupostos que não são sustentados pelos dados.[1,2]

As razões editoriais de rejeição incluem: estar fora do âmbito da revista; contributo insuficiente ou impacto científico considerado demasiado limitado para a revista; falta de cumprimento de princípios de ética em investigação, como a ausência de consentimento informado de participantes humanos ou de aprovação por uma comissão de ética; estrutura inadequada ou não conformidade com os requisitos de formatação da revista; falta de detalhe suficiente para que os leitores possam compreender plenamente e reproduzir as análises e experiências dos autores; referências desatualizadas ou com uma proporção excessiva de autocitações; qualidade linguística insuficiente, tornando o texto difícil de compreender; lógica difícil de seguir ou apresentação deficiente dos dados; violação da ética de publicação.[3-5]

A Acta Médica Portuguesa (AMP) e os seus editores não são diferentes das restantes revistas científicas: têm a responsabilidade de gerir o equilíbrio entre a qualidade editorial, a relevância científica e os recursos disponíveis. Embora seja inevitável que muitas decisões de rejeição desagradem aos autores, estas fazem parte de um processo exigente e necessário. Acreditamos, contudo, que estamos no caminho certo: o fator de impacto da AMP tem vindo a aumentar, e a revista passou recentemente do quarto para o terceiro quartil, refletindo o reconhecimento crescente da sua qualidade e relevância científica. O aumento do número de submissões traduz-se, inevitavelmente, num aumento da taxa de rejeição, e tal como acontece com outras revistas científicas com fator de impacto, a AMP apenas pode publicar uma pequena percentagem dos artigos que são submetidos. Em 2024, a Acta Médica Portuguesa, recebeu um total de 1342 submissões. A maioria dos artigos

1. Editor-Chefe. Acta Médica Portuguesa. Lisboa. Portugal.
2. Unidade de Saúde Familiar Reynaldo dos Santos. Unidade Local de Saúde Estuário do Tejo. Lisbon. Portugal.
3. Editora-Chefe Adjunta. Acta Médica Portuguesa. Lisboa. Portugal.
4. Serviço de Documentação e Informação Científica. Hospitais da Universidade de Coimbra. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
5. Faculdade de Medicina. Universidade de Coimbra. Coimbra. Portugal.
✉ **Autor correspondente:** Tiago Villanueva. tiago.villanueva@ordemdosmedicos.pt
Recebido/*Received*: 15/10/2025 - **Aceite/*Accepted*:** 15/10/2025 - **Publicado/*Published*:** 02/12/2025

submetidos é de autores sediados em Portugal, mas recebemos submissões do mundo inteiro, sobretudo de países europeus, Brasil e China. Destas 1342 submissões, 86% foram rejeitadas, incluindo 79% de *desk rejections* (rejeição prévia a revisão por pares) e 7% de rejeições após revisão por pares. As razões que justificaram a rejeição incluem artigos que não cumprem minimamente as normas de publicação, artigos fora do âmbito da revista, artigos mal escritos ou mal estruturados, artigos que constituem baixa prioridade editorial, artigos mais adequados a revistas mais especializadas, artigos originais com metodologias pouco robustas ou que não acrescentam o suficiente à literatura científica ou mesmo um artigo semelhante que tenha sido publicado recentemente ou esteja em vias de ser publicado. Outras razões menos frequentes incluem situações de plágio ou outras falhas éticas e ainda a utilização inadequada de ferramentas de inteligência artificial.

É de realçar que as prioridades editoriais da revista não são algo estático, mas sim algo dinâmico, e que têm em grande parte que ver com o fluxo editorial da revista. Por exemplo, se temos artigos originais suficientes para preencher as edições nos próximos seis meses, é natural que tenhamos de subir a bitola de exigência para essa tipologia, e vice-versa. Por outro lado, a dimensão reduzida da equipa editorial obriga-nos também a ser seletivos, dada a impossibilidade de gerir demasiados artigos em simultâneo. Finalmente, o número de artigos aceites tem de ser mantido dentro de uma margem estável sob pena de serem prejudicadas as métricas editoriais como o *Journal Impact Factor* (Clarivate Journal of Citation Reports), que têm um peso grande na escolha de uma revista por parte dos autores. Nas principais revistas científicas médicas de índole generalista a nível mundial, as taxas de rejeição são ainda maiores, em resultado do elevado número de submissões.

As rejeições são sempre um desfecho dececionante, e por vezes os autores podem sentir que a rejeição do seu artigo pela AMP foi injustificada. Mas os artigos nunca são rejeitados de ânimo leve. As decisões são tomadas em equipa e incidem sobre os manuscritos submetidos, não sobre os autores. Existe uma triagem e avaliação inicial feita pelos editores. Podem ainda ser envolvidos os editores associados, caso seja necessária uma terceira opinião, ou porque o manuscrito requer o parecer de alguém do corpo editorial com competências específicas. Durante a triagem, os editores estão igualmente atentos à prática da autocitação (*self-citation*) ou seja, a citação excessiva de trabalhos anteriores pelo próprio autor. Trata-se de uma prática comum e controversa, já que, em muitos casos, pode resultar da natureza cumulativa da investigação individual do próprio autor. No entanto, quando usada em excesso, esta prática pode conduzir a uma inflação artificial dos indicadores bibliométricos, distorcendo a perceção do impacto real do investigador e influenciando, de forma indevida, os seus resultados bibliométricos (como o índice h, número total de citações, etc.).[3,5]

Nesta triagem inicial, os editores têm de ser particularmente seletivos, pois a falta de bons revisores é uma das principais causas de atraso na publicação. Enviar para revisão artigos que dificilmente poderão ser publicados seria contraproducente para todo o processo editorial.[4]

A rejeição não é um ataque pessoal movido por editores ou revisores. Aliás, os editores da AMP declaram os seus conflitos de interesse quando se apercebem de que estão perante um artigo cujos autores pertencem ao seu círculo de relações pessoais ou profissionais, abstendo-se de tomar decisões sobre esse artigo.

Os editores tomam decisões sobre os manuscritos com base nos critérios já indicados, incluindo a avaliação pelos revisores. O facto de um artigo ser rejeitado não significa que a Acta Médica Portuguesa não esteja disposta a considerar o trabalho dos mesmos autores numa submissão futura.

ACKNOWLEDGMENTS

Os autores declaram não ter utilizado ferramentas de inteligência artificial na elaboração do artigo.

CONTRIBUTO DOS AUTORES

Os autores contribuíram de igual forma na escrita e revisão do texto.

Todos os autores aprovaram a versão final a ser publicada.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

REFERÊNCIAS

1. Bhende VV, Sharma TS, Krishnakumar M, Ramaswamy AS, Bilgi K, Mankad SP. Decoding the rejection code: understanding why articles get axed. Cureus. 2024;16:e56920.
2. Moore S. Submitting a manuscript to a scientific journal. Respir Care. 2023;68:1314-9.
3. Springer Nature. Common reasons for rejection. [consultado out 07 2025]. Disponível em: https://www.springer.com/gp/authors-editors/authorandreviewertutorials/submitting-to-a-journal-and-peer-review/what-is-open-access/10285582.
4. Teixeira da Silva JA, Al-Khatib A, Katavić V, Bornemann-Cimenti H.

Establishing sensible and practical guidelines for desk rejections. Sci Eng Ethics. 2018;24:1347-65.
5. Teixeira da Silva JA, Nazarovets M. Rejected papers in academic publishing: turning negatives into positives to maximize paper acceptance. Learned Publishing. 2025;38: e1649.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Addressing the Risks of the New Tobacco Product Wave in Portugal

Abordando os Riscos da Nova Vaga de Produtos de Tabaco em Portugal

André VICENTE [1], Luís NEVES [2], Teresa LEÃO [3,4]
Acta Med Port 2025 Dec;38(12):762-764 ▪ https://doi.org/10.20344/amp.23143

Keywords: Adolescent; Electronic Nicotine Delivery Systems; Portugal; Smoking; Tobacco Products; Vaping
Palavras-chave: Adolescente; Fumar; Portugal; Produtos do Tabaco; Sistemas Electrónicos de Administração de Nicotina; Vaporização

INTRODUCTION

In recent decades, policies implemented across various countries have successfully reduced tobacco consumption.[1] However, the emergence of new tobacco and nicotine products, such as electronic cigarettes (e-cigarettes), heated tobacco products (HTPs) and oral forms of tobacco has been posing a challenge to sustaining this downward trend. Euromonitor International forecasts that the global sales of these emerging products, especially of e-cigarettes and HTPs, will continue to increase, offsetting much of the decline in traditional cigarette sales.[2]

Invented in China in 2003, e-cigarettes, commonly referred to as 'vapes', were later introduced to Europe and the United States in 2006. This has led to a dramatic increase in the number and diversity of new products, many deliberately designed to appeal to younger demographics. They are generally equipped with a mouthpiece, a sensor, a battery, a reservoir/tank, and a heating element/atomizer.

Unlike e-cigarettes, which vaporize a liquid, HTPs heat tobacco directly to produce a nicotine-containing aerosol. Heated tobacco products were first conceptualized in the 1980s by major tobacco companies, but the early prototypes failed due to technical issues and the lack of consumer interest. Modern popular HTPs were officially launched in 2014, and despite being initially available only in limited markets, it marked the beginning of their growing global popularity. They typically consist of a tobacco stick or capsule, a heating chamber, a power source, and a control unit regulating temperature to prevent combustion.

Why action is important

Tobacco consumption continues to pose a significant public health challenge worldwide. In 2021, tobacco was the fourth most important risk factor – the first behavioral factor – for the loss of healthy life years in Portugal, responsible for 8100 deaths in that year, about 15.1% of total fatalities.[3]

The impact of traditional tobacco products is indisputable, but the emergence of HTPs and e-cigarettes has been introducing new challenges to risk communication. These products are marketed as less harmful alternatives to traditional tobacco, with claims of 'reduced risk', 'cleaner', and 'smoke-free' alternatives. Nonetheless, according to the World Health Organization (WHO) and the current scientific literature, there is no evidence to support those claims.[2] It is crucial to emphasize that all these nicotine delivery devices induce dependence, including among adolescents, raising significant public health concerns. Beyond addiction, the evidence of their negative impact, particularly on respiratory and cardiovascular diseases, oral health, and mental health, questions their safety claims.[2,4,5] As an example, an epidemic of severe pulmonary disease, named 'e-cigarette or vaping product use-associated lung injury' (EVALI), emerged in the United States in 2012. Although being marketed as non-combustion products, some HTPs devices may reach temperatures that cause partial combustion, sparking an ongoing debate on claims of their combustion-free aerosol.[2]

These new tobacco products are also marketed as effective cessation aids. Nonetheless, limited evidence supports this assertion. Data from several national studies in England showed that in stop-smoking services from 2020 to 2021, quit attempts involving a vaping product had only a slightly higher success rate (64.9%) compared to those that did not (58.6%).[6] This modest difference may be insufficient to outweigh the potential health risks associated with vaping as an alternative to complete cessation. In fact, current data do not indicate that smokers who start using HTPs switch successfully to exclusive use of these products. Instead, most become dual users and do not substantially reduce their risk.[2,5] This dual use is linked to higher health risks than smoking alone, increasing the odds of cardiovascular disease, stroke, metabolic dysfunction, asthma, chronic obstructive pulmonary disease, and oral disease.[7]

1. Serviço de Saúde Pública. Unidade Local de Saúde Gaia e Espinho. Vila Nova de Gaia. Portugal.
2. Unidade de Saúde Familiar Lusitana. Unidade Local de Saúde Viseu Dão Lafões. Viseu. Portugal.
3. EPIUnit ITR. Instituto de Saúde Pública. Universidade do Porto. Porto. Portugal.
4. Department of Forensic and Public Health Sciences and Medical Education. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** André Vicente. andre.vicente@ulsge.min-saude.pt
Recebido/*Received*: 24/03/2025 - **Aceite/*Accepted*:** 01/07/2025 - **Publicado *Online*/*Published Online*:** 12/09/2025 - **Publicado/*Published*:** 02/12/2025

Despite these risks, misconceptions persist. In Portugal, according to a 2020 Eurobarometer poll, the primary reasons for vaping were to reduce or quit smoking (53%), followed by the belief that vaping is less harmful than smoking (32%). In the case of HTPs, the most common reason was the belief in their reduced harm compared to conventional tobacco products (48%), followed by influence from friends (40%). Other significant factors included their use as a smoking cessation aid (32%) and their appeal as being attractive/cool (27%).[8]

Protecting younger generations

These misconceptions are particularly dangerous for adolescents, who are heavily targeted by marketing strategies, well described by Tobacco Tactics - a platform developed by the University of Bath that investigates and exposes the strategies of the tobacco industry to support public health and transparency. Young people may underestimate the risks of nicotine addiction and the harmful substances contained in these products. Its designs, aromas, flavors, and youth-targeted advertising are some of the examples the industry uses to create a gateway for early nicotine addiction, ensuring a new wave of lifelong consumers.[2]

Since 83% of smokers start smoking between the ages of 14 and 25, this age range presents a critical window for targeted prevention efforts.[9] In Portugal, 59% of smokers start before the age of 17, with this figure rising to 95% by the age of 25.[8] Effective prevention efforts, especially among young people, can save millions of lives, prevent morbidity, and significantly reduce healthcare costs. In many countries, including Portugal, the prevalence rate of smoking among individuals aged 15 to 24 exceeds 20%.[9] Between 2015 and 2019, the 12-month prevalence rate of e-cigarette use among Portuguese adolescents aged 13 to 18 increased from 12.5 to 13.4%, emphasizing the growing appeal of these products to younger demographics and highlighting the need for action. For HTPs, the 12-month prevalence rate for 2019 was 3.8%.[10] It is important to note that these are outdated data points that do not fully reflect current trends, especially given the rapid market dissemination of these products.

Preventing the use of tobacco products among younger age groups is also relevant since adolescence is a critical period for brain growth and development, especially of the

Table 1 – List of the proposed solutions, in alignment with the World Health Organization Framework Convention on Tobacco Control (WHO FCTC). Full table with details on current policy gaps can be read in the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23143/15747).

Solution	WHO FCTC
The nicotine content should be aligned with traditional cigarette regulations, limiting each tobacco stick of HTPs to 1 mg and reducing the content for each e-cigarette's reservoir to the equivalent of one pack of cigarettes (20 mg), making this information clear to the consumer.	Article 9
Ensure clear labeling, particularly for e-cigarettes, so consumers are fully informed about nicotine levels.	Articles 10 and 11.2
Ban flavorings on e-cigarettes for their appealing and harmful effects.	Article 9
Mandate neutral and standardized design (plain packaging) for vaping and heated tobacco devices, making them less attractive, such as in terms of colors or coloring properties, attractive or misleading imagery and descriptors, including names.	Article 11.1(a)
Establish two tobacco-free zones around educational institutions: one with a smaller radius where tobacco consumption is strictly prohibited, to prevent exposure and one with a larger radius where the sale of tobacco products is banned, to prevent access.	Articles 8.2 and 16.1(d)
Introduce different types of text advertising on all tobacco or nicotine delivery products to inform on their harms.	Article 11
Set a maximum battery power for e-cigarettes and HTPs, to limit the influence of power on nicotine and toxicant delivery.	Article 9
Prevent medical and scientific journals from publishing studies generated or funded by the tobacco industry.	Article 5.3
Invest in studies on the long-term impact of heated tobacco and vaping, particularly considering the challenges in generating evidence due to the wide variety of products on the market.	Article 20.1
Establish a national system to enforce the existing legislation and monitor the trends of use, sales, and marketing strategies of emerging tobacco products, particularly for young people.	Article 20.3
The issue of smoking prevention and control, including the risks of new tobacco products, should be addressed within the health education framework at the primary and secondary education level by properly trained professionals.	Article 12
Improve understanding regarding the tax burden differences between traditional tobacco products and newer alternatives to better assess whether alternative products are taxed effectively to discourage use.	Article 6
Ban disposable vapes due to their environmental impact, following other European countries.	Article 18

prefrontal cortex, responsible for executive functions, decision-making, and self-regulation.[5] This means that adolescents are particularly vulnerable to environmental toxicants like nicotine, which can trigger rewarding effects more intensely and lead to addiction more rapidly than in adults, even at lower or intermittent levels.[4,5] Nicotine exposure can also have lasting negative impacts on higher cognitive function and emotional regulation.

Taking action

In recent years, Portugal has implemented stricter regulations on emerging tobacco products. For instance, Law 5/2024, transposed the European Union (EU) Delegated Directive 2022/2100, extending some of the restrictions applied to traditional tobacco products to HTPs, namely banning aromas or flavorings (such as vanilla or menthol) and imposing health warnings. Furthermore, the Portuguese legislation aligns policies for traditional tobacco, HTPs, and vaping regarding smoking prohibitions in public spaces, advertising and sponsorship restrictions, and the ban on sales to minors under 18.

However, there are still notable gaps. Addressing them presents an opportunity for Portugal to strengthen its policies, safeguard vulnerable populations (particularly youth), and reduce environmental damage. Table 1 outlines specific solutions to consider, aligned with the WHO Framework Convention on Tobacco Control (WHO FCTC), ratified by Portugal in 2005. Further details on the current policy or legislation gaps, along with the rationale for each proposed solution, can be found in the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23143/15747).

As such, navigating through the wave of emerging tobacco products requires a coordinated and robust effort to provide a health-enabling environment to younger generations, enabling children and adolescents to live healthy, long, fulfilling lives.

AUTHOR CONTRIBUTIONS

AV: Study conception and design, writing and critical review of the manuscript.

LN: Writing and critical review of the manuscript.

TL: Critical review of the manuscript.

All authors reviewed and approved the final version to be published.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000–2030. 2024. [cited 2025 Feb 07]. Available from: https://iris.who.int/handle/10665/375711.
2. World Health Organization. Heated tobacco products: summary of research and evidence of health impacts. 2023. [cited 2025 Feb 10]. Available from: https://iris.who.int/handle/10665/368022.
3. Institute for Health Metrics and Evaluation. Health research by location – Portugal. [cited 2025 Feb 08]. Available from: https://www.healthdata.org/research-analysis/health-by-location/profiles/portugal.
4. Banks E, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. Med J Austr. 2023;218:267-75.
5. Greenhalgh E, Scollo M, Winstanley M. Tobacco in Australia: Facts and issues. 2024. [cited 2025 Feb 07]. Available from: https://www.tobaccoinaustralia.org.au/.
6. Office for Health Improvement & Disparities. Nicotine vaping in England: 2022 evidence update main findings. 2022. [cited 2025 Feb 10]. Available from: https://www.gov.uk/government/publications/nicotine-vaping-in-england-2022-evidence-update/nicotine-vaping-in-england-2022-evidence-update-main-findings.
7. Glantz SA, Nguyen N, da Silva ALO. Population-based disease odds for e-cigarettes and dual use versus cigarettes. NEJM Evidence. 2024;3:EVIDoa2300229.
8. European Union. Attitudes of Europeans towards tobacco and electronic cigarettes. 2021. [cited 2025 Feb 10]. Available from: https://europa.eu/eurobarometer/surveys/detail/2240.
9. Reitsma MB, Flor LS, Mullany EC, Gupta V, Hay SI, Gakidou E. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and initiation among young people in 204 countries and territories, 1990–2019. Lancet Public Health. 2021;6:e472-81.
10. Direção-Geral da Saúde. Programa nacional para a prevenção e controlo do tabagismo 2020. 2021. [cited 2025 Feb 07]. Available from: https://www.dgs.pt/portal-da-estatistica-da-saude/diretorio-de-informacao/diretorio-de-informacao/por-serie-1219790-pdf.aspx.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Retropharyngeal Lymph Node Metastases in Papillary Thyroid Carcinoma: A Case Series and Literature Review

Metástases Retrofaríngeas no Carcinoma Papilar da Tiroide: Série de Casos e Revisão da Literatura

Henrique PINA [1], Daniela CAVACO [2], Ricardo NOGUEIRA [3], Valeriano LEITE [2]
Acta Med Port 2025 Dec;38(12):765-772 ▪ https://doi.org/10.20344/amp.22908

ABSTRACT

Introduction: The prevalence of retropharyngeal lymph node metastases in papillary thyroid carcinoma is low. The objective of this retrospective study was to assess our institutional experience with the management of such metastases and to compare results with other published series.

Methods: We conducted a retrospective analysis of patients diagnosed with papillary thyroid carcinoma and retropharyngeal lymph node metastases who were followed at the Endocrinology Department of the Instituto Português de Oncologia de Lisboa Francisco Gentil. To identify published cases in the literature, a comprehensive search was conducted using the Medline and PubMed databases from January 1970 to June 2025.

Results: We have identified a total of 15 patients. Twelve (80.0%) were women. The median age at initial surgery was 55.7 years (range 20.6 - 84.0 years) and the median duration of follow-up was 9.8 years (range 0.5 - 36.3 years). Five patients (33.3%) were diagnosed with retropharyngeal lymph node metastases during initial tumor staging and 10 (66.7%) in the follow-up, in eight patients (80.0%) due to biochemical persistence of the disease, and in two (20.0%) after cervical lymph node recurrence. Of the 15 patients, seven (46.7%) received no treatment for retropharyngeal lymph node metastases (surveillance group), and eight (53.3%) were treated (therapy group) and, from these, four (26.7%) underwent surgery, two (13.3%) received radiotherapy, one (6.7%) underwent radiosurgery and one (6.7%) underwent both surgery and radiotherapy.

Conclusion: Most patients with retropharyngeal lymph node metastases are diagnosed post-thyroidectomy, due to biochemical persistence of the disease or cervical lymphatic recurrence. Retropharyngeal lymph node metastases are commonly single and located ipsilaterally to the primary tumor and co-occur frequently with distant metastases.

Keywords: Carcinoma, Papillary; Pharyngeal Neoplasms; Thyroid Cancer, Papillary/secondary

RESUMO

Introdução: A prevalência de metástases retrofaríngeas no carcinoma papilar da tiroide é baixa. O objetivo deste estudo retrospetivo foi avaliar a nossa experiência institucional na gestão destas metástases e comparar os resultados com outras séries publicadas.

Métodos: Foi realizada uma análise retrospetiva de doentes com carcinoma papilar da tiroide e metástases no espaço retrofaríngeo, seguidos no Serviço de Endocrinologia do Instituto Português de Oncologia de Lisboa Francisco Gentil. Para identificar casos publicados na literatura, foi realizada uma pesquisa bibliográfica nas bases de dados Medline e PubMed, de janeiro de 1970 a junho de 2025.

Resultados: Foram identificados 15 doentes, dos quais 12 (80,0%) eram do sexo feminino. A idade mediana na primeira cirurgia foi de 55,7 anos (amplitude 20,6 - 84,0 anos), e a mediana do tempo de seguimento foi de 9,8 anos (amplitude 0,5 - 36,3 anos). Em cinco doentes (33,3%) foram identificadas metástases retrofaríngeas durante o estadiamento inicial e em 10 (66,7%) durante o seguimento, sendo que, em oito doentes (80,0%), o diagnóstico ocorreu devido a persistência bioquímica da doença, e em dois (20,0%) após recorrência de doença nos gânglios linfáticos cervicais. Dos 15 doentes, sete (46,7%) não receberam tratamento para as metástases retrofaríngeas (grupo de vigilância), e oito (53,3%) foram tratados (grupo de tratamento). Destes, quatro (26,7%) foram submetidos a cirurgia isolada, dois (13,3%) receberam radioterapia isolada, um (6,7%) foi submetido a radiocirurgia e um (6,7%) realizou cirurgia e radioterapia.

Conclusão: A maioria dos doentes com metástases retrofaríngeas é diagnosticada após a tiroidectomia total, devido à persistência bioquímica da doença ou recorrência linfática cervical. As metástases nos gânglios linfáticos retrofaríngeos são geralmente únicas, localizadas ipsilateralmente ao tumor primário e ocorrem frequentemente em simultâneo com metástases à distância.

Palavras-chave: Carcinoma Papilar; Carcinoma Papilar da Tiróide/secundário; Neoplasias Faríngeas

KEY MESSAGES

- Retropharyngeal lymph node metastases in papillary thyroid carcinoma are rare and most often diagnosed after thyroidectomy, due to biochemical persistence or cervical recurrence.
- These metastases are usually solitary, located ipsilaterally to the primary tumor, and frequently associated with distant metastases.
- Management of these patients is complex and should be individualized, with options ranging from active surveillance to therapeutic interventions such as surgery, radiotherapy, or a combination of both.
- The main limitation of this study is the small number of patients, inherent to the rarity of this condition.

1. Department of Endocrinology. Hospital Beatriz Ângelo. Loures. Portugal.
2. Department of Endocrinology. Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE. Lisbon. Portugal.
3. Department of Head and Neck Surgery. Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE. Lisbon. Portugal.
✉ **Autor correspondente:** Henrique Pina. henrique.costa.pina@ulslod.min-saude.pt
Revisto por/Reviewed by: Mariana Caldeira
Recebido/*Received*: 20/01/2025 - **Aceite/*Accepted*:** 09/09/2025 - **Publicado *Online*/*Published Online*:** 10/10/2025 - **Publicado/*Published*:** 02/12/2025

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the predominant histological subtype of differentiated thyroid carcinoma. Despite its favorable prognosis, generally with minor impact on survival, the presence of cervical lymph node metastases (CLNM) influences the course of the disease and treatment outcomes, as it increases the risk of postoperative recurrence, especially in younger patients.[1-3]

At the time of initial diagnosis, it is estimated that 30% - 80% of patients exhibit CLNM. The extension of PTC into the lymph nodes typically follows a consistent and predictable pattern, with the central compartment (level VI) being the primary site of lymph node involvement, followed by the lateral compartment (level III to V) and the superior mediastinal compartment (level VII).[4-6]

The retropharyngeal space (RS) extends from the clivus to the upper mediastinum. It lies anteriorly to the prevertebral muscles, posteriorly to the pharynx and esophagus and medially to the carotid space. Classically, it is divided into the suprahyoid and infrahyoid RS, each with different contents. The suprahyoid RS contains fat and lymph nodes, whereas the infrahyoid RS contains only fat and, thus, can be involved only by non-nodal disease. Small normal lymph nodes may be present in healthy patients, usually measuring < 1 cm in short axis diameter.[4,7]

Based on case reports and small series, the incidence of retropharyngeal lymph node metastases (RFLNM) in patients with PTC is estimated to be 0.28% - 5%.[5,8]

However, given the widespread use of imaging in patients with PTC and high serum thyroglobulin (Tg) levels, it is expected that the incidence of RFLNM is likely to increase.[5]

Additionally, in the 8th edition of the AJCC/TNM staging system of thyroid cancer, RFLNM are now staged as N1b, alongside metastasis to lateral neck lymph nodes,[9,10] because they affect survival rates in a similar fashion to lateral neck lymph node metastases.

However, the efficacy of surgical or non-surgical interventions in RFLNM has not been definitively established and it is important to balance between the potential benefits of treatment and the anticipated post-therapy quality of life. Complete surgical removal is the only curative treatment and is typically the treatment of choice. However, intraoperative injury of cranial nerves and vessels during dissection may lead to serious complications.

Considering that non-surgical approaches usually do not provide a cure for patients, their primary objective is to minimize symptoms and halt the progression of locoregional disease. There are three main modalities of nonsurgical therapy: radioactive iodine (RAI), external beam radiation therapy (EBRT), and systemic therapy.

The aim of this retrospective was to assess the prevalence of PTC-RFLNM in our institution and to compare results with the published series.

METHODS

Case series

We conducted a retrospective analysis of patients followed at the Endocrinology Department of the Instituto Português de Oncologia de Lisboa Francisco Gentil, with a diagnosis of PTC with RFLNM.

Patients were identified through a computerized search, looking for the word “retropharyngeal”, in the reports of cervical computed tomography (CT) scans performed during a period of eight years, between January 2015 and January 2023. From a total of 651 reports, 26 patients were identified with a neoplasia diagnosis of thyroid origin and retropharyngeal adenopathy compatible with metastasis. Eleven patients were excluded: two due to the diagnosis of another active synchronous neoplasm, two due to a histological diagnosis of anaplastic carcinoma, five due to histological diagnosis of medullary thyroid carcinoma and two due to histological diagnosis of oncocytic thyroid tumor (formerly Hürthle cell tumor), resulting in a total of 15 patients.

Literature review

To determine the cases published in the literature, a comprehensive search was conducted using Medline and PubMed databases, from January 1970 to June 2025. Search terms included “retropharyngeal lymph node metastasis” & “thyroid”, “papillary thyroid carcinoma” & “retropharyngeal” and “well-differentiated thyroid cancer” & “retropharyngeal”. Publications were considered relevant if they met the following inclusion criteria: (a) cases of PTC with RFLNM; (b) full text available; (c) written in English. Publications were excluded if: (a) it was not clearly defined whether the metastasis was to the retropharyngeal space rather than to the parapharyngeal space; (b) included other types of thyroid carcinoma (follicular, Hürthle cells, medullary, poorly differentiated, and anaplastic thyroid carcinomas); (c) if patients had synchronous tumors of other organs and no histologic confirmation of retropharyngeal metastasis.

Statistical analysis

Categorical variables are presented as absolute numbers and percentages. Continuous data are presented as medians and ranges. Qualitative data are described as frequencies and percentages. Continuous data were visually inspected with histograms/boxplots and did not follow a normal distribution. Therefore, comparisons between groups were performed with the Mann-Whitney U test for continuous variables. For categorical variables, Fisher’s exact test was used. All analyses were performed using SPSS

software v. 26. A *p* value of ≤ 0.05 was considered statistically significant.

Etics statement

This study was conducted in compliance with the Helsinki Declaration and was approved by the Ethics Committee of our Institution. Written informed consent was waived because of the retrospective nature of the study. The analysis used anonymous clinical data.

RESULTS

Patient clinical and pathological characteristics

We present a total of 15 patients with a history of PTC and RFLNM. Twelve were women (80.0%). The median age at initial surgery was 55.7 years (range 20.6 - 84.0 years), with seven (46.7%) below 55 years; five (33.3%) were diagnosed with RFLNM during initial tumor staging and 10 (66.7%) in the context of recurrent or persistent disease. Out of the 10 patients in the recurrence/persistent group, eight (80.0%) were diagnosed due to biochemical persistence of the disease, and two (20.0%) following imaging staging of cervical lymph node recurrence. The median duration of follow-up was 9.8 years (range 0.5 - 36.3 years) and patients with recurrence had a longer follow-up of 13.0 years (range 4.2 - 36.3 years) than patients diagnosed with upfront RFLNM, with 2.9 years (range 0.5 - 6.0 years). All patients (n = 15) underwent total thyroidectomy, and 10 patients (66.7%) central/lateral neck dissection. All patients had PTC, 10 (66.7%) were classical subtype, two (13.3%) tall-cell subtype, one (6.6%) unspecified follicular subtype and two (13.3%) were of an unknown subtype. The median size of the primary tumor was 32 mm (range 8 - 75 mm), multifocal tumors were present in five patients (33.3%), lymphovascular invasion and capsule invasion were each present in nine patients (60%). In our series, 10 patients (66.7%) had distant metastasis: three patients (20.0%) had lung metastasis diagnosed before RFLNM, four patients (26.7%) had synchronous diagnosis of distant metastasis (three with lung and one with bone), and three patients (20.0%) developed distant metastasis (two with lung and one with both lung and bone) after the RFLNM diagnosis.

Characteristics

One patient (6.7%) had bilateral RFLNM and 14 (93.3%) had a single RFLNM. Retropharyngeal lymph node metastases were ipsilateral to the primary tumor in 11 patients (73.3%). The main imaging modality used for diagnosis was CT scan (11 patients, 73.3%), followed by PET FDG (three patients, 20.0%) and MRI (one patient, 6.7%). The median maximum diameter of RFLNM was 15 mm (range 5 - 56 mm).

Therapeutic approach

Of the 15 patients, 14 (93.3%) received treatment with iodine-131 (I^{131}), as part of the treatment for the primary tumor. Of the 15 patients, seven (46.7%) received no treatment for RFLNM (surveillance group), and eight (53.3%) were treated (therapy group) and, from these, four (26.7%) underwent surgery alone, two (13.3%) received radiotherapy alone, one (6.7%) underwent radiosurgery and one (6.7%) underwent both surgery and radiotherapy.

In the five patients operated on RFLNM, a cervical approach was used and no complications were recorded. However, in the patient with a large RFLNM (49 x 25 x 15 mm) residual disease persisted, which was stable at the last follow-up CT scan. One of the patients treated with radiosurgery developed transient pharyngitis and dysgeusia.

In the surveillance group, two patients started treatment with lenvatinib in response to progression of pulmonary disease, and in one a favorable radiological response was observed in the RFLNM.

In the surveillance group, the median size of the RFLNM was 12 mm (range 5 - 32 mm) whereas in the therapy group the median size was 21 mm (range 11 - 56 mm), $p = 0.082$. The median age in the surveillance group was 48.5 years (range 20.6 - 58.1 years) and 69.5 years (range 41.0 - 84.0 years) in the therapy group, $p = 0.029$.

Outcomes at the end of follow-up

Our case series has three (20.0%) deaths to report during follow-up: one patient died at the age of 79, 13 years after the diagnosis of PTC, as a result of extensive poorly differentiated nodal recurrence, which occurred in anatomical regions other than the retropharyngeal space, one patient died at the age of 85, 38 years after the diagnosis of PTC, due to the progression of bone, lung, and retropharyngeal disease and one patient died at the age of 84 due to esophageal carcinoma, which might be a complication of cervical radiotherapy for the treatment of PTC-RFLNM performed six years before.

Additionally, at the last clinical evaluation, eight (53.3%) patients had stable structural disease (five patients with distant metastasis, 62.5%), two (13.3%) patients had biochemical evidence of disease, and two (13.3%) patients had no evidence of disease (Table 1).

Literature review

By June 2025, a total of 170 cases of PTC-RFLNM had been published.[5,6,8,10-21]

Most cases were published in the form of case series (Table 2), with only five being documented as case reports.[22-26]

The analysis of all reported cases is challenging: due to the frequent inclusion of heterogeneous histological

subtypes of thyroid carcinoma by various authors, as well as the inconsistent or indiscriminate grouping of parapharyngeal and retropharyngeal metastases.

DISCUSSION

We have identified a total of 15 patients. Twelve (80.0%) were women. The median age at initial surgery was 55.7

Table 1 – Clinical and pathological characteristics of patients with PTC-RFLNM (section 1 of 2)

	Total (n = 15)	**Surveillance group** (n = 7)	**Therapy group** (n = 8)	***p*-value**
Patients total, n (%)	15 (100)	7 (47)	8 (53)	
Age (years)				0.029
Median	55.7	48.5	69.5	
IQR	31.0	20.9	27.5	
Minimum	20.6	20.6	41.0	
Maximum	84.0	58.1	84.0	
Sex				0.569
Female	12 (80)	5 (71)	7 (88)	
Male	3 (20)	2 (29)	1 (13)	
Follow-up (years)				0.867
Median	9.8	9.1	11.0	
IQR	12.9	14.2	11.9	
Minimum	0.5	0.5	1.0	
Maximum	36.3	36.3	19.5	
Surgery, n (%)				
Total thyroidectomy	15 (100)	7 (100)	8 (100)	1.000
Neck dissection, n (%)				0.492
None	5 (33)	1 (14)	4 (50)	
Central	3 (20)	2 (29)	1 (13)	
Central + Unilateral	6 (40)	4 (57)	2 (25)	
Central + Bilateral	2 (13)	1 (14)	1 (13)	
Subtype of PTC, n (%)				0.188
Classical	10 (67)	6 (86)	4 (50)	
Tall-cell	2 (13)	0 (0)	2 (25)	
Unspecified follicular subtype	1 (7)	0 (0)	1 (13)	
Unknown	2 (13)	1 (14)	1 (13)	
Size (mm)				0.830
Median	32.0	28.5	33.0	
IQR	23.0	31.0	27.0	
Minimum	8.0	8.0	10.0	
Maximum	75.0	75.0	44.0	
Focality, n (%)				0.592
Focal	8 (53)	3 (43)	5 (63)	
Multifocal	5 (33)	3 (43)	2 (25)	
Unknown	2 (13)	1 (14)	1 (13)	
Lymphovascular invasion, n (%)				1.000
Yes	9 (60)	4 (57)	5 (63)	
No	4 (27)	2 (29)	2 (25)	
Unknown	2 (13)	1 (14)	1 (13)	

RFLNM: retropharyngeal lymph node metastases; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; I^{131}: radioactive iodine

years (range 20.6 - 84.0 years) and the median duration of follow-up was 9.8 years (range 0.5 - 36.3 years). Five patients (33.3%) were diagnosed with retropharyngeal lymph node metastases during initial tumor staging and 10 (66.7%) in the follow-up, in eight patients (80.0%) due to biochemical persistence of the disease, and in two (20.0%) after cervical lymph node recurrence. Of the 15 patients, seven (46.7%) received no treatment for retropharyngeal lymph node metastases (surveillance group), and eight (53.3%) were treated (therapy group) and, from these, four (26.7%) underwent surgery, two (13.3%) received radiotherapy, one (6.7%) underwent radiosurgery and one (6.7%) underwent both surgery and radiotherapy.

Table 1 – Clinical and pathological characteristics of patients with PTC-RFLNM (section 2 of 2)

	Total (n = 15)	**Surveillance group** (n = 7)	**Therapy group** (n = 8)	***p*-value**
Capsule invasion, n (%)				1.000
Yes	9 (60)	5 (71)	4 (50)	
No	4 (27)	2 (29)	2 (25)	
Unknown	2 (13)	1 (14)	1 (13)	
Extrathyroidal extension, n (%)				1.000
Yes	8 (53)	4 (57)	4 (50)	
No	4 (27)	3 (43)	1 (13)	
Unknown	1 (7)	1 (14)	0 (0)	
Surgical margins, n (%)				0.380
R0	9 (60)	4 (57)	5 (63)	
R1	4 (27)	2 (29)	2 (25)	
R2	1 (7)	1 (14)	0 (0)	
Unknown	2 (13)	1 (14)	1 (13)	
RFLNM size (mm)				0.082
Median	15.0	12.0	21.0	
IQR	17.0	8.0	30.0	
Minimum	5.0	5.0	11.0	
Maximum	56.0	32.0	56.0	
Time of RFLNM diagnosis, n (%)				0.608
Initial presentation	5 (33)	3 (43)	2 (25)	
Recurrent disease	10 (67)	4 (57)	6 (75)	
RFLNM location, n (%)				0.569
Ipsilateral	11 (73)	5 (71)	6 (75)	
Contralateral	3 (20)	2 (29)	1 (13)	
Bilateral	1 (7)	0 (0)	1 (13)	
Imaging for RFLNM detection, n (%)				
CT	11 (73)	6 (86)	5 (63)	0.569
MRI	1 (7)	1 (14)	0 (0)	0.467
PET	3 (20)	0 (0)	3 (38)	0.200
Therapy, n (%)				
I131	14 (93)	7 (100)	7 (88)	1.000
Surgery	4 (27)	0 (0)	4 (50)	
Radiotherapy	2 (13)	0 (0)	2 (25)	
Radiosurgery	1 (7)	0 (0)	1 (13)	
Radiotherapy + Surgery	1 (7)	0 (0)	1 (13)	

RFLNM: retropharyngeal lymph node metastases; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; I^{131}: radioactive iodine

Table 2 – Series of PTC with RFLNM published in the literature

Case series	Country	Number of cases	Year	Diagnosis at initial presentation/ recurrence
McCormack *et al*[6]	USA	2	1970	0/2
Leger *et al*[13]	France	4	2000	0/4
Otsuki N *et al*[11]	Japan	5	2007	0/5
Le *et al*[14]	USA	6	2007	2/4
Shellenberger *et al*[15]	USA	2	2007	0/2
Kaplan *et al*[16]	USA	3	2009	0/3
Kainuma K *et al*[17]	Japan	3	2011	1/2
Moore *et al*[18]	USA	2	2011	0/2
Fornage *et al*[19]	USA	3	2014	0/3
Togashi T *et al*[20]	Japan	12	2014	7/5
Hartl DM *et al*[12]	France	5	2015	0/5
Otsuki N *et al*[10]	Japan	16	2019	7/9
Sandler M *et al*[4]	USA	7	2020	4/3
Harries V *et al*[5]	USA	55	2020	10/45*
Chen S *et al*[21]	China	6	2022	5/1
Zhao J *et al*[3]	China	34	2024	7/27
Pina *et al*	Portugal	15	2025	5/10

*: data extrapolated, not directly available.
USA: United States of America

Mechanisms of metastatic spread to the retropharyngeal space

The mechanism behind the metastatic spread to this region remains poorly explained. However, two lymphatic pathways are present in this region. One pathway involves the jugular chain lymphatics, while the other involves the posterosuperior collecting vessel, present in 20% of the cases, which connects the upper posterior portion of the thyroid gland to the RS.[4,11,17] This anatomical connection may provide a direct route for lymphatic spread to the RS.

In our series, nine out of 15 patients (60.0%) had lymphovascular invasion at the time of total thyroidectomy, and 11 out of 15 patients (73.3%) had involvement of the ipsilateral lymph nodes, which could potentially justify the dissemination to the RS.

Additionally, previous studies have suggested that metastatic cervical lymph nodes or neck dissection procedures could potentially modify the flow of lymphatic drainage, leading to atypical metastasis in the retropharyngeal space, justifying most cases being diagnosed years after primary PTC surgery and cervical lymph node dissection.[11]

Diagnosis and imaging limitations

Since, in most patients with PTC, initial staging is usually performed with neck ultrasound, PTC-RFLNM are rarely detected due to its location deep in the neck. Most RFLNM are, indeed, detected by CT scan in cases of recurrent or persistent disease.[2,17,27] Out of the 170 published cases, only 45 (26.5%) were diagnosed at initial presentation.[11,12] This is also the case in our series, where five patients (33.3%) were diagnosed at the initial primary tumor staging and 10 (66.7%) in the context of recurrent or persistent disease.

These findings underscore the importance of including cross-sectional imaging in the evaluation of high-risk patients or those with unexplained biochemical persistence of disease.

Clinical features and biological behavior

In our series, none of the patients presented with clinical symptoms directly related to PTC-RFLNM. Furthermore, none of the patients exhibited signs of invasion of surrounding structures. However, there are reports of symptoms such as neck pain, syncope, and lower cranial nerve paralysis.[6,10] It is worth noting that, in our series, the main source of morbidity derived from progression of distant disease rather than from RFLNM progression/complications.

A noteworthy observation in our study is the high frequency of concurrent distant metastases (60%). While prior series report this association in 12.5% - 23.1% of cases,[4,5,10] our findings suggest that RFLNM may serve as a potential indicator of biologically aggressive disease or altered dissemination patterns.

Therapeutic implications

Management of RFLNM must be individualized. According to the literature, surgery remains the cornerstone

of treatment for patients with resectable RFLNM metastases. In situations where complete resection is not possible – such as in cases of unresectable disease, significant comorbidities, or unfavorable anatomical involvement – I^{131} therapy may be employed as an adjuvant or alternative modality. External-beam radiotherapy may also be considered in selected patients, particularly those with residual disease, non–iodine-avid metastases, or when surgery is contraindicated.[5,8,12]

Despite the limited number of cases, our findings suggest that certain clinical and pathological features may help guide the decision between active surveillance and intervention. Patients with small (< 15 mm), asymptomatic RFLNM and no evidence of progression over time may be good candidates for conservative management. In our case series, the surveillance group had a median size of PTC-RFLNM of 12 mm (*vs* 21 mm in the therapy group, $p = 0.082$).

Surgical resection of RFLNM is challenging due to the deep anatomical location and proximity to critical neurovascular structures. Approaches such as transoral robotic surgery and modified transcervical access have been described but carry non-negligible morbidity. Therefore, intervention is usually reserved for symptomatic lesions, progressive enlargement, or diagnostic uncertainty. Importantly, in our series, morbidity was predominantly related to distant metastatic disease rather than progression of RFLNM itself, reinforcing the need to tailor treatment to overall disease burden and progression.

Although our study was not designed to formally develop a predictive model, future multicenter studies may help identify independent predictors of progression or therapeutic response. Potential variables include RFLNM size, histological subtype (particularly aggressive variants of PTC), presence of lymphovascular invasion, timing of detection (initial staging *versus* recurrence), and coexistence of distant metastases. The development of such models could provide a valuable tool to support clinical decision-making in this rare but complex scenario.

CONCLUSION

In summary, RFLNM are an uncommon but clinically relevant manifestation of metastatic PTC. Most patients with RFLNM are diagnosed post-thyroidectomy, due to biochemical persistence of the disease or cervical lymphatic recurrence. Retropharyngeal lymph node metastases are commonly single and located ipsilaterally to the primary tumor and frequently co-occur with distant metastases. Diagnosis requires a high index of suspicion and appropriate cross-sectional imaging. While small, asymptomatic lesions can be managed conservatively, the presence of RFLNM may reflect a more aggressive tumor biology and warrants close multidisciplinary evaluation.

Future studies, ideally multicenter and with larger sample sizes, are needed to develop predictive models capable of stratifying patients according to the risk of progression and identifying those who will most likely benefit from active treatment *versus* surveillance.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

HP, DC, RN: Study conception and design, writing of the manuscript.

VL: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22:1144-52.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1-133.
3. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. J Clin Oncol. 2015;33:2370-5.

4. Sandler ML, Xing MH, Levy JC, Chai RL, Khorsandi AS, Gonzalez-Velazquez C, et al. Metastatic thyroid carcinoma to the parapharyngeal and retropharyngeal spaces: systematic review with seven newly reported cases describing an uncommon presentation of a common disease. Head Neck. 2021;43:1331-44.
5. Harries V, McGill M, Tuttle RM, Shaha AR, Wong RJ, Shah JP, et al. Management of retropharyngeal lymph node metastases in differentiated thyroid carcinoma. Thyroid. 2020;30:688-95.
6. McCormack KR, Sheline GE. Retropharyngeal spread of carcinoma of the thyroid. Cancer. 1970;26:1366-9.
7. Debnam JM, Guha-Thakurta N. Retropharyngeal and prevertebral spaces: anatomic imaging and diagnosis. Otolaryngol Clin North Am. 2012;45:1293-310.
8. Zhao J, Zheng W, Zhong M, Daming L, Guo L. Risk factors and prognosis of retropharyngeal lymph node metastasis from papillary thyroid carcinoma. Altern Ther Health Med. 2024;30:474-9.
9. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-9.
10. Otsuki N, Morita N, Furukawa T, Teshima M, Shinomiya H, Shinomiya H, et al. Functional and oncological outcomes after retropharyngeal node dissection for papillary thyroid carcinoma. Eur Arch Otorhinolaryngol. 2019;276:1809-14.
11. Otsuki N, Nishikawa T, Iwae S, Saito M, Mohri M, Nibu K. Retropharyngeal node metastasis from papillary thyroid carcinoma. Head Neck. 2007;29:508-11.
12. Hartl DM, Leboulleux S, Vélayoudom-Céphise FL, Mirghani H, Déandréis D, Schlumberger M. Management of retropharyngeal node metastases from thyroid carcinoma. World J Surg. 2015;39:1274-81.
13. Leger AF, Baillet G, Dagousset F, Vincenot MI, Izembart M, Clerc J, et al. Upper retropharyngeal node involvement in differentiated thyroid carcinoma demonstrated by 131I scintigraphy. Br J Radiol. 2000;73:1260-4.
14. Le TD, Cohen JI. Transoral approach to removal of the retropharyngeal lymph nodes in well-differentiated thyroid cancer. Laryngoscope. 2007;117:1155-8.
15. Shellenberger T, Fornage B, Ginsberg L, Clayman GL. Transoral resection of thyroid cancer metastasis to lateral retropharyngeal nodes. Head Neck. 2007;29:258-66.
16. Kaplan SL, Mandel SJ, Muller R, Baloch ZW, Thaler ER, Loevner LA. The role of MR imaging in detecting nodal disease in thyroidectomy patients with rising thyroglobulin levels. AJNR Am J Neuroradiol. 2009;30:608-12.
17. Kainuma K, Kitoh R, Yoshimura H, Usami S. The first report of bilateral retropharyngeal lymph node metastasis from papillary thyroid carcinoma and review of the literature. Acta Otolaryngol. 2011;131:1341-8.
18. Moore MW, Jantharapattana K, Williams MD, Grant DG, Selber JC, Holsinger FC. Retropharyngeal lymphadenectomy with transoral robotic surgery for papillary thyroid cancer. J Robot Surg. 2011;5:221.
19. Fornage BD, Edeiken BS, Clayman GL. Use of transoral sonography with an endocavitary transducer in diagnosis, fine-needle aspiration biopsy, and intraoperative localization of retropharyngeal masses. AJR Am J Roentgenol. 2014;202:W481-6.
20. Togashi T, Sugitani I, Toda K, Kawabata K, Takahashi S. Surgical management of retropharyngeal nodes metastases from papillary thyroid carcinoma. World J Surg. 2014;38:2831-7.
21. Chen S, Yang H, Su X, Yang A, Liu W. Transcervical dissection of metastatic suprahyoid retropharyngeal lymph nodes from papillary thyroid carcinoma through three anatomical barriers. Int J Oral Maxillofac Surg. 2021;50:158-62.
22. DiLeo MD, Baker KB, Deschler DG, Hayden RE. Metastatic papillary thyroid carcinoma presenting as a retropharyngeal mass. Am J Otolaryngol. 1998;19:404-6.
23. Ma QD, Grimm K, Paz BI, Maghami E. Transoral surgical approach for retropharyngeal node involvement in i-131-negative 18-fluoro-2-deoxyglucose positron emission tomography-positive recurrent thyroid cancer. Skull Base. 2009;19:431-6.
24. Goepfert RP, Liu C, Ryan WR. Trans-oral robotic surgery and surgeon-performed trans-oral ultrasound for intraoperative location and excision of an isolated retropharyngeal lymph node metastasis of papillary thyroid carcinoma. Am J Otolaryngol. 2015;36:710-4.
25. Fujiwara K, Fukuhara T, Koyama S, Donishi R, Kataoka H, Kitano H, et al. Ultrasound-guided transoral videolaryngoscopic surgery for retropharyngeal lymph node metastasis of papillary thyroid cancer. Case Rep Oncol. 2017;10:649-55.
26. Kholmatov R, Emejulu O, Murad F, Aslam R, Kandil E. Locally advanced asymptomatic papillary thyroid cancer presenting with retropharyngeal lymph node metastasis symptoms. Gland Surg. 2017;6:733-7.
27. Yang J, Zhang F, Qiao Y. Diagnostic accuracy of ultrasound, CT and their combination in detecting cervical lymph node metastasis in patients with papillary thyroid cancer: a systematic review and meta-analysis. BMJ Open. 2022;12:e051568.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Internato de Formação Especializada em Doenças Infeciosas: Caracterização e Perceção sobre o Ambiente Clínico de Aprendizagem

Residency Training in Infectious Diseases: Assessment and Perception of the Clinical Learning Environment

José GANICHO [1], Ana Raquel GARROTE [1], Maria José MANATA [1], Fernando MALTEZ [1], Raquel TAVARES [2]
Acta Med Port 2025 Dec;38(12):773-784 ▪ https://doi.org/10.20344/amp.23187

RESUMO

Introdução: A Organização Mundial de Saúde definiu as 13 mais importantes ameaças à Saúde Global da década, das quais se destacam a prevenção de doenças infeciosas e a resistência antimicrobiana. Dada a evolução célere da evidência científica e a necessidade de atualização, é imperativo discutir a formação em Doenças Infeciosas. Este estudo teve como objetivo caracterizar e explorar a perceção dos inquiridos relativamente à formação em Doenças Infeciosas e ao ambiente clínico de aprendizagem.

Métodos: Foi desenvolvido um questionário sobre os ambientes clínicos de aprendizagem, dirigido a médicos internos e recém-especialistas que tenham concluído o seu programa de formação nos últimos cinco anos, inclusive.

Resultados: O questionário obteve 73 respostas, 75,3% de médicos internos. A maioria concordou com a duração dos estágios de Medicina Interna (83,5%), Microbiologia (76,7%) e Infeciologia Geral (71,2%), mas considerou que o estágio de Medicina Intensiva deveria ter uma duração inferior a seis meses. Foi sugerido que as áreas de Controlo de Infeção/Prescrição Antibiótica e de Imunossupressão/Risco Infecioso tivessem estágios obrigatórios, por 84,9% e 65,8% dos participantes, respetivamente. A maioria (67,1%) dos inquiridos considerou prejudicial a realização de urgência externa de Medicina Interna para além do respetivo estágio, sendo que 84,6% dos participantes da ARS Norte realizaram esta atividade apenas durante o 1.º ano, em contraste com 86,8% da ARS LVT cuja atividade se prolongou pelo menos até ao 4.º ano. No que concerne à produção assistencial e científica, comparativamente aos médicos internos da ARS LVT, os da ARS Norte reportaram, em média, um maior número de consultas assistidas (21,7/17,1) e realizadas (20,8/17,7), semanalmente, assim como um maior número de participações (3,7/3,1) e apresentações (2,8/2,4) anuais em eventos científicos, artigos publicados (1,1/0,6) e horas de estudo semanais (7,4/4,5). As principais dificuldades reportadas foram a ausência de tempo de estudo dedicado no horário, a atualização científica e a realização de Urgência Externa de Medicina Interna. Sobre a avaliação do internato, apenas 2,7% concordaram totalmente com o modelo de exame atual e 1,37% com a grelha curricular atual. A maioria (64,4%) dos participantes consideraram-se, pelo menos, satisfeitos com a especialidade.

Conclusão: Os resultados sugerem uma necessidade de rever o programa formativo, incluir novas áreas de especialização e discutir os modelos de avaliação ao longo do Internato. Verificam-se assimetrias regionais ao nível do exercício de funções em contexto de urgência externa de Medicina Interna e da produção assistencial e científica, o que condiciona a equidade e qualidade da formação. A discussão da formação em Doenças Infeciosas é crucial para a adaptação do programa formativo aos desafios atuais e futuros.

Palavras-chave: Competência Clínica; Especialização; Infecciologia/educação; Inquéritos e Questionários; Internato e Residência; Médicos; Portugal

ABSTRACT

Introduction: The World Health Organization identified 13 critical threats to global health for the coming decade, including infectious disease prevention and antimicrobial resistance. Given the ongoing advancements in scientific evidence, it is imperative to discuss the Infectious Diseases training program. The aim of this study was to characterize and explore the respondents' perceptions regarding Infectious Diseases training and the clinical learning environment.

Methods: A survey was developed to assess the clinical learning environment, targeting residents and young specialists who completed their training within the past five years.

Results: The questionnaire received 73 responses, 75.3% from residents. Most respondents agreed with the duration of Internal Medicine (83.5%), Microbiology (76.7%), and General Infectious Diseases (71.2%) rotations, but considered that the Intensive Care rotation should last less than six months. The areas of Infection Control/Antibiotic Stewardship and Immunosuppression/Infectious Risk were suggested as mandatory rotations by 84.9% and 65.8% of participants, respectively. Most respondents (67.1%) considered prolonged Internal Medicine Emergency rotations beyond the first year detrimental. In contrast, 84.6% of ARS Norte participants only performed this activity during the first year, whereas 86.8% of ARS LVT participants continued, at least, until the fourth year. Regarding clinical and scientific output, ARS Norte interns reported, on average, higher numbers of weekly assisted (21.7 *vs* 17.1) and performed (20.8 *vs* 17.7) appointments, as well as higher annual participation (3.7 *vs* 3.1) and presentations (2.8 *vs* 2.4) in scientific events, published articles (1.1 *vs* 0.6), and weekly study hours (7.4 *vs* 4.5), compared with ARS LVT. The main challenges reported were a lack of dedicated study time during working hours, scientific updates, and clinical practice in Internal Medicine Emergency rotations. Regarding the evaluation of the residency program, only 2.7% agreed completely with the current exam model and 1.37% with the current curriculum grid. The majority (64.4%) of participants considered themselves at least satisfied with the specialty.

Conclusion: The results suggest a need to review the Infectious Diseases training program, include new areas of specialization, and discuss evaluation models throughout residency. Regional asymmetries were observed in emergency work, clinical and scientific output, which affect the equity and quality of training. Discussion of the Infectious Diseases training program is crucial for adapting the curriculum to current and future challenges.

Keywords: Clinical Competence; Infectious Disease Medicine/education; Internship and Residency/methods; Physicians; Portugal; Specialization; Surveys and Questionnaires

1. Serviço de Doenças Infeciosas. Hospital de Curry Cabral. Unidade Local de Saúde São José. Lisboa. Portugal.
2. Serviço de Doenças Infeciosas. Hospital Beatriz Ângelo. Unidade Local de Saúde Loures-Odivelas. Loures. Portugal.
✉ **Autor correspondente:** José Ganicho. jose.ganicho@gmail.com
Revisto por/Reviewed by: Leonor Fernandes, João Matos, Adriana Gaspar da Rocha.
Recebido/*Received*: 01/04/2025 - **Aceite/*Accepted*:** 15/09/2025 - **Publicado *Online*/*Published Online*:** 13/10/2025 - **Publicado/*Published*:** 02/12/2025

KEY MESSAGES

- No sentido de fomentar a discussão sobre a formação em Doenças Infeciosas, foi aplicado um questionário a médicos internos e recém-especialistas, com o objetivo de explorar a sua perceção sobre o Internato.
- Os dados destacam a necessidade de reforçar áreas como Controlo de Infeção, Prescrição Antibiótica e Risco Infecioso.
- Verificam-se assimetrias regionais na realização de urgência e na produção assistencial e científica.
- Os resultados sublinham a importância da monitorização contínua dos programas de Internato, garantindo uma formação robusta e equitativa.
- A ausência de dados oficiais que caracterizem o contingente médico limita a generalização nacional dos resultados.

INTRODUÇÃO

Em 2020, a Organização Mundial de Saúde (OMS) definiu as 13 mais importantes ameaças à saúde global da década, das quais se destacam a prevenção de doenças infeciosas, a preparação para epidemias e a resistência antimicrobiana.[1] Neste sentido, a especialidade de Doenças Infeciosas revela-se fulcral para enfrentarmos alguns dos desafios que impactarão os sistemas de saúde a nível mundial.

A nível nacional e de acordo com o Regulamento do Colégio da Especialidade de Doenças Infeciosas, Artigo 3.º,[2] a área de Doenças Infeciosas é entendida como uma área de intervenção vasta, no âmbito da medicina preventiva e curativa, ultrapassando o âmbito estrito das doenças infeciosas. Para isso, fundamenta-se no estudo da fisiopatologia e anatomopatologia de diferentes quadros clínicos, na formação em microbiologia e no conhecimento da epidemiologia de diferentes patologias.[2] A Portaria n.º 28/2011, de 10 de janeiro,[3] estabelece o Programa de Formação do Internato Médico da área profissional de especialização de Doenças Infeciosas em vigor, que engloba 12 meses de Medicina Interna, três meses de Microbiologia, 33 meses de Infeciologia Geral, seis meses de Medicina Intensiva e um total de seis meses dedicados a estágios opcionais.

Tendo em conta a evolução célere da evidência científica e as ameaças identificadas pela OMS importa discutir a formação em Doenças Infeciosas para garantir a preparação de profissionais adaptados ao contexto atual e futuro. Neste sentido, foi desenvolvido um questionário dirigido a médicos internos de formação especializada e a recém-especialistas que tenham concluído o seu programa de formação nos últimos cinco anos, inclusive, com o objetivo de caracterizar e explorar a sua perceção relativamente à formação em Doenças Infeciosas e ao ambiente clínico de aprendizagem.

MÉTODOS

Desenvolvimento do questionário

O presente estudo baseou-se num questionário quantitativo e qualitativo desenvolvido com o objetivo de caracterizar e explorar a perceção dos participantes relativamente à formação em Doenças Infeciosas e ao ambiente clínico de aprendizagem (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23187/15782). Previamente à conceção do questionário, realizou-se uma pesquisa de instrumentos formais e validados que fossem ao encontro dos objetivos do estudo. No entanto, não foi identificado nenhum questionário previamente validado aplicável ao contexto da formação pós-graduada em Portugal.

O questionário foi desenvolvido com base nos estágios preconizados pelo programa de formação específica em Doenças Infeciosas e na tipologia de atividades realizadas ao longo do Internato, tanto de carácter assistencial (Consulta, Urgência Externa, Urgência Interna e Internamento), como de carácter complementar, nomeadamente, no domínio da produção e atualização científica. O processo de construção integrou a formulação de perguntas abertas (curtas e longas) e fechadas, a definição de diferentes opções de resposta (dicotómicas, de escolha múltipla, em escala de Likert e de frequência), bem como a utilização de filtros para direcionar determinadas secções a subgrupos específicos de participantes. Um exemplo é a secção "Preparação para o desempenho das funções de especialista", aplicada exclusivamente aos médicos internos do 5.º ano de internato. As perguntas abertas tiveram como finalidade recolher dados quantitativos em escala contínua ou explorar a fundamentação dos inquiridos para as respostas apresentadas, prevendo-se igualmente a possibilidade de não resposta sempre que a situação não fosse aplicável ou o participante não soubesse responder. Por fim, foram incluídas instruções explícitas no início de cada parte, de modo a uniformizar a compreensão das questões e reduzir a variabilidade de interpretação entre os respondentes.

O presente questionário foi desenvolvido em conjunto e com o reconhecimento do Colégio de Especialidade de Doenças Infeciosas da Ordem dos Médicos.

A compreensão do questionário foi testada com a realização de um pré-teste a dois médicos internos e dois especialistas em Doenças Infeciosas, sendo o objetivo avaliar a construção frásica, a agradabilidade da leitura, a facilidade de compreensão e a qualidade de construção das frases, assim como comentários, críticas e sugestões. O questionário foi adaptado ao formato Google Forms® e apenas foram consideradas as respostas obtidas através do preenchimento completo do mesmo.

Caracterização da amostra

No que concerne à secção "informações sociodemográficas", a amostra foi caracterizada consoante o género – masculino, feminino ou outro –, faixa etária, região de internato – Administração Regional de Saúde (ARS) Norte, Centro, Lisboa e Vale do Tejo, Algarve e Região Autónoma da Madeira –, tipologia de local de internato e ano de internato – 1.º ao 5.º ano ou recém-especialista, conforme aplicável. As instituições de saúde foram divididas em Grupos I, II e III, de acordo com a Portaria n.º 82/2014, de 10 de abril.[4] Apenas foram incluídas as instituições de saúde identificadas como locais de internato, com idoneidade formativa e programa de formação específica em Doenças Infeciosas até cinco anos antes da realização do questionário.

Critérios de inclusão

O questionário foi dirigido a médicos internos e recém-especialistas que tenham concluído o programa de formação em Doenças Infeciosas nos últimos cinco anos, inclusive. No início do formulário, foi incluída uma pergunta com três opções: "Médico interno", "Recém-especialista (≤ 5 anos)" e "Especialista (> 5 anos)". Os participantes que selecionaram a opção "Especialista (> 5 anos)" foram excluídos da amostra, sendo automaticamente redirecionados para uma mensagem de encerramento do formulário.

Distribuição do questionário

O questionário foi partilhado em formato digital e distribuído a nível nacional pela Secção dos Colégios de Especialidade da Ordem dos Médicos, via correio eletrónico oficial. Por esta via, o questionário foi enviado apenas a médicos especialistas registados no Colégio de Doenças Infeciosas e a médicos internos que iniciaram a sua formação na especialidade referida. Para além disso, o questionário foi partilhado através de fóruns e plataformas informais de comunicação, com vista a maximizar o alcance do mesmo. O questionário esteve disponível desde o dia 12 de março de 2024 até ao dia 2 de abril de 2024.

Condições de participação

A participação no estudo foi voluntária e anónima, não tendo sido recolhidos contactos e dados identificativos, como o nome ou data de nascimento. O ficheiro de dados final foi armazenado num servidor seguro e acessível apenas pela equipa de investigação. O questionário incluiu uma secção introdutória com os termos de participação e consentimento informado, que pressupunham a partilha dos resultados com a comunidade científica.

Análise estatística

Os dados foram submetidos a uma análise estatística descritiva das variáveis em estudo, utilizando o *Statistical Package for the Social Sciences*® (SPSS®), versão 25.0 para Microsoft Windows®. As variáveis categóricas foram descritas através de frequências absolutas e relativas (%), enquanto as variáveis contínuas foram apresentadas como média e desvio-padrão ou, na ausência de distribuição normal, como mediana e intervalo interquartil. A normalidade da distribuição foi avaliada com base nos testes de Kolmogorov-Smirnov e Shapiro-Wilk, bem como nos coeficientes de assimetria e curtose, conforme aplicável. Na secção relativa à produção e atualização científica, procedeu-se à contabilização do número de consultas assistidas e realizadas autonomamente, participações e apresentações em eventos científicos ou no serviço, artigos científicos publicados e número de horas de estudo, sendo esta última variável baseada no reporte subjetivo dos inquiridos. Nos casos em que a questão não se aplicou, os participantes tiveram a possibilidade de selecionar a opção "Caso não se aplique, responda 999999", tendo estas respostas sido posteriormente excluídas da análise.

Comissão de Ética

Este trabalho foi desenvolvido em colaboração com o Colégio da Especialidade de Doenças Infeciosas e foi aceite e divulgado pelo Departamento de Colégios da Ordem dos Médicos, o que se considerou suficiente como forma de validação institucional. À data da sua elaboração e divulgação, a Ordem dos Médicos não dispunha de um órgão constituído para a apreciação deste tipo de projetos e, tendo em conta o seu âmbito nacional, não se considerou adequado submetê-lo à Comissão de Ética de um hospital local. Importa ainda referir que não houve intervenção em seres humanos, recolha de dados identificáveis ou contacto direto com participantes, tratando-se da análise de dados agregados e anónimos. O questionário aplicado incluía ainda uma secção introdutória com os termos de participação e consentimento informado, nos quais se explicitava a partilha dos resultados com a comunidade científica. Por estas razões, não se considerou necessária a submissão a uma Comissão de Ética formalmente constituída.

RESULTADOS

Caracterização da amostra

O questionário obteve 73 respostas, apresentando-se a caracterização da amostra na Tabela 1. Dos inquiridos, 49 (67,1%) eram do sexo feminino e 24 (32,9%) do sexo masculino, 55 (75,3%) eram médicos internos e 18 (24,7%) recém-especialistas. A maioria dos participantes (n = 38, 52,1%) realizou o seu Programa de Formação Especializada na ARS de Lisboa e Vale do Tejo. No que concerne à tipologia de local de internato, a maioria dos inquiridos (n = 48, 65,8%) realizou o seu internato num hospital pertencente ao Grupo III.

Estrutura do internato em doenças infeciosas

A maioria dos participantes considerou adequada a duração dos estágios de Medicina Interna (n = 61; 83,5%), Microbiologia (n = 56; 76,7%) e Infeciologia Geral (n = 52; 71,2%). Relativamente ao estágio de Medicina Intensiva, 47 (64,4%) sugeriram uma redução do tempo previsto, sendo que apenas 24 (32,9%) inquiridos consideraram a

Tabela 1 – Caracterização da amostra, nomeadamente etapa formativa, faixa etária, região e tipologia do local de internato

Caracterização	**Frequência absoluta** (%)
Sexo	
Feminino	49 (67,1)
Masculino	24 (32,9)
Etapa Formativa	
1.º Ano	11 (15,0)
2.º Ano	13 (17,8)
3.º Ano	12 (16,5)
4.º Ano	8 (11,0)
5.º Ano	11 (15,0)
Recém-Especialista (< 5 anos)	18 (24,7)
Faixa Etária	
< 23 anos	0 (0)
24 anos - 29 anos	37 (50,7)
30 anos - 35 anos	32 (43,8)
36 anos - 41 anos	3 (4,1)
> 42 anos	1 (1,4)
Região do Local de Internato	
ARS Norte	26 (35,6)
ARS Centro	9 (12,3)
ARS de Lisboa e Vale do Tejo	38 (52,1)
ARS do Algarve	0 (0)
Região Autónoma da Madeira	0 (0)
Tipologia do Local de Internato	
Grupo I (Unidade Local de Saúde de Matosinhos, Centro Hospitalar do Baixo Vouga, Hospital Prof. Dr. Fernando Fonseca, Hospital de Loures e Centro Hospitalar de Setúbal)	14 (19,2)
Grupo II (Centro Hospitalar Vila Nova de Gaia/Espinho, Hospital de Braga, Centro Hospitalar de Lisboa Ocidental, Hospital Garcia de Orta, Centro Hospitalar Universitário do Algarve e Hospital Central do Funchal)	11 (15,0)
Grupo III (Centro Hospitalar Universitário de Santo António, Centro Hospitalar Universitário de São João, Centro Hospitalar e Universitário de Coimbra, Centro Hospitalar Universitário de Lisboa Central e Centro Hospitalar Universitário de Lisboa Norte)	48 (65,8)

ARS: Administração Regional de Saúde

duração atual adequada. Relativamente aos estágios opcionais, a maioria (n = 44; 60,3%) dos participantes sugeriu uma duração superior. A distribuição das respostas encontra-se apresentada na Fig. 1.

A maioria dos inquiridos (n = 59; 80,8%) sugeriu a divisão do estágio de Infeciologia Geral em áreas distintas. Na avaliação do grau de importância dessas áreas, numa escala Likert de 1 (nada importante) a 5 (muito importante), as áreas em que pelo menos metade dos participantes considerou muito importante, por ordem decrescente, foram: Controlo de Infeção e Prescrição Antibiótica (n = 63; 86,3%), Imunossupressão e Risco Infecioso (n = 60; 82,2%), Zoonoses (n = 42; 57,5%) e Dermato-Venereologia e Infeções Sexualmente Transmissíveis (n = 41; 56,2%). Subsequentemente, foi questionado quais as áreas que deveriam ser obrigatórias, tendo 62 participantes (84,9%) referido Controlo de Infeção e Prescrição Antibiótica e 48 (65,8%) referido Imunossupressão e Risco Infecioso.

Início do internato em doenças infeciosas – 1.º ano

A maioria dos participantes (n = 56; 76,7%) referiu que teve contacto com a especialidade no 1.º ano de internato, sendo as principais formas de contacto com a especialidade através da participação em cursos (n = 48; 65,8%) e em congressos (n = 42; 57,5%). Subsequentemente, os inquiridos foram questionados se consideraram importante ter mais contacto com a especialidade de Doenças Infeciosas durante o 1.º ano de Internato, sendo que 56 (76,7%) responderam afirmativamente. No que concerne ao orientador de formação, a maioria (n = 46; 63,0%) respondeu desconhecer a atribuição de um tutor no início do internato; no entanto, numa escala Likert de 1 (nada importante) a 5 (muito importante), 55 (75,3%) consideraram, pelo menos, importante esta definição no início do internato. Subsequentemente, os participantes foram convidados a justificar a importância da atribuição de um orientador no início do internato, destacando o papel desta figura na organização de estágios e cursos, na integração no serviço e na motivação do médico interno.

Consulta e externa

A maioria dos participantes começou a assistir a consultas a partir do 2.º ano (n = 59; 80,8%) e iniciou consulta em nome próprio entre o 2.º e 3.º ano (n = 25; 34,2% e n = 24; 32,9%, respetivamente) de internato (Tabela 2).

Urgência externa

Relativamente à realização de urgência externa de Medicina Interna, evidencia-se uma diferença percentual quanto ao ano de internato até o qual os inquiridos a desempenham, com 24 (32,9%) limitando-se ao 1.º ano e 25 (34,2%) prolongando-a até ao 4.º ano de internato. A nível regional, também se evidenciam diferenças neste aspeto, sendo que na ARS Norte, 84,6% (n = 22) dos médicos internos realizam esta atividade apenas durante o 1.º ano, enquanto na ARS LVT, 86,8% (n = 33) a efetuam, pelo menos, até ao 4.º ano.

Quando questionados sobre a importância da realização de Urgência Externa para além do 1.º ano de Internato, 49 (67,1%) participantes responderam negativamente e 60 (82,2%) referiram que a realização de urgência externa de Medicina Interna após o 1.º ano de internato prejudicava o seu internato.

Subsequentemente, solicitou-se aos participantes que

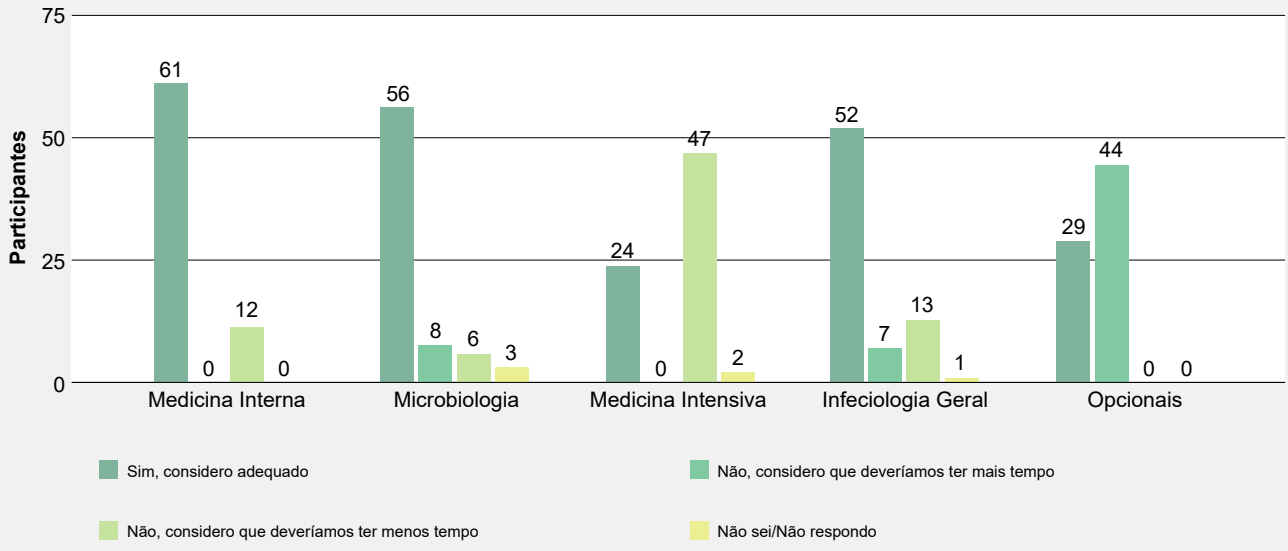


Figura 1 – Distribuição das respostas relativas ao tempo previsto de cada estágio

justificassem a importância da realização deste tipo de atividade assistencial para além do 1.º ano de Internato, sendo elencadas as respostas mais frequentes:

- Consolidação da anamnese e exame objetivo, diagnóstico diferencial, triagem/encaminhamento e gestão do doente crítico, mantendo contacto com patologia aguda de diferentes especialidades;
- Aumento da capacidade de decisão, autonomia e segurança na abordagem de diferentes patologias, assim como conhecimento do funcionamento hospitalar;
- Identificação e abordagem precoce a casos de apresentação aguda de patologia infeciosa, assegurando ligação entre o serviço de urgência e o serviço de Doenças Infeciosas.

A destacar, que, apesar de não ser o objetivo desta secção, alguns participantes manifestaram a sua perspetiva sobre por que não consideravam importante a realização deste tipo de atividade assistencial para além do 1.º ano de internato, que se elencam, de seguida:

- Observação de casos não relacionados com a especialidade, não-alinhados com os objetivos preconizados no programa formativo, prejudicando a diferenciação do médico interno;
- Redução do número de horas de contacto com a especialidade de Doenças Infeciosas, nomeadamente no internamento, consulta e urgência da própria especialidade;
- Sobrecarga de horários, cansaço e redução do tempo destinado ao estudo autónomo ou repouso,

Tabela 2 – Caracterização da atividade assistencial em contexto de Consulta, Urgência Externa e Interna, por região de local de internato

Ano de Internato	Frequência absoluta (%)			
	Nacional (n = 73)	**ARS Norte** (n = 26)	**ARS Centro** (n = 9)	**ARS LVT** (n = 38)
A partir de que ano de internato começou/começará a assistir a consultas?				
1.º ano	3 (4,1)	0	0	3 (7,9)
2.º ano	59 (80,8)	22 (84,6)	8 (88,9)	29 (76,3)
3.º ano	2 (2,8)	1 (3,9)	0	1 (2,6)
4.º ano	0	0	0	0
5.º ano	0	0	0	0
Não sei/Não respondo	9 (12,3)	3 (11,5)	1 (11,1)	5 (13,2)
A partir de que ano de internato iniciou/iniciará consulta própria, no âmbito da especialidade?				
1.º ano	0	0	0	0
2.º ano	25 (34,3)	0	8 (88,9)	17 (44,7)
3.º ano	24 (32,9)	14 (53,9)	1 (11,1)	9 (23,7)
4.º ano	5 (6,8)	3 (11,5)	0	2 (5,3)
5.º ano	5 (6,8)	3 (11,5)	0	2 (5,3)
Não sei/Não respondo	14 (19,2)	6 (23,1)	0	8 (21,0)
Até que ano realizou/realizará Urgência Externa de Medicina Interna durante o internato?				
1.º ano	24 (32,9)	22 (84,6)	2 (22,2)	0
2.º ano	7 (9,5)	3 (11,5)	1 (11,1)	3 (7,9)
3.º ano	3 (4,1)	1 (3,9)	0	2 (5,3)
4.º ano	25 (34,3)	0	4 (44,5)	21 (55,3)
5.º ano	14 (19,2)	0	2 (22,2)	12 (31,5)
A partir de que ano começou/começará a realizar Urgência Interna de Doenças Infeciosas durante o internato?				
1.º ano	3 (4,1)	0	0	3 (7,9)
2.º ano	38 (52,1)	25 (96,1)	2 (22,2)	11 (28,9)
3.º ano	2 (2,7)	0	0	2 (5,3)
4.º ano	4 (5,5)	1 (3,9)	0	3 (7,9)
5.º ano	16 (21,9)	0	7 (77,8)	9 (23,7)
Não sei/Não respondo	10 (13,7)	0	0	10 (26,3)

ARS: Administração Regional de Saúde; LVT: Lisboa e Vale do Tejo
Foram excluídas da Tabela 2 as Regiões que não obtiveram qualquer resposta ao questionário.

exacerbados por turnos noturnos e fins de semana, sem benefício formativo proporcional.

Nesta secção, os participantes foram ainda questionados sobre diferentes modelos de prestação de cuidados em contexto de urgência, sendo que 63 (86,3%) consideraram pertinente a existência de um modelo de triagem para a especialidade de Doenças Infeciosas, dos quais 16 (21,9%) sugeriram uma triagem direta, 21 (28,8%) sugeriram triagem indireta e 26 (35,6%) consideraram pertinente a existência de triagem em moldes a definir. A referir que três (4,1%) participantes não consideraram pertinente a existência de triagem e sete (9,6%) não formaram uma opinião sobre o assunto.

Quando questionados sobre de que forma poderia ser criada uma triagem, os participantes sugeriram um modelo misto: por um lado direto, mediante critérios de referenciação definidos, e por outro indireto, após observação inicial por colegas de outra especialidade. Destacaram situações de referenciação direta como exposições de risco sexual, infeções sexualmente transmissíveis, pessoas que vivem com infeção por vírus da imunodeficiência humana em abandono terapêutico, suspeita de doenças infetocontagiosas (sarampo, varicela) e doentes regressados de viagem com aparente quadro infecioso.

Urgência de doenças infeciosas

Relativamente à urgência de doenças infeciosas, a maioria dos participantes (n = 71; 97,3%) reconheceu a importância de realizar este tipo de atividade assistencial durante o internato. Quanto ao momento de início, 38 (52,1%) inquiridos referiram iniciar esta atividade a partir do 2.º ano e 45 (61,6%) salientaram a importância de iniciar nesse mesmo período. Contudo, importa destacar que 10 (13,7%) participantes não tinham conhecimento de quando esta atividade se inicia ao longo do seu programa formativo.

Produção assistencial e científica

No sentido de aferir a produção assistencial e científica dos participantes, foi feita uma contabilização do número de consultas assistidas e dirigidas autonomamente, participações e apresentações em eventos científicos ou no serviço, artigos científicos publicados e número de horas de estudo, através do relato subjetivo dos mesmos. Na Tabela 3, encontra-se a contabilização da produção assistencial e científica, por região do local de internato, comparativamente à média nacional de respostas. Dentro do horário laboral, a quase totalidade (n = 72; 98,6%) dos participantes referiu que não tinha tempo dedicado para o estudo autónomo e produção científica, embora 63 (86,3%) considerassem este aspeto muito importante.

Dificuldades globais do internato

O questionário incluía uma secção onde se pretendia que os participantes classificassem como percecionam o impacto de nove desafios na sua formação, classificando-os numa escala ordinal decrescente (1.º - maior desafio; 9.º - menor desafio). Posteriormente, foi convertido o posicionamento do desafio num sistema de pontuação inversa (1.º - 9 pontos; 9.º - 1 ponto) e calculada a média de pontos obtida por cada um, permitindo quantificar e hierarquizar, de forma agregada, a perceção dos inquiridos relativamente à relevância de cada desafio. De seguida, encontram-se as respostas ordenadas do maior para o menor desafio:

1. Ausência de tempo de estudo dedicado no horário;
2. Atualização científica;
3. Realização de urgência externa de medicina interna;
4. Volume de trabalho associado às consultas;

Tabela 3 – Contabilização da produção assistencial e científica, por região

Tipo de Atividade	Média ± DP			
	Nacional	ARS Norte	ARS Centro	ARS LVT
Número semanal de consultas assistidas	18,1 ± 15,4	21,7 ± 16,1	9,677 ± 14,0	17,1 ± 13,9
Número semanal de consultas dirigidas autonomamente	18,3 ± 12,4	20,8 ± 16,1	15,4 ± 7,3	17,7 ± 10,4
Número de participações em congressos e/ou reuniões científicas no último ano	3,4 ± 2,6	3,7 ± 2,5	3,8 ± 2,8	3,1 ± 2,6
Número de apresentações em congressos e/ou reuniões científicas no último ano	2,7 ± 2,2	2,8 ± 2,6	3,4 ± 2,7	2,4 ± 1,4
Número de artigos científicos publicados no último ano	0,7 ± 1,2	1,1 ± 1,4	0,1 ± 0,4	0,6 ± 0,9
Número de apresentações no Serviço no último ano	2,8 ± 2,3	2,8 ± 3,0	2,9 ± 1,5	2,8 ± 1,9
Número semanal de horas de estudo	5,6 ± 5,9	7,4 ± 8,8	5,0 ± 2,7	4,5 ± 3,1

ARS: Administração Regional de Saúde; DP: desvio padrão; LVT: Lisboa e Vale do Tejo

5. Complexidade científica das doenças infeciosas;
6. Volume de trabalho associado ao internamento;
7. Sobrecarga de produção científica;
8. Burocracia associada aos cuidados de saúde;
9. Falta de apoio e financiamento à formação.

Exame final e grelha curricular

Nesta secção, os participantes foram questionados quanto ao seu nível de concordância com o atual modelo de exame final de especialidade e grelha curricular, segundo uma escala de Likert de 1 (não concordo) a 5 (concordo totalmente). No que concerne ao exame final de especialidade, 27 (37%) inquiridos não tinham uma resposta sobre o tema, 17 (23,3%) não concordavam com o modelo atual, 15 (20,5%) concordavam pouco, nove (12,3%) concordavam, mas fariam alterações e 2 (2,7%) concordavam totalmente com o formato atual. No que concerne à grelha curricular, 26 (35,6%) inquiridos responderam "Não sei/Não respondo", 12 (16,4%) responderam que não concordavam com o modelo atual, 14 (19,2%) concordavam pouco, 14 (19,2%) concordavam, mas fariam alterações e apenas um (1,37%) participante concordava totalmente com o modelo atual. A destacar que, respetivamente, 3 (4,1%) e 6 (8,2%) participantes demonstraram-se indiferentes ao formato dos dois instrumentos de avaliação mencionados. Subsequentemente, perguntou-se aos participantes que alterações fariam ao exame final de especialidade, sendo destacada a pertinência de critérios de avaliação mais objetivos em todas as componentes, metodologias de avaliação teórica mais diversificadas, rigorosas e menos díspares e dependentes do júri, a definição de uma matriz nacional com temas de estudo, ordenados por importância e/ou dificuldade, a implementação de casos clínicos em lugar da elaboração da história clínica formal e a diminuição da importância do exame na avaliação final, com múltiplos momentos de avaliação ao longo de um período maior do internato. No que concerne às alterações à grelha curricular, os participantes sugeriram reduzir globalmente a valorização do número de trabalhos de investigação e privilegiar a qualidade dos mesmos, assim como a não valorização da realização de programas de mestrado e doutoramento durante o internato. Os participantes sugeriram ainda a valorização de competências não formais, nomeadamente a interação com os doentes e a relação entre elementos da equipa assistencial, assim como a introdução de números mínimos que valorizem a atividade assistencial e a participação em projetos com impacto comunitário.

Preparação para desempenhar as funções de especialista

Relativamente à questão "Quão preparado se considera para desempenhar as funções de especialista em Doenças Infeciosas?", seis (54,6%) participantes reportaram sentir-se, pelo menos, preparados para o exercício autónomo da especialidade (Fig. 2).

Satisfação global com a especialidade

A maioria (n = 47; 64,4%) dos participantes considera-se, pelo menos, satisfeita com a especialidade (Fig. 3). Subsequentemente, os participantes destacaram, como pontos positivos, a diversidade de patologias e de contextos de aplicação do conhecimento, a população de doentes com faixas etárias mais jovens e a flexibilidade de opções de carreira. Em oposição, destacaram a exigência de atualização contínua, a elevada carga assistencial, as reduzidas opções profissionais fora do Sistema Nacional de Saúde (SNS) e respetiva remuneração, a ausência de incentivos para a produção científica, a desvalorização da profissão e a falta de reconhecimento entre especialidades.

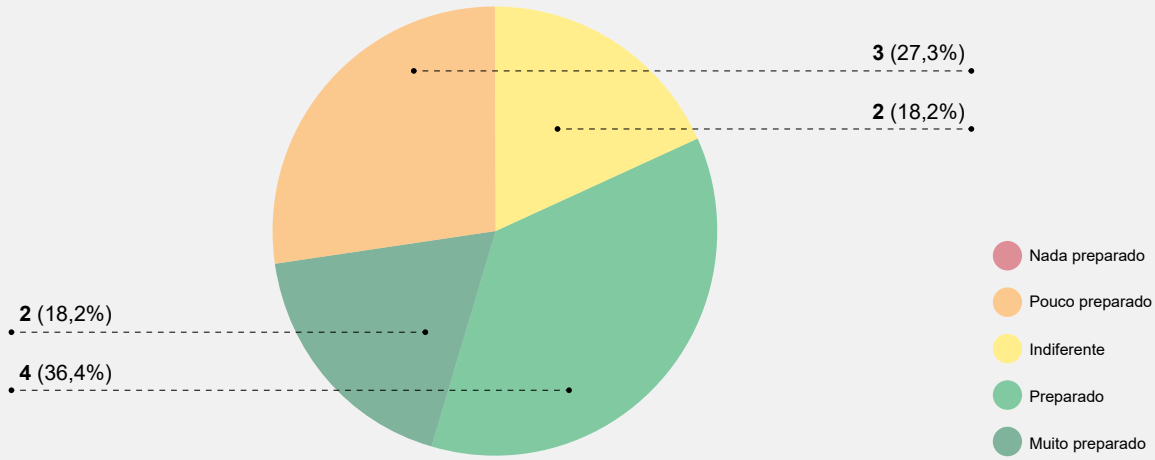


Figura 2 – Distribuição das respostas relativas à perceção de preparação para desempenhar as funções de especialista

DISCUSSÃO

A formação médica pós-graduada em Doenças Infeciosas desempenha um papel crucial na preparação dos médicos internos para enfrentarem os desafios emergentes à saúde global enquanto futuros especialistas. Neste sentido, a discussão dos programas formativos é fundamental para garantir que os profissionais de saúde são capazes de responder às necessidades da população que pretendem servir. Relativamente à formação pós-graduada em Doenças Infeciosas, importa destacar que a nível europeu, a mesma varia entre países, com alguns a definirem-na formalmente enquanto especialidade médica; outros encaram-na como subespecialidade de outras especialidades, mais frequentemente de Medicina Interna. Em Portugal, não se encontraram outros trabalhos que pretendam explorar especificamente a formação em Doenças Infeciosas, pelo que este questionário pretendeu ser um contributo inicial para uma discussão ampla sobre o programa de formação especializada em Doenças Infeciosas.

Relativamente à estrutura do internato, a maioria dos participantes concordou com a duração dos estágios, exceto no que concerne ao estágio de Medicina Intensiva, que consideraram que a duração deveria ser inferior a seis meses. Não obstante a concordância da duração do estágio de Infeciologia Geral, a maioria sugeriu a sua divisão em áreas distintas, salientando as áreas de Controlo de Infeção e Prescrição Antibiótica e Imunossupressão e Risco Infecioso como obrigatórias. Relativamente à primeira área, estes resultados estão em concordância com as prioridades definidas pela OMS, que identifica a resistência aos antibióticos como uma preocupação central e que reportou que esta poderá ter sido responsável por 1,27 milhões de mortes em 2019.[5] Os resultados obtidos por Bischoff *et al* num estudo alemão publicado em 2023 estão em linha com os obtidos neste questionário, onde mais de 80% dos participantes reforça a pertinência de integrar esta área na formação de especialistas em Doenças Infeciosas.[6] Sobre a segunda área, embora não existam dados quantitativos que evidenciem a sua importância, a mesma pode ser inferida pelo número crescente de indivíduos candidatos e submetidos a transplante[7] ou sob terapêutica imunomoduladora,[8] nomeadamente nas áreas de Hematologia, Reumatologia, Dermatologia e Gastroenterologia.

Apesar de a maioria dos inquiridos ter tido contacto com a especialidade logo no 1.º ano, este foi considerado insuficiente. Um maior contacto com a especialidade e a atribuição de um tutor desde o início do internato, teria facilitado a transição e a integração do médico interno no serviço, contribuído para a sua motivação.

A nível nacional, a maioria dos inquiridos começou a assistir a consultas e iniciou consulta própria a partir do 2.º ano; contudo, a Tabela 2 remete para assimetrias regionais no programa de internato, uma vez que os participantes da ARS Norte reportaram iniciar consulta apenas a partir do 3.º ano de internato.

Relativamente às tipologias de urgência, a maioria dos participantes realizou urgência externa de Medicina Interna para além do 1.º ano de internato, prolongando-se em muitos casos até ao 4.º ano. Regionalmente, na ARS Norte, os médicos internos realizaram-na sobretudo nos dois primeiros anos, enquanto na ARS LVT a sua realização prolongou-se até fases mais avançadas da formação. Para além disso, a maioria dos participantes não considerou importante a realização de urgência externa de medicina Interna para além do 1.º ano, referindo que a mesma prejudicou o seu internato. Estes resultados sugerem a necessidade de discutir a pertinência formativa da urgência externa e de uniformizar o modelo entre regiões. Embora alguns participantes reconheçam ganhos de autonomia e consolidação de conhecimentos, a maioria reportou que os casos observados não estavam relacionados com a especialidade, aspeto concordante com a literatura que descreveu como mais frequentes, em contexto de urgência, diagnósticos dos grupos nosológicos “Doenças do sistema nervoso e dos órgãos dos sentidos”, “Doenças do aparelho osteomuscular e do tecido conjuntivo” e “Lesões e intoxicações”, em oposição a uma percentagem relativamente pequena do grupo “Doenças infeciosas e parasitárias”.[9] Para além disso, os participantes consideraram que a prestação de cuidados de saúde neste contexto, para além do 1.º ano de internato, não só pode contribuir para uma redução do número global de horas de contacto com a especialidade, como representar um risco potencial para o doente, uma vez que, a partir do 2.º ano, os médicos internos focam naturalmente o seu estudo na sua área de especialização e conhecimentos e as atualizações em outras áreas deixam de ser uma prioridade. A maioria defendeu que a transição para a urgência de Doenças Infeciosas deveria ocorrer a partir do 2.º ano de internato, permitindo um contacto mais precoce e estruturado com a área de especialização.

No que diz respeito à produção assistencial e científica, a Tabela 3 evidencia grandes diferenças entre regiões a nível de consultas assistidas e dirigidas, assim como no envolvimento e participação em congressos, reuniões científicas, publicação de artigos e apresentações extra-serviço. Os médicos internos da ARS Norte reportaram um maior número de consultas assistidas e realizadas, assim como um maior número de participações e apresentações em congressos e reuniões científicas, sendo pertinente explorar em estudos posteriores as razões que justifiquem estas diferenças. Uma forma de ultrapassar estas diferenças poderá passar pela definição de tempo dedicado ao estudo autónomo e à produção científica dentro do horário laboral, algo que a maioria dos inquiridos referiu não ter garantido,

mas que considera importante de forma a completar os objetivos do programa de formação especializada.

Efetivamente, os resultados obtidos na secção "Dificuldades globais do internato" espelham as respostas dadas pelos participantes nas secções previamente discutidas: ausência de tempo de estudo dedicado no horário, atualização científica e realização de urgência externa de Medicina Interna.

Quanto à secção "Exame Final e Grelha Curricular", destaca-se algum desconhecimento por parte dos participantes relativamente aos moldes do atual exame final da especialidade e grelha curricular, o que pode ser justificado pelo facto de a maioria das respostas provir de médicos internos que ainda não completaram o 4.º ano do internato. Não obstante, cerca de metade dos inquiridos não concorda, ou concorda pouco, com o atual modelo de exame final, e cerca de um terço tem a mesma opinião relativamente à grelha curricular. Relativamente ao primeiro, os inquiridos propuseram uma avaliação mais objetiva, sugerindo o uso de casos clínicos em oposição à história clínica, a definição de uma matriz nacional com temas de estudo e a diminuição da importância do exame na avaliação final, com múltiplos momentos de avaliação ao longo de um período maior do internato. Os participantes defendem uma grelha curricular mais sumária, que valorize a qualidade da produção científica em alternativa à quantidade, e a valorização de competências não formais, da atividade assistencial e da participação em projetos com impacto comunitário.

Na análise da secção "Perceção e satisfação global com a especialidade", importa destacar que menos de dois terços dos participantes se encontrava, pelo menos, satisfeito com a especialidade, salientando como pontos negativos a elevada carga assistencial, as reduzidas opções profissionais fora do SNS e respetiva remuneração, a ausência de incentivos para a produção científica, a desvalorização da profissão, a falta de reconhecimento entre especialidades e a exigência de atualização contínua. Em linha com os aspetos mencionados, um estudo nacional francês destaca que apesar dos médicos internos considerarem a especialidade intelectualmente estimulante pela abordagem multissistémica e desafio diagnóstico, manifestam reservas quanto à sua remuneração e carga assistencial.[10] Outros estudos de abrangência europeia revelaram um padrão semelhante, com especial destaque para os participantes da Europa do Sul e de Leste (SEE – região que inclui Portugal), onde mais de metade dos participantes manifestou insatisfação com a sua formação. Nestes países, os médicos reportaram um ambiente de trabalho com reduzido estímulo científico e menos oportunidades formativas, quando comparados com colegas de outras regiões europeias?.[11]

Limitações

Relativamente à metodologia de divulgação e recolha de respostas, não foi possível controlar a eventual duplicação das mesmas, uma vez que, para manter o anonimato do questionário, não foram recolhidos endereços de *email*, nem era necessário efetuar qualquer registo. Relativamente à análise dos dados, destaca-se a ausência de comparação de respostas entre médicos internos e recém-especialistas. Contudo, é importante realçar que apenas um quarto dos inquiridos são recém-especialistas, pelo que se encontram menos representados na amostra. Outro aspeto a destacar é o número limitado de respostas: não se encontrou uma contabilização do número de médicos internos e recém-especialistas que tenham concluído o seu programa de formação nos últimos cinco anos, o que dificultou o cálculo da representatividade da amostra face ao panorama nacional. Assim, recomenda-se a realização de um censo nacional para contabilização do número de especialistas e número de médicos internos, assim como a sua intervenção no contexto da especialidade de Doenças Infeciosas, seja atividade assistencial ou de consultoria, investigação em contexto epidemiológico ou clínico, assim como o âmbito de ação (nacional ou internacional).

Destaca-se ainda o facto de a ARS do Algarve e a Região Autónoma da Madeira não apresentarem quaisquer respostas, o que limita a representatividade nacional deste estudo. Não obstante, importa realçar que, de acordo com o mapa de vagas anualmente publicado pela Administração Central do Sistema de Saúde, o número total de vagas de internato em ambas as regiões, nos últimos cinco anos, é inferior a seis.

Relativamente ao perfil dos inquiridos, realça-se o viés de seleção, particularmente na análise das respostas sobre a atratividade da especialidade; o viés de memória na contabilização da produção assistencial e científica, que foi apurada pelo reporte subjetivo dos mesmos; e o viés de desejabilidade social, especialmente nas respostas dos médicos internos que, dada a sua posição hierárquica institucional, podem predispor à resposta socialmente desejável.

Da análise dos resultados, os investigadores consideram não ser possível excluir um grau de viés cognitivo na interpretação qualitativa das respostas abertas.

CONCLUSÃO

Tendo em conta os desafios identificados pela OMS, que impactarão os sistemas de saúde a nível mundial, a discussão sobre a formação em Doenças Infeciosas revela-se crucial. Neste contexto, o presente trabalho pretendeu realizar o primeiro levantamento nacional estruturado sobre a formação nesta área em Portugal e caracterizar a perceção dos médicos internos e recém-especialistas

relativamente à sua experiência formativa.

Os resultados revelam que a maior parte dos participantes considera adequada a duração dos estágios preconizados atualmente, exceto nos estágios de Medicina Intensiva e opcionais, que merecem discussão adicional. Para além disso, foram valorizadas áreas como Controlo de Infeção e Prescrição Antibiótica e Imunossupressão e Risco Infecioso, em linha com as ameaças identificadas pela OMS e a evolução terapêutica a nível da imunomodulação e transplantação.

Da análise dos resultados, fica patente a importância de garantir um sólido contacto com a especialidade ao longo do internato, seja através da atribuição de um tutor e da participação em atividades no 1.º ano, da transição da urgência externa de Medicina Interna para a urgência de Doenças Infeciosas a partir do 2.º ano, ou da definição de tempo dedicado para o estudo autónomo e produção científica.

Outro aspeto a destacar é a clara assimetria regional na realização de urgência externa e na produção assistencial e científica, já que maioria dos médicos internos da ARS Norte referiu apenas realizar urgência externa de Medicina Interna no 1.º ano de internato, em contraste com os da ARS LVT, cuja atividade se prolonga, pelo menos, até ao 4.º ano de internato. No que concerne ao segundo aspeto, os médicos internos da ARS Norte reportaram um maior número de consultas assistidas e realizadas, assim como um maior número de participações e apresentações em congressos e reuniões científicas. Esta diferença evidencia a necessidade de medidas que promovam uma uniformização da experiência formativa, assegurando oportunidades equitativas de desenvolvimento científico e clínico em todo o país.

Estes resultados reforçam a pertinência de discutir continuamente os programas de especialização, de forma a garantir a preparação robusta para o exercício autónomo da especialidade, a existência de condições formativas uniformes nos diferentes locais de internato e a adequação das expectativas dos médicos internos às necessidades atuais e futuras das especialidades.

ACKNOWLEDGMENTS

Um agradecimento a todos os médicos internos e especialistas que, através da sua participação, contribuíram para a discussão da formação médica em Doenças Infeciosas.

Os autores declaram não ter utilizado ferramentas de inteligência artificial na elaboração do artigo.

CONTRIBUTO DOS AUTORES

JG: Conceptualização do estudo, construção e aplicação do questionário, tratamento de dados, redação do manuscrito.

ARG, FM, RT: Revisão crítica do questionário e do manuscrito.

MJM: Revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

RT recebeu honorários de consultoria de ViiV, Gilead, MSD e Jansen; recebeu pagamentos ou honorários para palestras, apresentações, congressos, redação de manuscritos ou eventos educativos de ViiV, Gilead, MSD e Jansen; recebeu apoio para comparecer em reuniões/viagens de ViiV; participou numa comissão de monitorização da segurança dos dados de Viiv; é a Presidente do Colégio de Doenças Infeciosas.

Os restantes autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

REFERÊNCIAS

1. World Health Organisation. Urgent health challenges for the next decade. [consultado 2024 ago 18]. Disponível em: https://www.who.int/news-room/photo-story/photo-story-detail/urgent-health-challenges-for-the-next-decade.
2. Ordem dos Médicos. Regulamento do Colégio de Especialidade de Doenças Infeciosas. [consultado 2024 jan 07]. Disponível em: https://ordemdosmedicos.pt/a-ordem/orgaos-tecnicos/colegios/especialidades/doencas-infecciosas/sobre-nos.
3. Portugal. Ministério da Saúde. Portaria n.º 28/2011. Diário da República, I Série, n.º 6 (2010/01/10). p.180-90.
4. Portugal. Ministério da Saúde. Portaria n.º 82/2014. Diário da República, I Série, n.º 71 (2014/04/01). p.2364-6.
5. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet.

2022;399:629-55.
6. Bischoff J, Schneitler V, Duettmann W, Fuchs A, Schneitler S. The state of infectious disease training in Germany before introduction of the new board certification in internal medicine and infectious diseases: past experience and future expectations. Infection. 2023;51:589-98.
7. Ivo da Silva M, Coordenação Nacional da Transplantação, Instituto Português do Sangue e da Transplantação (IPST). Atividade Nacional Anual. 2023. [consultado 2024 nov 10]. Disponível em: https://www.ipst.pt/files/TRANSPLANTACAO/DOACAOETRANSPLANTACAO/DadosAnuaisAtividadeDoacaoTransplantacao2023retificado17junho2024.pdf.
8. Fernández-Ruiz M, Meije Y, Manuel O, Akan H, Carratalà J, Aguado JM, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction). Clin Microbiol Infect. 2018;24:S2-9.
9. Rodrigues JM. Episódios não urgentes e pouco urgentes na urgência do Hospital Senhora da Oliveira: caracterizar para planear. Porto: Universidade do Porto; 2020.
10. Peiffer-Smadja N, Ardellier FD, Thill P, Beaumont AL, Catho G, Dubée V, et al. How and why do French medical students choose the specialty of infectious and tropical diseases? A national cross-sectional study. BMC Med Educ. 2020;20:397.
11. Maraolo AE, Ong DS, Cortez J, Dedić K, Dušekc D, Martin-Quiros A, et al. Personal life and working conditions of trainees and young specialists in clinical microbiology and infectious diseases in Europe: a questionnaire survey. Eur J Clin Microbiol Infect Dis. 2017;36:1287-95.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

The Involuntary-To-Voluntary Hospitalization Transition and the Risk of Psychiatric Decompensation: A Retrospective Cohort Study

A Transição de Internamento Involuntário para Voluntário e o Risco de Descompensação Psiquiátrica: Um Estudo de Coorte Retrospetivo

Margarida CASTRO [1], Joana TAVARES COELHO [2,3], Ana Rita FERREIRA [3,4], Henrique SALGADO [2,3]
Acta Med Port 2025 Dec;38(12):785-794 ▪ https://doi.org/10.20344/amp.23398

ABSTRACT

Introduction: Involuntary hospitalization of a patient with a mental disorder is broadly defined as the admission to an inpatient unit without the patient's consent. Literature suggests that involuntary hospitalizations are associated with low levels of treatment satisfaction, avoidance of mental health care, and an increased risk of emergency involuntary re-hospitalization. Despite being a lifesaving treatment, involuntary admissions can also be stigmatizing, undermine the long-term therapeutic relationship and reduce adherence to care. In this context, little research has been conducted to evaluate how shifting a patient's hospitalization from involuntary to voluntary affects health outcomes, such as psychiatric decompensation and healthcare use. The main aim of this study was to identify and assess the frequency of readmissions within one year among patients who transitioned to voluntary treatment, compared with those who remained involuntarily treated.

Methods: An observational retrospective study was conducted using secondary data from medical records of adult inpatients involuntarily admitted to the inpatient psychiatry department of Unidade Local de Saúde São João. All involuntary hospitalizations occurring between January 1st and December 31st, 2022, were classified into two distinct groups: patients who were initially admitted involuntarily and subsequently converted to voluntary hospitalization during their stay or patients who remained under involuntary hospitalization until discharge. Data registered in medical records within one year after the index hospitalization was collected and assessed (whether structured data or free text entries). Descriptive and comparative analyses were performed.

Results: A total of 120 patients were included. More patients converted to voluntary hospitalization (60.8%) than remained involuntarily hospitalized (39.2%). In comparison to voluntary inpatients, involuntary inpatients had significantly higher readmission rates within one year (36.2% *vs* 15.3%, $p = 0.009$) and were more often readmitted under involuntary status (88.2% *vs* 45.5%, $p = 0.030$).

Conclusion: Involuntary hospitalization was associated with worse outcomes within one year, underscoring the need for its use to be proportional to the risk and subject to periodic review. Conversion to voluntary hospitalization is reasonable, respects patient autonomy and, provided that appropriate treatment is maintained, does not worsen psychiatric decompensation.

Keywords: Hospitalization; Inpatients; Involuntary Treatment; Mental Disorders; Patient Compliance; Portugal; Psychiatry; Readmission; Risk Factors

RESUMO

Introdução: O internamento involuntário de um doente com doença mental é definido como a admissão numa unidade de internamento sem o seu consentimento. A literatura sugere que o internamento involuntário está associado a baixos níveis de satisfação com o tratamento, ao evitamento dos cuidados de saúde mental e um risco aumentado de reinternamentos involuntários urgentes. Apesar de ser um tratamento que pode salvar vidas, o internamento involuntário também pode ser estigmatizante, prejudicar a relação terapêutica a longo prazo e reduzir a adesão ao tratamento. Nesse sentido, há pouca investigação científica sobre o impacto da mudança de internamento involuntário para voluntário na saúde do doente, como a descompensação psiquiátrica e utilização de cuidados de saúde. O principal objetivo deste estudo foi identificar e avaliar a frequência de readmissões, a um ano, de doentes que transitaram para tratamento voluntário, em comparação com aqueles que permaneceram em tratamento involuntário.

Métodos: Foi realizado um estudo observacional retrospectivo utilizando dados clínicos dos doentes internados involuntariamente em Psiquiatria na Unidade Local de Saúde São João. Todos os internamentos involuntários decorridos entre 1 de janeiro e 31 de dezembro de 2022 foram categorizados em dois grupos: doentes inicialmente admitidos involuntariamente, posteriormente convertidos em internamento voluntário e doentes que permaneceram em internamento involuntário até à data de alta. Os dados registados nos processos clínicos no período de um ano após o internamento inicial foram recolhidos e analisados (tanto dados estruturados como entradas de texto livre). Foram realizadas análises descritivas e comparativas.

Resultados: No total, foram incluídos 120 doentes. Um maior número de doentes passou para internamento voluntário (60,8%) comparativamente ao número de doentes que permaneceu em internamento involuntário (39,2%). Comparativamente aos doentes em internamento voluntário, os doentes que permaneceram em internamento involuntário apresentaram um número de reinternamentos ao fim de um ano significativamente superior (36,2% *vs* 15,3%, $p = 0,009$) e apresentaram maior número de reinternamentos involuntários (88,2% *vs* 45,5%, $p = 0,030$).

Conclusão: O internamento involuntário mostrou estar associado a piores resultados a um ano, sublinhando que a sua utilização deve ser proporcional ao risco apresentado e sujeita a reavaliação regular. A transição para internamento voluntário é uma abordagem razoável, respeita a autonomia do paciente e, desde que seja assegurado o tratamento adequado, não agrava descompensação psiquiátrica.

Palavras-chave: Cooperação do Doente; Doentes Internados; Factores de Risco; Hospitalização; Perturbações Mentais; Portugal; Psiquiatria; Readmissão; Tratamento Involuntário

1. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
2. Psychiatry Service. Unidade Local de Saúde São João. Porto. Portugal.
3. Department of Clinical Neurosciences and Mental Health. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
4. RISE-Health. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Margarida Castro. up201806056@edu.med.up.pt
Revisto por/Reviewed by: Diogo Mota da Silva.
Recebido/*Received*: 19/05/2025 - **Aceite/*Accepted*:** 29/09/2025 - **Publicado/*Published*:** 02/12/2025

KEY MESSAGES

- Involuntary hospitalizations can be stigmatizing, undermine the long-term therapeutic relationship and reduce adherence to care, and therefore should only be used when proportional to the risk posed.
- To the best of our knowledge, this is the first study to compare outcomes in patients with mental illness who were discharged under voluntary status following an initial involuntary hospitalization, with the aim of assessing the prognostic value of this change in legal status.
- We found that patients who converted to voluntary hospitalization experienced fewer readmissions within one year compared to patients who remained under involuntary hospitalization, and those readmissions were less likely to occur under involuntary status. In contrast, involuntary inpatients had longer lengths of stay during the index hospitalization and a greater history of previous admissions. Additionally, they were more likely to be subjected to coercive measures, including the administration of injectable medication without consent, both during previous involuntary outpatient treatment and during the index hospitalization.
- Since this is a retrospective study, the quality of the data presented is dependent on the accuracy and completeness of the information registered by the clinicians. Despite the existence of some limitations, this study was able to describe and detail the clinical outcomes and sociodemographic trends of these patients.

INTRODUCTION

Involuntary hospitalization of a patient with a mental disorder is defined as the admission to an inpatient unit without the patient's consent.[1] It consists of a legal procedure to hospitalize individuals with a serious mental illness, and it is a common practice around the world. However, it should only be applied in exceptional circumstances, when it is absolutely necessary to guide a person who is either unaware of or unwilling to address their condition. Because of the nature of mental illness, such measures are primarily intended to mitigate the risk of harm posed by the patients' behavior, both toward themselves (e.g., suicide, self-injury, or aggression) and towards the community.[2]

European countries have diverse regulations governing involuntary hospitalization in mental health facilities. The length of the hospitalization, the reasons for admission and the necessity of treatment can differ. Some countries, such as Denmark, France, Portugal, and Spain, do not set a fixed time limit for involuntary hospitalization. In contrast, Italy and the United Kingdom establish maximum durations. Most European countries require a diagnosis of a mental disorder before involuntary admission.[1]

In Portugal, the Mental Health Law No. 35/2023 of July 21st, 2023, defines involuntary hospitalization as the hospitalization of a person with a mental illness, ordered by a court. This law stipulates that involuntary hospitalization should only be used as a measure of last resort, used when outpatient treatment is not possible or sufficient and should cease as soon as the grounds for such commitment no longer exist. Involuntary hospitalization can only be ordered if it is proportional to the risk posed and the legal interests involved. It must be periodically reviewed by a judge and carried out in appropriate mental health units with medical and psychological support. Additionally, individuals involuntarily admitted have the right to visits, communication, and access to free activities.[3]

There is still considerable debate regarding the ethical dimension of involuntary hospitalization due to the restriction of personal liberty involved in providing adequate treatment under medical supervision.[4] For example, a study conducted in Norway introduced a 24-hour re-evaluation period for patients referred for involuntary hospitalization. This approach appeared to provide a meaningful opportunity to reduce unnecessary admissions while safeguarding the patient's right to opt for voluntary hospitalization.[2]

The literature suggests that severe psychiatric disorders, such as schizophrenia, coupled with aggressive behavior and treatment non-adherence, are significant predictors of involuntary hospitalization.[5] Moreover, some studies suggest that organic, psychotic, and bipolar disorders are associated with a higher rate of involuntary admissions. Additionally, patients discharged involuntarily often experience a higher incidence of crisis situations, receive fewer pharmacologic intervention and therapy, and exhibit overall poorer prognostic outcomes.[6] The prognosis following discharge from involuntary hospitalization is also associated with an increased risk of readmission, particularly among patients with schizophrenia.[7] However, to date, limited research has been conducted to assess the clinical decompensation and prognosis associated with transitioning patients from involuntary hospitalization to voluntary treatment.[8]

In this context, studies comparing the risks associated with involuntary versus voluntary admission found that involuntary patients had equal or longer lengths of stay, higher rates of readmission, and an increased risk of subsequent involuntary readmissions. While no increase in overall mortality was observed among involuntary patients, they

did exhibit higher suicide rates compared to those admitted voluntarily. In addition, involuntarily admitted patients were found to have lower levels of social functioning, both at admission and at discharge, were less satisfied with treatment and more frequently perceived their hospitalization as unjustified. No significant differences were observed in levels of psychopathology or treatment compliance.[9,10]

Involuntary hospitalization is intended to improve the quality of medical treatment for patients with mental disorders and to mitigate the risk posed by those who discontinue or receive insufficient psychiatric care, as a proportion of criminal acts are committed by psychiatric patients.[11] However, despite being a potentially lifesaving treatment, involuntary admissions can also be stigmatizing, undermine the long-term therapeutic relationship, and reduce adherence to treatment.

With this retrospective cohort study, we aimed to identify and assess the frequency of readmission, within one year, among patients who transitioned to voluntary treatment, compared with those who remained involuntarily treated; to determine the time to readmission, legal status and length of stay of readmission of the cohort; and to assess the occurrence of in-hospital mortality or suicide.

We expect to clarify how transitioning involuntarily hospitalized patients to voluntary status affects psychiatric decompensation. Through this comparative analysis, we hope to provide evidence supporting the prioritization of voluntary treatment whenever feasible.

METHODS

Study design

An observational single-site retrospective cohort study was conducted using administrative and clinical data of patients who were involuntarily admitted to the inpatient psychiatry department of Unidade Local de Saúde São João (ULSSJ), a university hospital located in northern Portugal that is part of the Portuguese National Health Service (NHS). Data analysis, reporting, and manuscript formatting complied with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement recommendations.[12]

Setting

The study encompassed all cases of involuntary psychiatric hospitalization that occurred within ULSSJ between January 1st and December 31st, 2022.

Participants and study duration

All hospitalization episodes of adult patients (≥ 18 years old) involuntarily admitted to the inpatient psychiatry department of ULSSJ between January 1st, 2022, and December 31st, 2022, were considered for inclusion, regardless of diagnosis and sex. No other criteria were established.

Hospitalization episodes were assigned to individual patients, who were the unit of analysis of the present study. Patients were then assigned to one of two groups: patients who were initially admitted involuntarily and subsequently converted to voluntary hospitalization during their stay, or patients who remained under involuntary hospitalization until discharge, hereafter referred to as voluntary or involuntary inpatients, respectively. To assess the primary outcome, defined as the frequency of readmission within one year, data registered in medical records within one year following the index hospitalization were extracted and analyzed (whether structured data or free-text entries).

Data collection and management

De-identified data were extracted from patients' clinical records. For each patient, demographic characteristics and administrative data were collected. To ensure data security, information was stored in a database on an encrypted USB drive. All identifiable information, including patient names and process numbers, was removed upon completion, warranting data anonymity. Information was used exclusively for this study, with access restricted to members of the research team and was deleted upon completion.

Variables and outcomes

Each patient's collected data included socio-demographic characteristics and administrative data such as admission date, age at admission, sex, marital status (single, married, divorced/separated or widowed), occupation (employed, unemployed, retired or student), and migration status (migrant or non-migrant). Clinical data was also collected, including the main diagnosis and other comorbid conditions such as cardiovascular comorbidities. Diagnoses were classified according to the International Classification of Diseases 10 version (ICD-10).[13] Psychiatric diagnoses were categorized into eleven diagnostic groups, to obtain more representative and larger patient groups, as follows: unspecified dementia (F03), substance use disorders (F12 - F19), schizophrenia spectrum disorders (F20), delusional disorders (F22), acute and transient psychotic disorders (F23), schizoaffective disorders (F25), unspecified psychosis (F29), mania and bipolar disorder (F30 - F31), depressive disorder (F32 - F33), personality disorders (F60), and others (F09, F44, F79). We classified cardiovascular comorbidities based on the presence of cardiovascular risk factors such as smoking, diabetes, hypertension, obesity, as well as the presence of cardiovascular diseases, including myocardial infarction, cerebrovascular accident, acute coronary syndrome or stable coronary disease.

Data on previous admissions, their number and legal status were also extracted, as well as information on

involuntary ambulatory treatment. Additionally, we collected information on the index hospitalization, such as the length of stay (LoS), treatment administered (oral or injectable), specific injectable medication administered, and discharge destination.

Regarding the outcome measures, these included the number of readmissions within one year, time to readmission, legal status and LoS of readmission. In-hospital mortality and suicide outcomes were also extracted and analyzed.

Statistical analysis

The data was organized into a Microsoft® Excel® spreadsheet and was further exported to IBM® SPSS Statistics version 30.0 to perform the statistical analysis.

Categorical variables were described using absolute values and relative frequencies. As for quantitative variables, including age, index hospitalization LoS, number of previous admissions and readmission LoS, these were described using median and interquartile range (IQR), as normality was not observed, as assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests (p-values < 0.05).

Comparative analyses of sociodemographic and clinical variables, as well as of prognosis outcomes, were performed between the two groups. Quantitative variables were recoded and categorized as appropriate. The chi-square test or Fisher's exact test were used, depending on the variables. P-values of < 0.05 were considered to be statistically significant (two-tailed).

Additional analyses were conducted among voluntary and involuntary inpatients, focusing on potentially more severe diagnoses with a higher risk of readmission, defined as the F20 - F31 subgroup following previous studies.[5]

In cases of missing data due to incomplete clinical registries, the missing values were explicitly indicated for each variable.

Ethical considerations

As this study involved a retrospective review of existing clinical data and posed no risk to participants, we requested a waiver of informed consent from the ethics committee. The study was submitted to and authorized by the Ethics Committee of ULSSJ (Authorization no. 373/2024).

Data sharing

The technical appendix, dataset creation plan/protocol, and statistical code are available from the corresponding author upon reasonable request.

RESULTS

Participants

Between January 1st, 2022, and December 31st, 2022, a total of 144 involuntary hospitalizations occurred, corresponding to 120 patients admitted to the inpatient psychiatry department.

There were more patients that converted to voluntary hospitalization (60.8%, n = 73) than patients who remained under involuntary hospitalization (39.2%, n = 47). The median age of the cohort was 40.00 years (IQR 30.00; 60.00 years). There was predominance of male patients (64.2% *vs* 35.8%). Patients were mostly single (58.0%, n = 69), followed by divorced/separated (20.2%, n = 24), married (17.6%, n = 21), and widowed (4.2%, n = 5). The majority were unemployed (40.2%, n = 47), followed by those who were retired (30.8%, n = 36), employed (25.6%, n = 30) and finally students (3.4%, n = 4). Most patients were non-migrants (85.8%, n = 103), and 14.2% (n = 17) were migrants. Among the primary diagnoses, the most frequently recorded were: F29 (26.7%, n = 32), F20 and F30 - F31 (both with 16.7%, n = 20) and F12 - F19 (13.3%, n = 16). Cardiovascular comorbidities were coded in 54 patients (45.0%). Previous admissions were registered for 73 patients (60.8%), with a median of 3.00 previous admissions (IQR 1.00; 7.00). Moreover, 48 of these patients (69.6%) presented previous involuntary admissions. Of all the patients admitted, 20 (16.7%) were in involuntary ambulatory treatment. The median LoS for the index hospitalization was 16.50 days (IQR 12.00; 22.00). During hospitalization, 58 patients (48.3%) received injectable treatment, including paliperidone (39.7%, n = 23), haloperidol (36.2%, n = 21), aripiprazole (17.2%, n = 10) and risperidone (6.9%, n = 4). The most frequent destination after discharge was the outpatient clinic (77.5%, n = 93), followed by the day hospital (15.0%, n = 18), and external facilities (7.5%, n = 9), with the latter including another hospital or healthcare unit outside ULSSJ (Table 1).

Compared to involuntary inpatients, voluntary inpatients were predominantly aged 60 - 69 (27.4% *vs* 8.5%, p = 0.012), married (25.0% *vs* 6.4%, p = 0.009), employed (34.3% *vs* 12.8%, p = 0.009), and significantly more likely to have an F30 - F31 diagnosis (23.3% *vs* 6.4%, p = 0.016). On the other hand, involuntary inpatients were mostly single (72.3% *vs* 48.6%, p = 0.009), unemployed (53.2% *vs* 31.4%, p = 0.016), more likely to have an F20 diagnosis (29.8% *vs* 8.2%, p = 0.002) and to be referred to the day hospital (23.4% *vs* 9.6%, p = 0.036).

Additionally, involuntary inpatients had previous admissions more frequently (83.0% *vs* 46.6%, p < 0.001), as well as a prior involuntary admission (86.8% *vs* 48.4%, p < 0.001), were more often in involuntary ambulatory treatment (36.2% *vs* 4.1%, p < 0.001), presented higher LoS (> 20 days) for the index hospitalization (42.6% *vs* 23.3%, p = 0.026) and were more often administered injectable treatments (80.9% *vs* 27.4%, p < 0.001) (Table 2).

Table 1 – Sociodemographic and clinical characteristics of involuntary hospitalizations (section 1 of 2)

Variable	Category	n	%	Valid %
Hospitalization status at discharge	Voluntary	73	60.8%	60.8%
	Involuntary	47	39.2%	39.2%
	Total	120	100.0%	100.0%
Age groups	Median (IQR)	44.00 (30.00 - 60.00)		
	19 - 29	29	24.2%	24.2%
	30 - 39	21	17.5%	17.5%
	40 - 49	23	19.2%	19.2%
	50 - 59	15	12.5%	12.5%
	60 - 69	24	20.0%	20.0%
	70 - 79	8	6.7%	6.7%
	Total	120	100.0%	100.0%
Sex	Female	43	35.8%	35.8%
	Male	77	64.2%	64.2%
	Total	120	100.0%	100.0%
Marital status	Single	69	57.5%	58.0%
	Married	21	17.5%	17.6%
	Divorced/separated	24	20.0%	20.2%
	Widowed	5	4.2%	4.2%
	Total (Valid)	119	99.2%	100.0%
	Missing	1	0.8%	
	Total	120	100.0%	
Occupation	Employed	30	25.0%	25.6%
	Unemployed	47	39.2%	40.2%
	Retired	36	30.0%	30.8%
	Student	4	3.3%	3.4%
	Total (Valid)	117	97.5%	100.0%
	Missing	3	2.5%	
	Total	120	100.0%	
Migration status	Migrant	17	14.2%	14.2%
	Non-migrant	103	85.8%	85.8%
	Total	120	100.0%	100.0%
Main diagnosis	F03	5	4.2%	4.2%
	F12 - F19	16	13.3%	13.3%
	F20	20	16.7%	16.7%
	F22	8	6.7%	6.7%
	F23	1	0.8%	0.8%
	F25	5	4.2%	4.2%
	F29	32	26.7%	26.7%
	F30 - F31	20	16.7%	16.7%
	F32 - F33	6	5.0%	5.0%
	F60	3	2.5%	2.5%
	F09, F44, F79	4	3.3%	3.3%
	Total	120	100.0%	100.0%
Cardiovascular comorbidities	Yes	54	45.0%	45.0%
	No	66	55.0%	55.0%
	Total	120	100.0%	100.0%
Previous admissions	Yes	73	60.8%	60.8%
	No	47	39.2%	39.2%
	Total	120	100.0%	100.0%

Abbreviations: F03 (unspecified dementia); F12 - F19 (substance use disorders); F20 (schizophrenia spectrum disorders); F22 (delusional disorders); F23 (acute and transient psychotic disorders); F25 (schizoaffective disorders); F29 (unspecified psychosis); F30 - F31 (mania and bipolar disorder); F32 - F33 (depressive disorder); F60 (personality disorders); F09, F44, F79 (others).

Table 1 – Sociodemographic and clinical characteristics of involuntary hospitalizations (section 2 of 2)

Variable	Category	n	%	Valid %
Number of previous admissions	Median (IQR)	3.00 (1.00 - 7.00)		
	1 - 5	51	69.9%	69.9%
	6 - 10	12	16.4%	16.4%
	11 - 15	5	6.8%	6.8%
	16 - 20	2	2.7%	2.7%
	21 - 37	3	4.1%	4.1%
	Total	73	100.0%	100.0%
Previous involuntary admission	Yes	48	65.8%	69.6%
	No	21	28.8%	30.4%
	Total (Valid)	69	94.5%	100.0%
	Missing	4	5.5%	
	Total	73	100.0%	
Involuntary ambulatory treatment	Yes	20	16.7%	16.7%
	No	100	83.3%	83.3%
	Total	120	100.0%	100.0%
Length of stay	Median (IQR)	16.50 (12.00 - 22.00)		
	≤ 20 days	83	69.2%	69.2%
	> 20 days	37	30.8%	30.8%
	Total	120	100.0%	100.0%
Injectable treatment	Yes	58	48.3%	48.3%
	No	62	51.7%	51.7%
	Total	120	100.0%	100.0%
Which injectable treatment	Haloperidol	21	36.2%	36.2%
	Risperidone	4	6.9%	6.9%
	Paliperidone	23	39.7%	39.7%
	Aripiprazole	10	17.2%	17.2%
	Total	58	100.0%	100.0%
Orientation after discharge	Outpatient clinic	93	77.5%	77.5%
	Day hospital	18	15.0%	15.0%
	External facilities	9	7.5%	7.5%
	Total	120	100.0%	100.0%
Readmission within one year	Yes	28	23.3%	23.5%
	No	91	75.8%	76.5%
	Total (Valid)	119	99.2%	100.0%
	Omitted	1	0.8%	
	Total	120	100.0%	
Legal status of readmission	Voluntary	8	28.6%	28.6%
	Involuntary	20	71.4%	71.4%
	Total	28	100.0%	100.0%
Time to readmission	≤ 3 months	16	57.1%	57.1%
	> 3 months	12	42.9%	42.9%
	Total	28	100.0%	100.0%
Length of stay of readmission	Median (IQR)	17.50 (14.00 - 28.75)		
	≤ 20 days	17	60.7%	60.7%
	> 20 days	11	39.3%	39.3%
	Total	28	100.0%	100.0%
In-hospital mortality	Yes	0	0.0%	0.0%
	No	120	100.0%	100.0%
	Total	120	100.0%	100.0%
Suicide	Yes	0	0.0%	0.0%
	No	120	100.0%	100.0%
	Total	120	100.0%	100.0%

Abbreviations: F03 (unspecified dementia); F12 - F19 (substance use disorders); F20 (schizophrenia spectrum disorders); F22 (delusional disorders); F23 (acute and transient psychotic disorders); F25 (schizoaffective disorders); F29 (unspecified psychosis); F30 - F31 (mania and bipolar disorder); F32 - F33 (depressive disorder); F60 (personality disorders); F09, F44, F79 (others).

No statistically significant differences were observed between involuntary and voluntary inpatients regarding sex, migration status, and cardiovascular comorbidities.

Outcome data

Readmission within one year occurred in 28 patients (23.5% voluntary inpatients *vs* 76.5% involuntary inpatients). Among those readmitted within one year, 20 patients (71.4%) were involuntarily admitted and eight (28.6%) were voluntarily admitted. Also, 16 (57.1%) patients were readmitted in three months or less after the first discharge. The median LoS of readmissions was 17.50 days (IQR 14.00; 28.75). There were no cases of in-hospital mortality or suicide (Table 1).

Involuntary inpatients were readmitted more frequently in comparison to voluntary inpatients (36.2% *vs* 15.3% respectively, $p = 0.009$). Additionally, they were more often readmitted under involuntary status (88.2% *vs* 45.5%, $p = 0.030$). However, involuntary inpatients presented lower LoS (≤ 20 days) of readmission (76.5% *vs* 36.4%) and a longer time interval from discharge to readmission (52.9% *vs* 27.3%), although these differences were not statistically significant (Table 2).

Other analyses

The F20-F31 subgroup consisted of 85 patients, including 37 involuntary inpatients (51.5%) and 48 voluntary inpatients (48.5%). Within this subgroup, 10 involuntary inpatients were readmitted (27.0%), compared with seven voluntary inpatients (14.6%). There were no statistically

Table 2 – Patients' characterization according to discharge status: voluntary *versus* involuntary (section 1 of 2)

Variable	Category	Voluntary inpatients	Involuntary inpatients	Total	*p*-value
Age	19 - 29	16 (21.9%)	13 (27.7%)	29 (24.2%)	0.484
	30 - 39	11 (15.1%)	10 (21.3%)	21 (17.5%)	0.368
	40 - 49	13 (17.8%)	10 (21.3%)	23 (19.2%)	0.617
	50 - 59	6 (8.2%)	9 (19.1%)	15 (12.5%)	0.072
	60 - 69	20 (27.4%)	4 (8.5%)	24 (20.0%)	0.012
	70 - 79	7 (9.6%)	1 (2.1%)	8 (6.7%)	0.109
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Sex	Female	30 (41.1%)	13 (27.7%)	43 (35.8%)	
	Male	43 (58.9%)	34 (72.3%)	77 (64.2%)	0.134
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Marital status	Single	35 (48.6%)	34 (72.3%)	69 (58.0%)	0.009
	Married	18 (25.0%)	3 (6.4%)	21 (17.6%)	0.009
	Divorced/separated	14 (19.4%)	10 (21.3%)	24 (20.2%)	0.841
	Widowed	5 (6.9%)	0 (0.0%)	5 (4.2%)	0.072
	Total	72 (100.0%)	47 (100.0%)	119 (100.0%)	
Occupation	Employed	24 (34.3%)	6 (12.8%)	30 (25.6%)	0.009
	Unemployed	22 (31.4%)	25 (53.2%)	47 (40.2%)	0.016
	Retired	21 (30.0%)	15 (31.9%)	36 (30.8%)	0.841
	Student	3 (4.3%)	1 (2.1%)	4 (3.4%)	0.549
	Total	70 (100.0%)	47 (100.0%)	117 (100.0%)	
Migration status	Migrant	13 (17.8%)	4 (8.5%)	17 (14.2%)	
	Portuguese	60 (82.2%)	43 (91.5%)	103 (85.8%)	0.154
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Main diagnosis	F03	5 (6.8%)	0 (0.0%)	5 (4.2%)	0.072
	F12 - F19	7 (9.6%)	9 (19.1%)	16 (13.3%)	0.134
	F20	6 (8.2%)	14 (29.8%)	20 (16.7%)	0.002
	F22	5 (6.8%)	3 (6.4%)	8 (6.7%)	0.920
	F23	1 (1.4%)	0 (0.0%)	1 (0.8%)	0.424
	F25	2 (2.7%)	3 (6.4%)	5 (4.2%)	0.317
	F29	18 (24.7%)	14 (29.8%)	32 (26.7%)	0.549
	F30 - F31	17 (23.3%)	3 (6.4%)	20 (16.7%)	0.016
	F32 - F33	6 (8.2%)	0 (0.0%)	6 (5.0%)	0.045
	F60	3 (4.1%)	0 (0.0%)	3 (2.5%)	0.162
	F09, F44, F79	3 (4.1%)	1 (2.1%)	4 (3.3%)	0.549
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	

F03 (unspecified dementia); F12 - F19 (substance use disorders); F20 (schizophrenia spectrum disorders); F22 (delusional disorders); F23 (acute and transient psychotic disorders); F25 (schizoaffective disorders); F29 (unspecified psychosis); F30 - F31 (mania and bipolar disorder); F32 - F33 (depressive disorder); F60 (personality disorders) and F09, F44, F79 (others).

Table 2 – Patients' characterization according to discharge status: voluntary *versus* involuntary (section 2 of 2)

Variable	Category	Voluntary inpatients	Involuntary inpatients	Total	*p*-value
Cardiovascular comorbidities	Yes	36 (49.3%)	18 (38.3%)	54 (45.0%)	
	No	37 (50.7%)	29 (61.7%)	66 (55.0%)	0.236
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Previous admissions	Yes	34 (46.6%)	39 (83.0%)	73 (60.8%)	
	No	39 (53.4%)	8 (17.0%)	47 (39.2%)	< 0.001
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Previous involuntary admission	Yes	15 (48.4%)	33 (86.8%)	48 (69.6%)	
	No	18 (51.6%)	5 (13.2%)	21 (30.4%)	< 0.001
	Total	31 (100.0%)	38 (100.0%)	69 (100.0%)	
Involuntary ambulatory treatment	Yes	3 (4.1%)	17 (36.2%)	20 (16.7%)	
	No	70 (95.9%)	30 (63.8%)	100 (83.3%)	< 0.001
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Injectable treatment	Yes	20 (27.4%)	38 (80.9%)	58 (48.3%)	
	No	53 (72.6%)	9 (19.1%)	62 (51.7%)	< 0.001
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Length of stay of index admission	≤ 20 days	56 (76.7%)	27 (57.4%)	83 (69.2%)	
	> 20 days	17 (23.3%)	20 (42.6%)	37 (30.8%)	0.026
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Orientation after discharge	Outpatient clinic	58 (79.5%)	35 (74.5%)	93 (77.5%)	0.549
	Day hospital	7 (9.6%)	11 (23.4%)	18 (15.0%)	0.036
	External facilities	8 (11.0%)	1 (2.1%)	9 (7.5%)	0.072
	Total	73 (100.0%)	47 (100.0%)	120 (100.0%)	
Readmission within one year	Yes	11 (15.3%)	17 (36.2%)	28 (23.5%)	
	No	61 (84.7%)	30 (63.8%)	91 (76.5%)	0.009
	Total	72 (100.0%)	47 (100.0%)	119 (100.0%)	
Legal status of readmission	Voluntary	6 (54.5%)	2 (11.8%)	8 (100.0%)	
	Involuntary	5 (45.5%)	15 (88.2%)	20 (100.0%)	0.030
	Total	11 (100.0%)	17 (100.0%)	28 (100.0%)	
Length of stay of readmission	≤ 20 days	4 (36.4%)	13 (76.5%)	17 (60.7%)	
	> 20 days	7 (63.6%)	4 (23.5%)	11 (39.3%)	0.053
	Total	11 (100.0%)	17 (100.0%)	28 (100.0%)	
Time to readmission	≤ 3 months	8 (72.7%)	8 (47.1%)	16 (57.1%)	
	> 3 months	3 (27.3%)	9 (52.9%)	12 (42.9%)	0.253
	Total	11 (100.0%)	17 (100.0%)	28 (100.0%)	

F03 (unspecified dementia); F12 - F19 (substance use disorders); F20 (schizophrenia spectrum disorders); F22 (delusional disorders); F23 (acute and transient psychotic disorders); F25 (schizoaffective disorders); F29 (unspecified psychosis); F30 - F31 (mania and bipolar disorder); F32 - F33 (depressive disorder); F60 (personality disorders) and F09, F44, F79 (others).

significant differences in readmissions between involuntary and voluntary inpatients in this subgroup ($p = 0.155$) (Table 3).

DISCUSSION

The aim of the present study was to evaluate whether patients discharged under voluntary status after an initial involuntary admission had a different risk of psychiatric decompensation, as assessed by the frequency of readmission within one year. No increase in readmission rates was observed among patients discharged under voluntary status.

We found that 60.8% of patients transitioned to voluntary hospitalization, while 39.2% remained involuntarily hospitalized. Regarding readmission within one year, 17 involuntary inpatients (36.2%) were readmitted, compared with 11 voluntary inpatients (15.3%) ($p = 0.009$). Involuntary inpatients were also more often readmitted under involuntary status

Table 3 – Readmissions within one year in the F20 - F31 subgroup

Variable	Category	Voluntary inpatients	Involuntary inpatients	Total	*p*-value
Readmission	Yes	7 (14.6%)	10 (27.0%)	17 (20.0%)	
Within one year	No	41 (85.4%)	27 (73.0%)	68 (80.0%)	0.155
	Total	48 (100.0%)	37 (100.0%)	85 (100.0%)	

(88.2% *vs* 45.5%, p = 0.030). Although the length of stay during readmission was higher among voluntary inpatients, this difference was not statistically significant. Similarly, the time to readmission was longer for involuntary inpatients, but the difference between the two groups did not reach statistical significance.

The most frequent diagnoses in the sample were F29, followed by F20, F30 - F31, and F12 - F19. Involuntary inpatients presented previous admissions more frequently, as well as previous involuntary admissions, had a higher length of stay during the index hospitalization, a greater need for injectable treatment, and were more frequently in involuntary ambulatory treatment.

The findings suggest that both the frequency of readmission and the frequency of involuntary readmission were higher for involuntary inpatients, corroborating previous results reported in the literature. These results also align with the findings by Hung *et al*, who observed that a prior history of involuntary admission was associated with an increased risk of readmission within one year.[14]

Our findings on the risk factors for involuntary hospitalization are consistent with previous research, including Portuguese studies on sociodemographic and clinical determinants. Among involuntary hospitalizations, the most frequent diagnosis was F29, and marital status was associated with voluntary discharge.[15] Additionally, a longer length of stay during the index hospitalization and a history of previous admissions were more common among involuntary inpatients.[9,16] Furthermore, these patients were significantly more likely to be subjected to coercive measures, including the administration of injectable medication without consent, both during previous involuntary outpatient treatment and during the index hospitalization.[6]

On the other hand, the F20 - F31 subgroup analysis showed a trend toward lower readmission rates among involuntary inpatients, but this difference did not reach statistical significance, consistent with the findings of Hung *et al*.[14] This result contrasts with the main sample, suggesting that patients with severe diagnoses need cautious consideration when transitioning to voluntary treatment.

To the best of our knowledge, this is the first study to compare outcomes for patients with mental illness who were discharged under voluntary status after an initial involuntary hospitalization, in order to assess the prognostic value of this change in legal status. However, some limitations warrant consideration.

One limitation of our study is that voluntary inpatients may have less severe diagnoses, and the transition to voluntary treatment may be an indicator of a better prognosis when compared with patients who remained under involuntary hospitalization, which potentially explains the lower readmission rates within one year. Therefore, this study is subject to potential selection bias in causal inference, given that the transition to a voluntary treatment regimen is inherently reactive and typically occurs among individuals with a more favorable clinical course, lower baseline severity, and higher adherence to treatment. Consequently, observed associations may be explained by these prognostic factors rather than a direct causal effect of the treatment regimen change. Moreover, since this is a retrospective study which relies on the information registered on the patients' clinical records, some data were incomplete or missing. Being a single-center study also limits the generalizability of the findings. Finally, this study is limited by its small sample size and the lack of a control group, which could have led to selection bias.

Future studies could adopt an observational prospective design to strengthen the validity of causal inferences in this area. Additionally, further research could examine readmission frequency by creating subgroups based on longer index hospitalization lengths or the type of injectable treatment administered during the index hospitalization, as proxys of baseline severity.

In addition to patient characteristics, future research should also investigate organizational and systemic factors - such as limited staffing or structural resources in inpatient units, as well as the admission via the emergency department - as potentially contributing factors to involuntary hospitalization. Understanding how these factors could influence the likelihood of transitioning to voluntary treatment and subsequent readmission rates could provide important insights for improving patient outcomes and optimizing mental health care delivery.[17]

CONCLUSION

Involuntary hospitalization was associated with worse outcomes within one year, underscoring that its use should be proportional to the risk and subject to periodic review due to its ethical and legal implications. Conversion to voluntary hospitalization did not worsen psychiatric decompensation, supporting the role of specialist re-evaluation. This transition process is both reasonable and respectful of patient autonomy, while ensuring appropriate treatment without compromising psychiatric stability.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

MMC: Study conception and design, data collection and analysis, writing of the manuscript.

JTC: Study conception and design, data collection, critical review of the manuscript.

ARF, HS: Study conception and design, data collection, literature review, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

JTC and HS received support for attending meetings and/or travel from Johnson & Johnson Innovative Medicine (Janssen), Lundbeck Portugal and Jaba Recordati.

All other authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Aguirre L, Padovano M, Scopetti M, La Russa R, Manetti F, D'Errico S, et al. Mental health law: a comparison of compulsory hospital admission in Italy and the UK. Front Public Health. 2023;11:1265046.
2. Hustoft K, Larsen TK, Brønnick K, Joa I, Johannessen JO, Ruud T. Voluntary or involuntary acute psychiatric hospitalization in Norway: a 24h follow up study. Int J Law Psychiatry. 2018;56:27-34.
3. Portugal. Lei n.° 35/2023. Diário da República, I Série, n.° 141 (2023/07/24). p.2-23.
4. Gültekin BK, Çelik S, Tihan A, Beşkardeş AF, Sezer U. Sociodemographic and clinical characteristics of psychiatric inpatients hospitalized involuntarily and voluntarily in a mental health hospital. Noro Psikiyatr Ars. 2013;50:216-21.
5. Lachner C, Maniaci MJ, Vadeboncoeur TF, Dawson NL, Rummans TA, Roy A, et al. Are pre-existing psychiatric disorders the only reason for involuntary holds in the emergency department? Int J Emerg Med. 2020;13:4.
6. Hofmann AB, Schmid HM, Hofmann LA, Noboa V, Seifritz E, Vetter S, et al. Impact of compulsory admission on treatment and outcome: a propensity score matched analysis. Eur Psychiatry. 2022;65:e6.
7. Lin CE, Chung CH, Chen LF, Chen PC, Cheng HY, Chien WC. Compulsory admission is associated with an increased risk of readmission in patients with schizophrenia: a 7-year, population-based, retrospective cohort study. Soc Psychiatry Epidemiol. 2019;54:243-53.
8. Draghetti S, Alberti S, Borgiani G, Panariello F, De Ronchi D, Atti AR. Compulsory and voluntary admissions in comparison: a 9-year long observational study. Int J Soc Psychiatry. 2022;68:1716-6.
9. Kallert TW, Glöckner M, Schützwohl M. Involuntary vs. voluntary hospital admission. a systematic literature review on outcome diversity. Eur Arch Psychiatry Clin Neurosci. 2008;258:195-209.
10. Drakonakis N, Stylianidis S, Peppou LE, Douzenis A, Nikolaidi S, Tzavara C, et al. Outcome of voluntary vs involuntary admissions in greece over 2 years after discharge: a cohort study in the psychiatric hospital of Attica "Dafni". Community Ment Health J. 2022;58:633-44.
11. Shiina A, Sato A, Iyo M, Fujii C. Outcomes of administrative involuntary hospitalization: a national retrospective cohort study in Japan. World J Psychiatry. 2019;9:99-106.
12. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Medicine. 2015;12:e1001885.
13. World Health Organization. International statistical classification of diseases and related health problems. 10th revision. Geneva: WHO; 2019.
14. Hung YY, Chan HY, Pan YJ. Risk factors for readmission in schizophrenia patients following involuntary admission. PLoS One. 2017;12:e0186768.
15. Silva M, Antunes A, Azeredo-Lopes S, Loureiro A, Saraceno B, Caldas-de-Almeida JM, et al. Factors associated with involuntary psychiatric hospitalization in Portugal. Int J Ment Health Syst. 2021;15:37.
16. Ziltener T, Möller J, Imfeld L, Lieb R, Lang UE, Huber CG. Time to readmission in psychiatric inpatients with a therapeutic leave. J Psychiatr Res. 2021;144:102-9.
17. Aluh DO, Santos-Dias M, Silva M, Pedrosa B, Grigaitė U, Silva RC, et al. Contextual factors influencing the use of coercive measures in Portuguese mental health care. Int J Law Psychiatry. 2023;90:101918.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Long-term Follow-up of Resected EGFR-mutated Non-small Cell Lung Cancer: A Real-world Study in a Portuguese Centre

Seguimento a Longo Prazo de Carcinoma Pulmonar Não-pequenas Células EGFR-mutado Ressecado: Um Estudo de Vida Real num Centro Português

Inês SPENCER [1], Maria CAVACO [2], Ana Sofia VILARIÇA[3], Mariana ANTUNES [4], Filipa FERRO [3], Andrea Lopes MACHADO [3], Direndra HASMUCRAI [3], Paula ALVES[3]
Acta Med Port 2025 Dec;38(12):795-799 ▪ https://doi.org/10.20344/amp.23507

ABSTRACT

Surgically resected epidermal growth factor receptor-mutated non-small cell lung cancer continues to carry a substantial risk of recurrence. The aim of this retrospective, single-center study, conducted at a Portuguese tertiary hospital was to evaluate the clinical course of these patients, diagnosed between 2016 and 2020, with the final clinical data review in November, 2024. A total of 48 patients were included, predominantly female (72.9%) and non-smokers (70.8%), most presenting exon 21 *L858R* or exon 19 deletion mutations. Mutations were identified by Sanger sequencing or next-generation sequencing. Programmed death-ligand 1 expression was < 1% in 58.3% of cases. At a median follow-up of 73.6 months, 31.3% of patients experienced relapse, all progressing to stage IV disease. The five-year disease-free survival and overall survival rates were 70% and 81%, respectively. Staging significantly influenced prognosis, with five-year disease-free survival ranging from 84% in stage IB to 20% in stage III. No significant differences were observed between epidermal growth factor receptor mutation subtypes. These findings are consistent with previous real-world studies and the placebo arm of the ADAURA trial, supporting the use of adjuvant osimertinib to reduce recurrence and improve long-term outcomes, while also emphasizing the need for improved perioperative risk assessment – including staging, histopathologic features, and molecular and genetic profiling – to guide personalized treatment.
Keywords: Carcinoma, Non-Small-Cell Lung/surgery; ErbB Receptors/genetics; Mutation; Neoplasm Staging

RESUMO

O carcinoma pulmonar de não pequenas células com mutação no recetor do fator de crescimento epidérmico ressecado cirurgicamente mantém um risco elevado de recidiva. Este estudo retrospetivo, realizado num hospital terciário português, avaliou 48 doentes diagnosticados entre 2016 e 2020, com revisão final dos dados em novembro de 2024. A maioria dos doentes era do sexo feminino (72,9%), não fumadores (70,8%) e apresentava sobretudo mutações no exão 21 (*L858R*) ou deleções no exão 19. As mutações foram identificadas por sequenciação de Sanger ou de nova geração. Em 58,3% dos casos, a expressão do ligando associado à morte celular programada foi inferior a 1%. Após um seguimento mediano de 73,6 meses, 31,3% dos doentes apresentaram recidiva, todos evoluindo para estádio IV. As taxas de sobrevivência livre de doença e global aos cinco anos foram de 70% e 81%, respetivamente. O estadiamento inicial influenciou significativamente o prognóstico, com a sobrevivência livre de doença a cinco anos a variar entre 84% (estádio IB) e 20% (estádio III). Não se observaram diferenças significativas entre os subtipos de mutação. Estes resultados são consistentes com estudos prévios e com o braço placebo do estudo ADAURA, apoiando a integração do osimertinib adjuvante na prática clínica para reduzir a recidiva e melhorar a sobrevivência a longo prazo, bem como enfatizando a necessidade de uma avaliação perioperatória mais abrangente – incluindo estadiamento, características histopatológicas e perfil genético e molecular – para orientar estratégias terapêuticas personalizadas.
Palavras-chave: Carcinoma do Pulmão de Não-pequenas Células; Estadiamento de Neoplasia; Mutação; Receptor ErbB/genética

INTRODUCTION

Lung cancer remains a major health burden, with non-small cell lung cancer (NSCLC) comprising 85% of cases.[1] Epidermal growth factor receptor (EGFR) mutations in NSCLC represent 12.8% of cases in Europe and 49.1% in Asia.[2] In early stages, surgical resection provides the best outcomes.[3] Traditionally, adjuvant chemotherapy was recommended for stages II–III and for stage IB tumors > 4 cm, offering a modest 4% - 5% survival benefit at five years.[4]

In the phase 3 ADAURA trial, adjuvant osimertinib significantly improved 4-year disease-free survival (DFS) compared with placebo in resected stage IB–IIIA EGFR-mutated NSCLC, establishing a new standard of care.[5] Further real-world evidence, however, is still limited. The aim of this study was to describe the clinicopathological features, recurrence patterns, and survival outcomes of patients with resected EGFR-mutated NSCLC at a Portuguese tertiary center.

STUDY DESIGN

This retrospective study at the Department of Pulmonary Oncology of Unidade Local de Saúde de Santa Maria, in Lisbon, included patients ≥ 18 years, ECOG performance status 0 - 1, and resected EGFR-mutated NSCLC (staged I–IIIB, TNM 8th edition),[6] diagnosed between January, 2016,

1. Pulmonology Unit. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
2. Pulmonology Department. Unidade Local de Saúde do Oeste. Caldas da Rainha. Portugal.
3. Department of Pulmonary Oncology. Hospital Pulido Valente. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
4. Thoracic Surgery Department. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
✉ **Autor correspondente:** Inês Spencer. ines.spencer@ulssm.min-saude.pt
Revisto por/Reviewed by: Fernanda Estevinho
Recebido/*Received*: 08/06/2025 - **Aceite/*Accepted*:** 08/09/2025 - **Publicado/*Published*:** 02/12/2025

and June, 2020, with data extracted from medical records up to November, 2024. Synchronous neoplasms were excluded. Epidermal growth factor receptor mutations were identified by Sanger or next-generation sequencing.

The primary endpoints were DFS (time from surgery to recurrence), and OS (time from surgery to death).

We used SPSS Statistics®, version 29. A *p*-value < 0.05 was considered significant. Descriptive statistics included medians for continuous variables and percentages for categorical variables. Median follow-up was calculated using the reverse Kaplan-Meier method. Disease-free survival and OS were analyzed with Kaplan-Meier curves, and Cox regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

MAIN FINDINGS

Of 48 patients (Table 1), most were female (72.9%), non-smokers (70.8%), ECOG performance status 0 (75.0%), and a median age of 67 years (range 44 - 85). All had adenocarcinoma histology; 58.3% had negative programmed death ligand-1 (PD-L1) expression. The most frequent mutations were exon 21 *L858R* (41.7%) and exon 19 deletion (27.1%). Five had exon 18 (10.4%) and one had an exon 20 (2.1%) mutation.

Patients underwent lobectomy with lymph node dissection and 93.8% achieved R0 resection. A minority were staged according to the 7th TNM edition, with staging unchanged according to the 8th edition.[6,7] Postoperative stages included 10 patients (20.8%) with stage IA, 25 (52.1%) with IB, 8 (16.7%) with II and 5 (10.4%) with III.

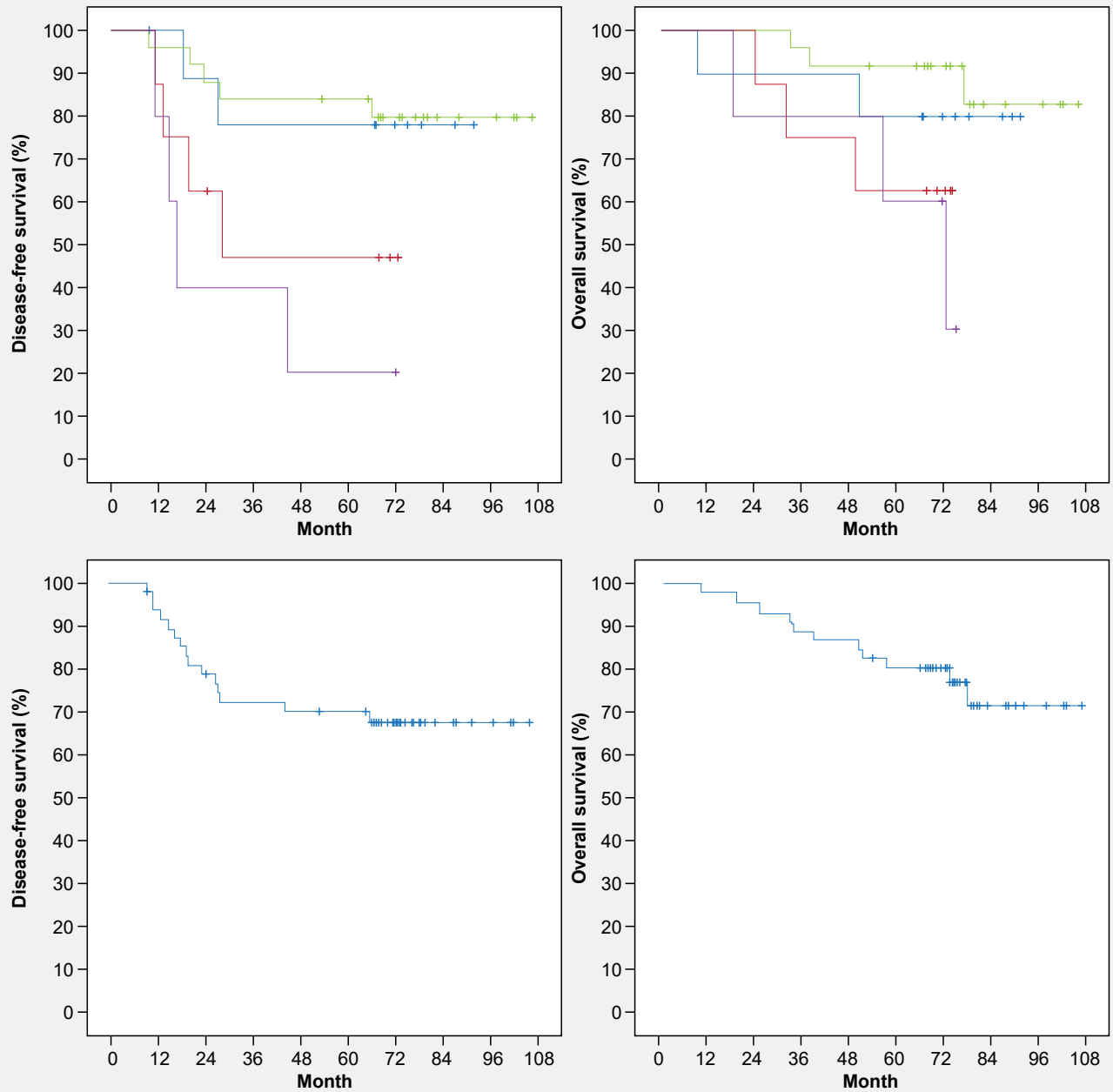
A total of 34 patients (70.8%) received adjuvant treatment: 54.1% chemotherapy and 16,9% chemoradiotherapy. With a median follow-up of 73.6 months (95% CI: 71.0 - 76.2), 15 patients (31.3%) relapsed, all with stage IV disease. Relapses occurred in all stages except IIA: 2 of 10 patients in IA, 5 of 25 (IB), 4 of 7 (IIB), 3 of 4 (IIIA), and the only patient staged IIIB. Most relapses were extra-thoracic (n = 8, 53.3%), involving the lung (53.3%), pleura (26.7%), brain (20.0%) and bone (20.0%). All relapsed patients received a TKI (osimertinib 73.3%, afatinib 20.0% and erlotinib 6.7%). Of the 15 relapses, 11 patients died, nine from disease progression (1 IA, 3 IB, 2 IIB, 2 IIIA, and 1 IIIB). Three received second-line systemic therapy and one received a third-line regimen. Median survival post-relapse was 43.80 months, and 36.37 months in patients with central nervous system (CNS) metastases. Four maintain osimertinib at follow-up.

Median DFS and OS were not reached (Fig. 1). Five-year DFS and OS were 70% and 81%, respectively. By stage, the 5-year DFS was 78% for IA, 84% for IB, 49% for II, and 20% in stage III. Patients with postoperative staging I had significantly longer DFS (HR 0.22, 95% CI: 0.08 - 0.61, $p = 0.004$) and OS (HR 0.20, 95% CI: 0.06 - 0.73, $p = 0.014$)

Table 1 – Baseline patient and disease characteristics of total population and patients with relapse. Reported variables include age, gender, ECOG PS, smoking status, TNM stage, EGFR mutation, PD-L1 expression, surgery performed, resection margins and adjuvant treatment.

Characteristics	Total (n = 48) n (%)	With relapse (n = 15) n (%)
Age		
Median [range]	67 [44 - 85]	64 [44 - 73]
≥ 65 years	29 (59.1)	7 (46.7)
Sex		
Male	13 (27.1)	6 (40.0)
Female	35 (72.9)	9 (60.0)
Performance status		
0	36 (75.0)	11 (73.3)
1	12 (25.0)	4 (26.7)
Smoking status		
Never	34 (70.8)	11 (73.3)
Current or former	14 (29.2)	4 (26.7)
TNM staging		
IA	10 (20.8)	2 (13.3)
IB	25 (52.1)	5 (33.3)
IIA	1 (2.1)	0 (0.0)
IIB	7 (14.6)	4 (26.7)
IIIA	4 (8.3)	3 (20.0)
IIIB	1 (2.1)	1 (6.7)
EGFR exons identified		
18	5 (10.4)	2 (13.3)
19	20 (41.7)	6 (40.0)
20	1 (2.1)	0 (0.0)
21	22 (45.8)	7 (46.7)
EGFR status*		
Exon 21 *L858R*	20 (41.7)	7 (46.7)
Exon 19 deletion	13 (27.1)	2 (13.3)
Other	12 (25.0)	6 (40.0)
PD-L1 status		
< 1%	28 (58.3)	7 (46.7)
1 - 49%	13 (27.1)	6 (40.0)
> 49%	0 (0.0)	0 (0.0)
Unknown	7 (14.6)	2 (13.3)
Location of lobectomy		
Upper right lobe	15 (31.3)	5 (33.3)
Medium lobe	2 (4.2)	1 (6.7)
Lower right lobe	9 (18.7)	2 (13.3)
Upper left lobe	10 (20.8)	4 (26.7)
Lower left lobe	12 (25.0)	3 (20.0)
Surgical outcome		
R0	45 (93.8)	13 (86.7)
R1	3 (6.2)	2 (13.3)
Adjuvant treatment		
Chemotherapy	26 (54.1)	8 (53.3)
Chemoradiotherapy	8 (16.7)	5 (33.3)
No adjuvant treatment	14 (29.2)	2 (13.3)

* EGFR mutation testing was performed on tumor tissue obtained at surgery using Sanger sequencing (12/48, 25.0%) or next-generation sequencing (36/48, 75.0%). NGS included institutional level 1 (n = 28), level 2 (n = 2), and standard (n = 6) panels.



No. at risk	48	44	37	33	32	31	20	7	4	0
No. at risk by stage										
IA	10	9	8	7	7	7	4	2	0	0
IB	25	24	22	21	21	20	15	5	4	0
II	8	7	5	3	3	3	1	0	0	0
III	5	4	2	2	1	1	0	0	0	0

48	47	46	43	43	42	37	26	8	4	0
10	9	9	9	9	8	5	3	0	0	0
25	25	25	24	23	21	16	5	4	0	0
8	8	8	6	6	5	3	0	0	0	0
5	5	4	4	4	3	2	0	0	0	0

Figure 1 – Kaplan-Meier curves of disease-free survival (DFS) and overall survival (OS) for the overall population (n = 48) and stratified by postoperative stage (IA–III, TNM 8th edition).[6] Numbers at risk are shown below each curve.

compared with stage II-III. No statistically significant differences in DFS or OS were found between stages IA and IB or between EGFR mutation subtypes.

CLINICAL IMPLICATIONS

The clinical characteristics of our patients were consistent with the literature on EGFR-mutated NSCLC, with predominance of women, non-smokers, median age, exon 19 deletions and exon 21 *L858R* mutations, and mostly negative PD-L1 expression. One patient carried a rare exon 20 indel (p.Ser768_Val769delinsIleLeu), distinct from classical insertions, and has remained relapse-free.

All relapses occurred as stage IV disease, and, notably, two of 10 stage IA patients also relapsed, highlighting that recurrence risk persists in early stages. This aligns with French (n = 171) and Canadian (n = 156) cohorts, which reported early relapse rates of around 20% in stage IA–IB.[8,9]

Staging significantly influenced DFS and OS, in line with other real-world series. In our cohort, the five-year DFS was 84% (stage IB), 49% for stage II, and 20% for stage III, illustrating the prognostic impact of stage at diagnosis. Although ADAURA excluded stage IA and IIIB, our DFS and OS results were similar to its placebo arm, with a four-year DFS of 73%, 56%, and 32% for IB, II, and IIIA, respectively; OS was also comparable: 92% (IB), 63% (II), 60% (III) in our cohort versus 91%, 85%, and 66% in ADAURA.[5] In contrast, ADAURA patients treated with osimertinib achieved far superior four-year DFS (90% IB, 91% II, 88% IIIA) and OS (94% *vs* 73%), supporting adjuvant osimertinib as the current standard of care.

Relapse patterns are also relevant. Osimertinib's superior CNS penetration reduces brain metastases and improves intracranial control, which is critical given the high rate of CNS relapse, also observed in our study.[5]

Prognostic factors reported in other real-world cohorts also deserve consideration. In Singapore (n = 389), five-year DFS without adjuvant TKI was 37.2%, and adverse features included nonacinar or nonlepidic histology, sublobar resection, positive margins, and lymphovascular invasion,[10] while Canadian data linked uncommon EGFR mutations to worse four-year survival (56% *vs* 73% - 82%).[9] Beyond clinicopathologic factors, genomic, transcriptomic, and proteomic profiling may aid risk stratification and enable individualized adjuvant strategies.[11,12]

The retrospective design, single-center setting, small sample size, and absence of co-mutation or control group constitute the main limitations of this study. Nevertheless, it adds meaningful long-term real-world evidence from a Portuguese cohort, complementing the existing data from Western populations.

CONCLUSION

This real-world study highlights that relapse is common in resected EGFR-mutated NSCLC, even at early stages, and often involves extrathoracic spread associated with poor prognosis. Enhanced perioperative risk assessment and personalized adjuvant treatment strategies are promising to improve long-term outcomes.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

IS, MC, ASV: Study design, data collection and analysis, writing of the manuscript.

MA: Data collection.

FF, ALM, DH, PA: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

FF received payment or honoraria from AstraZeneca for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support for attending meetings and/or travel from Takeda and Pharmamar.

AM received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche and Takeda; received support for attending meetings and/or travel from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Roche, Takeda; participated on data safety monitoring boards or advisory boards for AstraZeneca and Daiichi Sankyo.

All other authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Li C, Lei S, Ding L, Xu Y, Wu X, Wang H, et al. Global burden and trends of lung cancer incidence and mortality. Chin Med J. 2023;136:1583-90.
2. Melosky B, Kambartel K, Häntschel M, Bennetts M, Nickens DJ, Brinkmann J, et al. Worldwide prevalence of epidermal growth factor receptor mutations in non-small cell lung cancer: a meta-analysis. Mol Diagn Ther. 2022;26:7-18.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology (NCCN Guidelines®): non-small cell lung cancer. Version 3.2025. 2025. [cited 2025 Jan 30]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
4. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res. 2015;4:191-7.
5. Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB–IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. J Clin Oncol. 2023;41:1830-40.
6. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming, 8th ed. J Thorac Oncol. 2016;11:39-51.
7. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming. 7th ed. J Thorac Oncol. 2007;2:706-14.
8. Auliac JB, Thomas PA, Bylicki O, Guisier F, Curcio H, Alain-Vegnenègre, et al. Resected EGFR-mutated non-small-cell lung cancers: incidence and outcomes in a European population (GFPC Exerpos Study). Ther Adv Med Oncol. 2024;16:17588359241236451.
9. Kuruvilla SM, Liu G, Syed I, Gwadry-Sridhar F, Sheffield BS, Sachdeva R, et al. EGFR mutation prevalence, real-world treatment patterns, and outcomes among patients with resected, early-stage, non-small cell lung cancer in Canada. Lung Cancer. 2022;173:58-66.
10. Saw SP, Zhou S, Chen J, Lai G, Ang MK, Chua K, et al. Association of clinicopathologic and molecular tumor features with recurrence in resected early-stage epidermal growth factor receptor-positive non-small cell lung cancer. JAMA Netw Open. 2021;4:e2131892.
11. Wu YL, Liu SY, Wang Q, Zhou C, Lu S, Chen G, et al. A comprehensive model of genetic features predicts outcome of personalized adjuvant treatment in resected EGFR-mutant stage II–IIIA NSCLC: results from a phase III trial (CTONG 1104-ADJUVANT). Ann Oncol. 2019;30:v586.
12. Jao K, Tomasini P, Kamel-Reid S, Korpanty GJ, Mascaux C, Sakashita S, et al. The prognostic effect of single and multiple cancer-related somatic mutations in resected non-small-cell lung cancer. Lung Cancer. 2018;123:22-9.

AMP ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Artigo corrigido / Updated article
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23301

Pediatric Sarcopenia: What do We Know?

Sarcopenia Pediátrica: O que Sabemos?

Marília MARQUES [1,2], Fátima BAPTISTA [2]
Acta Med Port 2025 Dec;38(12):800-807 ▪ https://doi.org/10.20344/amp.23301

ABSTRACT

Pediatric sarcopenia is an emerging health issue that affects muscle development, strength, and overall well-being in children and adolescents. While it was initially linked to aging, recent studies highlight its presence in younger populations, particularly among those with chronic conditions. This condition affects growth and neurodevelopment in the short term and is associated with an increased risk of long-term complications, namely metabolic and cardiovascular diseases. Several factors contribute to pediatric sarcopenia, including inadequate prenatal nutrition, low birth weight, genetic susceptibility, insufficient dietary protein intake, sedentary behaviors, obesity, metabolic imbalances, and chronic illnesses. Reduced muscle mass impairs bone health, delays growth spurts, and affects physical performance, which may result in a lower quality of life. In children with chronic diseases, sarcopenia exacerbates clinical outcomes, prolongs hospital stays, and increases the likelihood of complications. Diagnosing sarcopenia in children is complex due to differing growth patterns. Existing assessment methods, such as imaging techniques and body composition analysis, lack standardized reference values tailored to pediatric populations, which makes early detection challenging. Preventive strategies emphasize physical activity, especially resistance exercises (muscle strengthening), reduced screen time, improved dietary habits, and sleep hygiene. Innovative treatments are being explored, including targeted drug delivery to the muscle to minimize side effects, regenerative approaches utilizing nanoparticles, and myostatin inhibitors for stimulating muscle growth. Stem cell therapy and biomaterial-based muscle reconstruction are also under investigation; however, pediatric-specific therapeutic guidelines remain undefined. Early intervention is crucial for reducing its negative effects and fostering healthier developmental paths.
Keywords: Child; Sarcopenia/diagnosis; Sarcopenia/etiology; Sarcopenia/prevention and control

RESUMO

A sarcopenia pediátrica é um problema de saúde emergente que afeta o desenvolvimento muscular, a força e o bem-estar geral em crianças e adolescentes. Embora inicialmente associada ao envelhecimento, estudos recentes destacam a sua presença em populações mais jovens, especialmente entre aqueles com doença crónica. Esta condição afeta o crescimento e o neurodesenvolvimento a curto prazo, estando associada a um maior risco de complicações a longo prazo, nomeadamente doenças metabólicas e cardiovasculares. Diversos fatores contribuem para a sarcopenia pediátrica, incluindo uma nutrição pré-natal inadequada, baixo peso ao nascimento, suscetibilidade genética, ingestão insuficiente de proteínas na dieta, estilo de vida sedentário, obesidade, desequilíbrios metabólicos e doenças crónicas. A redução da massa muscular compromete a saúde óssea, atrasa o pico de crescimento e afeta o desempenho físico, o que pode levar a uma redução da qualidade de vida. Em crianças com doenças crónicas, a sarcopenia agrava o prognóstico, prolongando o internamento hospitalar e aumentando a probabilidade de complicações. O diagnóstico da sarcopenia em crianças continua a ser complexo devido aos padrões de crescimento variáveis. Os métodos de avaliação disponíveis, como as técnicas de imagem e a análise da composição corporal, carecem de valores de referência padronizados adaptados às populações pediátricas, o que dificulta a deteção precoce. As estratégias preventivas enfatizam a atividade física, especialmente os exercícios de resistência (fortalecimento muscular), juntamente com a redução do tempo de ecrã, a melhoria dos hábitos alimentares e a higiene de sono. Tratamentos inovadores estão a ser desenvolvidos, incluindo medicação dirigida ao músculo para minimizar os efeitos secundários, abordagens regenerativas utilizando nanopartículas e inibidores de miostatina para estimular o crescimento muscular. O uso da terapia com células estaminais e com biomateriais para reconstrução muscular também está a ser estudado, mas as normas de orientação clínica específicas para pediatria ainda não estão definidas. A intervenção precoce é crucial para mitigar os seus efeitos adversos e promover trajetórias de desenvolvimento mais saudáveis.
Palavras-chave: Criança; Sarcopenia/diagnóstico; Sarcopenia/etiologia; Sarcopenia/prevenção e controlo

INTRODUCTION

Skeletal muscle is the most abundant tissue in the human body and plays vital physiological roles, including maintaining posture, facilitating locomotion, and supporting metabolic homeostasis. It serves as a reservoir for amino acids and triglycerides, with approximately 25% of ingested glucose mobilized when needed for energy.[1] Additionally, skeletal muscle at rest accounts for a significant portion of energy expenditure.[2] This tissue is fundamental to metabolic processes and is closely linked to childhood development, making it a valuable tool for assessing growth and age- and sex-specific psychomotor milestones.[3]

Lean mass acquisition from birth has been linked to enhanced neurodevelopment in hospitalized low-birth-weight infants, improved brain growth in preterm infants,[4] quicker neuronal processing, and superior speech development by two years of age,[5] independently of prenatal, postnatal, or parental influences.[6]

Optimal muscle mass and strength development during childhood and adolescence is also critical for bone growth and the prevention of conditions such as sarcopenia and osteoporosis in adulthood.[7]

Myokines secreted by skeletal muscle can cross the blood-brain barrier, promoting neurogenesis and synaptic plasticity.[8] They also mediate communication between muscle and

1. Hospital Lusíadas Lisboa. Lisboa. Portugal.
2. Departamento de Desporto e Saúde. Centro Interdisciplinar de Performance Humana (CIPER). Faculdade de Motricidade Humana. Universidade de Lisboa. Lisboa. Portugal.
✉ **Autor correspondente:** Marília Marques. marilia.marques.galinha@lusiadas.pt
Recebido/*Received*: 29/04/2025 - **Aceite/*Accepted*:** 20/06/2025 - **Publicado *Online*/*Published Online*:** 17/10/2025 - **Publicado/*Published*:** 02/12/2025

other organs (e.g., the liver and adipose tissue). Consequently, impaired muscle function can significantly impact lipid and carbohydrate metabolism, leading to increased adipose tissue, elevated inflammatory adipokines, intramuscular lipid accumulation, free radical production, and reduced mitochondrial oxidative activity.[9,10]

The detrimental effects of reduced muscle mass in children have been documented across neurological, metabolic, and skeletal domains.[11–14]

Pediatric sarcopenia is characterized by inadequate muscle development, whether in strength or function, compared to the normal physiological requirements for age, sex, and maturation stage. This condition can adversely affect growth, psychomotor development, metabolic health, and mental well-being in children and adolescents, both in the short and long term.[12,15,16]

The European Working Group on Sarcopenia in Older People, in 2019, established the diagnosis and severity of sarcopenia with the presence of low muscle strength, low muscle quantity and low physical performance (handgrip strength by dynamometry and/or chair test).[17]

Although initially focused on the elderly, sarcopenia has emerged as a growing concern among pediatric populations, particularly in children with chronic diseases. Recently, some studies have suggested that it may also be present in asymptomatic children.[18]

Accurately assessing body composition in children and adolescents is essential for a thorough evaluation of their health, especially as it must account for growth-related changes. This approach can help identify and address potential future health issues. The aim of this review is to compile current knowledge and offer a structured overview of the existing literature on this subject.

RISK FACTORS FOR PEDIATRIC SARCOPENIA

Risk factors for pediatric sarcopenia encompass a broad range of prenatal and postnatal influences, as well as underlying medical conditions. Prenatal factors include maternal nutrition during pregnancy and genetic predisposition. Postnatal contributors include inadequate protein intake, physical inactivity, sedentary behavior, and hormonal imbalances and insufficient sleep.[18] In addition, chronic diseases, metabolic disorders (such as obesity and insulin resistance), and neuroendocrine or neuromuscular conditions may also play a significant role in the development of pediatric sarcopenia (Fig. 1).

Barker's hypothesis posits that fetal growth and development are programmed by the intrauterine environment and maternal lifestyle.[19] Maternal malnutrition during pregnancy reduces the size and density of muscle fibers in mammals.[20] This effect extends beyond fetal life, as studies show that individuals born with low birth weight exhibit impaired muscle growth[21] and reduced handgrip strength, persisting into their 30s.[22] A meta-analysis of 13 longitudinal studies with over 20 000 participants also found a link between birth weight and future muscle strength, where each kilogram of birth weight corresponded to an additional 0.86 kg of muscle strength from ages 9.3 to 67.5 years.[23]

Physical inactivity is a critical factor in muscle loss postnatally. For example, one week of bed rest can result in a 3% loss of thigh muscle mass, while three months of inactivity can reduce quadriceps and gastrocnemius and soleus muscle volume by 30%.[24] A sedentary behavior combined with an unhealthy diet is also an independent risk factor for sarcopenia in youth.[25]

Metabolic syndrome (characterized by obesity, hypertension, hyperglycemia, and dyslipidemia) has been

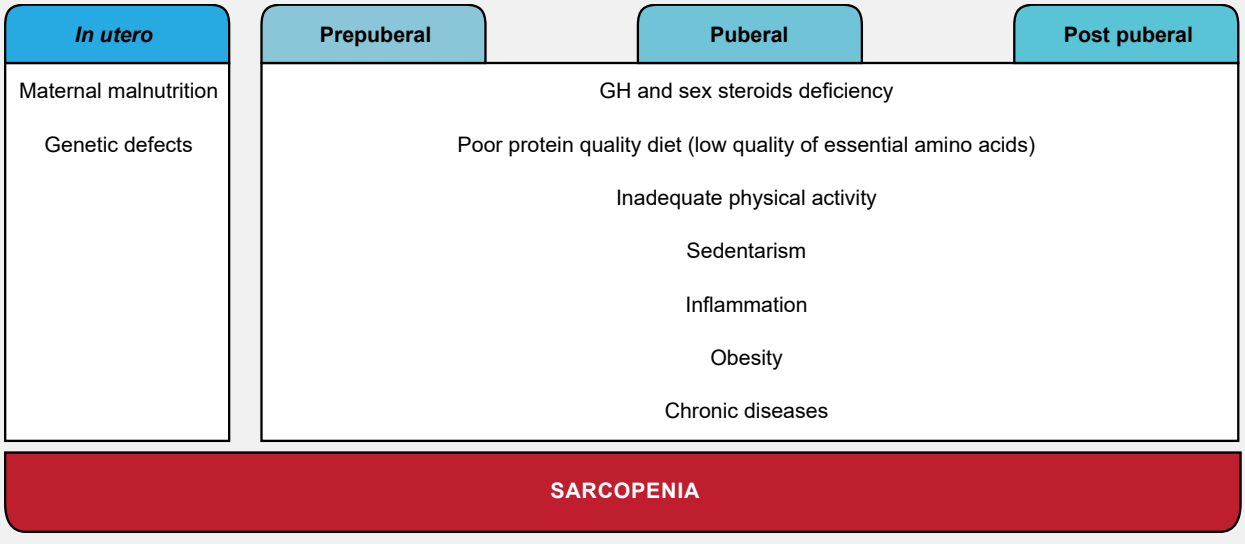


Figure 1 – Factors promoting sarcopenia during childhood and adolescence

identified as a risk factor for sarcopenia in children and adolescents.[26,27] Hyperinsulinemia associated with metabolic syndrome promotes protein degradation and inhibits protein synthesis.[28] Insulin resistance further increases myostatin production, a growth differentiation factor (GDF-8) that negatively regulates muscle growth by reducing muscle mass and suppressing growth hormone (GH) production.[29]

Obesity contributes to muscle mass reduction by promoting fat accumulation within and around muscles, impairing satellite cell function and myoblast proliferation[30] and adipocytes exacerbate muscle loss by inducing systemic inflammation.

Chronic diseases are a major risk factor for pediatric sarcopenia, acting through mechanisms such as reduced protein synthesis, accelerated catabolism, inflammatory cytokine production, nutritional deficits, corticosteroid therapy, and physical inactivity.[31,32]

Genetic factors, including hereditary conditions affecting muscle metabolism (e.g., neurodegenerative diseases) or endocrine function (e.g., congenital hypothyroidism, type 1 diabetes, hypogonadism, hypopituitarism), are also significant contributors.[18]

Inadequate sleep (quality or quantity) is another risk factor, as sleep is essential for growth and muscle recovery. Sleep deprivation can impair muscle function, increase injury risk, and contribute to chronic inflammation, insulin resistance, and reduced physical activity, all promoting muscle loss.[33,34]

The gut microbiome plays a crucial role in muscle health by influencing nutrient absorption, inflammation, and energy metabolism.[35] A balanced microbiome improves insulin sensitivity, enhances muscle glucose uptake, and reduces inflammation. Conversely, dysbiosis can lead to systemic inflammation and insulin resistance, which in turn contribute to muscle loss. Promoting a healthy microbiome through a fiber-rich diets and probiotics may help prevent pediatric sarcopenia.

The ongoing pandemic of sedentary behavior in childhood exacerbates sarcopenia, obesity, and sarcopenic obesity (which is more severe than either condition individually).

THE IMPACT OF SARCOPENIA IN CHILDREN AND ADOLESCENTS

Growth

Normal growth depends on multiple factors (genetic, hormonal, nutritional, and environmental) and reflects the health and well-being of children or adolescents.[36]

Growth and maturation depend on available energy levels and the regulation of energy homeostasis, with muscle and adipose tissue playing a crucial role in this process.[37] Most researchers focus on linear growth (height change over time), but changes in body composition and regional fat distribution are key for growth and sexual maturation.[38] Assessing cardiovascular risk in adults strongly depends on regional fat distribution (especially abdominal). The precursors of adult fat distribution patterns are present in adolescents and, in some cases, even in younger children.

Adipose tissue and body mass index (BMI) are inversely related to sexual maturation (onset of secondary sexual characteristics, due to the activation of the hypothalamic-pituitary-gonadal axis) and somatic maturation (pubertal growth spurt).[39,40] In other words, a higher BMI in a prepubertal child is associated with an earlier onset of the growth spurt but a reduced overall magnitude of the pubertal growth spurt.[40] If a child has a body composition with a deficit in muscle mass (risk of sarcopenia), the peak growth velocity in height will be lower and occur later than in obese children for both sexes.[41] In sarcopenic individuals, insufficient musculature may compromise the child's or adolescent's growth and final adult height.[41]

Bone development

During childhood and adolescence, muscle development occurs alongside bone tissue differentiation, and several observational studies have shown a positive correlation between muscle mass, strength, and bone parameters: bone mineral density (BMD), bone mineral content (BMC), and bone area.[42-44] This association can be explained by the mechanostat theory, which posits that bone mass and geometry adapt to the mechanical loads imposed by muscle force.[45] Muscles generate mechanical loads on bones during contraction, promoting bone formation (osteoblasts) and preventing bone loss (osteoclasts). In sarcopenia, this mechanical traction is reduced, decreasing the stimulus for bone remodeling and resulting in lower BMD.[44]

Lean mass significantly influences bone development and co-determines the peak bone mass maintained throughout adulthood,[46] potentially contributing to osteosarcopenia. The effect of muscle mass and strength variation (mechanical load) on bone mass is well known. Several studies have demonstrated that 40% of postnatal bone development is determined by muscle development.[47] Ensuring the maintenance of excellent muscle mass during childhood and adolescence contributes to peak muscle and bone strength and has beneficial effects on the cardiovascular system and overall health in adulthood.[12]

Physical development

Evidence shows that suboptimal muscle development, known as the sarcopenic-like phenotype, affects children's physical development.

Sarcopenia increases the risk of injury and contributes to sedentary behavior. It reduces physical activity levels,

impacting musculoskeletal health and development. Children with sarcopenia often face difficulties in daily activities like running, jumping, or playing, which are vital for physical and social development. Physical inactivity worsens muscle strength and mass loss, creating a vicious cycle.

Consequences for physical activity, quality of life and general health

Sarcopenia significantly affects quality of life, leading to social difficulties, exclusion, and frustration due to physical limitations. This can result in isolation, low self-esteem, and poorer academic and social performance. Reduced participation in physical activities is linked to higher anxiety and depression symptoms.[48] Severe sarcopenia can cause difficulties in basic motor activities, leading to reduced cardiopulmonary performance and increased sedentary behavior, which exacerbates the condition.[49]

Sedentary behavior, even with low physical activity, is associated with adverse health outcomes: reduction of insulin sensitivity that contributes to fat accumulation in the liver, proxy of metabolic syndrome and type 2 diabetes.[50] Sarcopenia is associated with an unfavorable metabolic profile (measured by high-density lipoprotein, low-density lipoprotein cholesterol, and/or triglycerides) and hypertension, increasing the risk of premature cardiovascular disease.[14]

Patients with chronic disease

Sarcopenia worsens the prognosis of patients with chronic diseases, leading to more comorbidities, prolonged hospitalization, higher risk of complications (e.g., nosocomial infections), and increased mortality.[51]

In oncology**,** patients with acute lymphoblastic leukemia manifest a significant decrease in lean muscle mass early in

Table 1 – Summary of commonly used techniques for sarcopenia assessment in pediatrics

Methods	Components measured	Strengths	Limitations
Skinfold	Subcutaneous fat surrogate measure of muscle mass	Inexpensive. Noninvasive. Simple to perform.	Intraobserver and interobserver variability. Prone to errors in obese children and children with edema.
BIA	Fat mass, fat-free mass	Inexpensive. Quick and simple to perform. Noninvasive.	Potential errors due to altered hydration. Underestimates total body fat in leaner children and overestimates in obese.
DXA	Fat mass, lean mass, tissue mass, bone mineral content and density	Precise. Validated against MRI and with equation to determine skeletal muscle mass (SMM).	Trained technician required. Potential errors due to altered hydration (less than BIA). With anthropometric limitations (200 kg and 197 cm). Low dose of radiation.
MRI		Gold standard. No radiation. Precise.	High cost. Trained technician required. Lack of normative data (especially for healthy subjects).
CT	Total, subcutaneous, intramuscular, visceral and adipose tissue, SMM	Gold standard. Very precise. Normative data.	High cost. Trained technician required. Radiation.
Ultrasound		Quick. Portable. No radiation. Inexpensive.	Lack of normative data for pediatric population.
Total body potassium	Total body water	Gold standard to estimate fat-free mass. Easy to carry out. Suitable for infants and toddlers.	Expensive equipment. Labor intensive for analysis.
D3-creatine dilution(63)	Total body muscle mass	Noninvasive. Can be used in premature infant	Risk of overestimation. Lack of normative data.

treatment.[52] Adverse events are more common in sarcopenic cancer patients, and this condition significantly reduces the patient's quality of life[53] and the prognosis of the disease.

Sarcopenia is more harmful when combined with obesity than obesity alone.[54] Sarcopenic obesity is becoming increasingly important in the pediatric population due to rising childhood obesity rates linked to sedentary behaviors.[55] Obesity is often underdiagnosed in children because they may appear to have a normal weight while having reduced muscle mass.

Increased adipose tissue exacerbates sarcopenia through lipotoxicity to muscle cells.[56] This condition maintains a moderate pro-inflammatory state, with cytokine secretion and activation that affects muscle cell proliferation and differentiation.[57] Muscle neural activation also seems impaired in obese children compared to non-obese children.

In patients with severe chronic diseases, detecting sarcopenia helps monitor disease progression and improve prognosis by reducing complications.

DIAGNOSTIC METHODS AND THEIR LIMITATION

Currently, there is no standardized method for diagnosing sarcopenia. In children, muscle mass has been assessed using various methods, including anthropometry,[58] ultrasound,[59] bioelectrical impedance analysis (BIA),[60] DXA,[3] computed tomography (CT),[61] magnetic resonance imaging (MRI),[62] plethysmography,[63] creatinine excretion,[64] total body potassium,[65] and neutron activation (Table 1).[66] Despite this variety, there is no consensus on diagnostic criteria for sarcopenia.

Diagnosing sarcopenia in children is particularly challenging due to the varying rates of muscle growth and development, influenced by age, pubertal growth spurts, and biological maturation, which differ significantly even among peers of the same age group. These factors make it difficult to establish accurate cutoff values for identifying sarcopenia in children and adolescents.

Signs of sarcopenia in children are often subtle and may not become apparent until significant muscle mass and function are lost. More sensitive methods are needed to detect early-stage pediatric sarcopenia.

PREVENTION OF SARCOPENIA IN CHILDREN AND FUTURE DIRECTIONS

The incidence of pediatric sarcopenia is rising due to sedentary behavior, particularly from excessive screen time. Without early intervention, it may progress to sarcopenic obesity, increasing the risk of metabolic and cardiovascular diseases. Early intervention prevents both short- and long-term complications (reduces the risk of sarcopenia in adulthood, promoting healthier aging).

The consequences of sarcopenia affect physical growth, development, and health. Prevention and early detection are the best approaches for effective treatment and reducing public health costs. Nutritional interventions and exercise programs are most effective when starting early (Table 2).

Educating parents and healthcare professionals is essential to prevent, detect, and manage sarcopenia in children and adolescents. Informed parents and professionals can recognize early signs of sarcopenia, such as muscle weakness, fatigue, and loss of muscle mass, and risk

Table 2 – Preventive measures to reduce the risk of sarcopenia in children and adolescents

Preventive measure	Recommendation
Regular physical activity	At least 60 minutes/day of moderate to vigorous physical activity. Include resistance exercises (e.g., jumping rope, squats, push-ups) 2 - 3 times per week. Bone-strengthening activities (e.g., running, jumping, sports) at least 3 times per week.
Limiting sedentary behaviors	Reduce screen time to less than 1 hour per day. Encourage frequent active breaks (e.g., walking, stretching) and outdoor play.
Balanced diet	Ensure adequate high-quality protein intake (e.g., meat, fish, eggs, beans, dairy) and essential nutrients (vitamins D, B complex, calcium, iron, antioxidants) to support muscle growth and repair.
Education on healthy habits	Promote awareness of physical activity and nutrition among children, parents, and caregivers to establish lifelong health behaviors.
Active play & sports	Encourage participation in structured and unstructured physical activities to stimulate musculoskeletal development and improve coordination and motor skills.
Adequate sleep	Ensure 9 - 11 hours of sleep per night (ages 5 - 13) and 8 - 10 hours (ages 14 - 17) for optimal muscle recovery, growth, and hormone regulation.

factors like sedentary behaviors or poor diets.

Parents should implement healthy practices at home, such as balanced diets and regular physical activity. Healthcare professionals must be well-informed to provide specific guidance to parents during routine check-ups and in cases of hospitalization. This knowledge enables early detection and referral to specialized services, such as physiotherapy, exercise physiology, and nutritional support, ensuring targeted interventions that improve the quality of life for affected children.

With informed parents and healthcare professionals, the number of cases advancing to critical stages is reduced, lowering the need for complex interventions and reducing healthcare system costs.

Further research on age-appropriate muscle mass and reference values for body composition at each stage of development is necessary for accurate health assessments in children and adolescents.

FUTURE PERSPECTIVES

Due to the multifactorial nature of sarcopenia, there is an urgent need to develop validated biomarker panels for clinical use in both children and adults.

Genomic studies have identified certain sequences linked to an increased risk of sarcopenia in older men and women, such as the *rs34415150* variant of *HLA-DQA1*, *rs143384* of *GDF5*, and *rs62102286* of DYM.[67] Additionally, in sarcopenic patients, genes like *MT1X* and ARHGAP36 have shown higher diagnostic precision compared to *FAM171A1, GPCPD1, ZNF415*, and *RXRG*, indicating their potential as predictive markers for early screening.[68] Circulating microRNAs (e.g., microRNA-1, microRNA-29a, microRNA-29b) have also been observed in adult patients with reduced physical performance.[69]

Regarding treatment, there are new developments like delivering medication directly to the muscle, minimizing metabolization in other organs and reducing side effects. For example, we have the generation 5 polyamidoamine dendrimer (G5-PAMAM), a peptide for cell and gene therapy in sarcopenia.[70] Other research groups are developing nanoparticles for muscle regeneration,[71] myostatin inhibition via iontophoresis,[72] transdermal testosterone,[73] mitochondrial antioxidants (MitoQ 90), and exosome-based systems.[74]

Mesenchymal stem cell therapies derived from various tissues (e.g., umbilical cord, bone marrow, adipose tissue) are being explored to improve stem cell proliferation, angiogenesis, and differentiation via paracrine signaling and/or immune modulation.[75] Transplanting these cells into sarcopenic individuals may enhance musculoskeletal health by restoring cellular function and reducing inflammation.[76]

With advances in regenerative medicine, research is also being conducted into replacing muscle with natural polymers, synthetic polymers or hybrid materials that mimic the mechanical and morphological characteristics of muscle tissues.

There is still a lack of consistent studies regarding the most appropriate treatment for pediatric sarcopenia, including dosage, treatment duration, and expected side effects. The mechanisms and risk factors for sarcopenia in children, as well as its long-term impact on children, adolescents, and young adults, are not fully understood.

CONCLUSION

It is critical to establish universal criteria for assessing body composition in children and adolescents, including reference values for muscle mass and strength.

Integrating body composition assessments into routine pediatric consultations, combined with early intervention, is essential to mitigate the long-term impact of sarcopenia. Longitudinal studies and the inclusion of diverse populations are crucial for defining more effective diagnostic and treatment strategies.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

MM: Writing of the manuscript.

FB: Critical review of the manuscript.

All authors approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS

Ethical approval is not required for this review as it is a secondary study based on public and published data.

FUNDING SOURCES

MM is partly supported by the Lusíadas Knowledge Center, Hospital Lusíadas Lisboa; FB is partly supported by Centro Interdisciplinar de Estudo da Performance Humana (CIPER) [Grant UIDB/00447/2020].

REFERENCES

1. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84:475-82.
2. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J Endocrinol. 2016;229:R67-81.
3. Guo B, Wu Q, Gong J, Xiao Z, Tang Y, Shang J, et al. Relationships

between the lean mass index and bone mass and reference values of muscular status in healthy Chinese children and adolescents. J Bone Miner Metab. 2016;34:703-13.
4. Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. J Pediatrics. 2016;173:108-15.
5. Abera M, Tesfaye M, Girma T, Hanlon C, Andersen GS, Wells JC, et al. Relation between body composition at birth and child development at 2 years of age: a prospective cohort study among Ethiopian children. Eur J Clin Nutr. 2017;71:1411-7.
6. Pfister KM, Gray HL, Miller NC, Demerath EW, Georgieff MK, Ramel SE. Exploratory study of the relationship of fat-free mass to speed of brain processing in preterm infants. Pediatr Res. 2013;74:576-83.
7. Henriksson H, Henriksson P, Tynelius P, Ortega FB. Muscular weakness in adolescence is associated with disability 30 years later: a population-based cohort study of 1.2 million men. Br J Sports Med. 2019;53:1221-30.
8. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. Front Neurol. 2018;9:698.
9. Ahima RS, Park HK. Connecting Myokines and metabolism. Endocrinol Metab. 2015;30:235-45.
10. Stump CS, Henriksen EJ, Wei Y, Sowers JR. The metabolic syndrome: role of skeletal muscle metabolism. Ann Med. 2006;38:389-402.
11. Crabtree NJ, Kibirige MS, Fordham JN, Banks LM, Muntoni F, Chinn D, et al. The relationship between lean body mass and bone mineral content in paediatric health and disease. Bone. 2004;35:965-72.
12. Orsso CE, Tibaes JR, Oliveira CL, Rubin DA, Field CJ, Heymsfield SB, et al. Low muscle mass and strength in pediatrics patients: why should we care? Clin Nutr. 2019;38:2002-15.
13. Kim JH, Park YS. Low muscle mass is associated with metabolic syndrome in Korean adolescents: the Korea national health and nutrition examination survey 2009-2011. Nutrition Res. 2016;36:1423-8.
14. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: a cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895-902.
15. Smith JJ, Eather N, Morgan PJ, Plotnikoff RC, Faigenbaum AD, Lubans DR. The health benefits of muscular fitness for children and adolescents: a systematic review and meta-analysis. Sports Med. 2014;44:1209-23.
16. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN. 1,25(OH)2Vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. Endocrinol. 2011;152:2976-86.
17. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16-31.
18. Inoue T, Wakabayashi H, Kawase F, Kokura Y, Takamasu T, Fujiwara D, et al. Diagnostic criteria, prevalence, and clinical outcomes of pediatric sarcopenia: a scoping review. Clin Nutr. 2024;43:1825-43.
19. Kwon EJ, Kim YJ. What is fetal programming? a lifetime health is under the control of in utero health. Obstet Gynecol Sci. 2017;60:506-19.
20. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol. 2008;586:2371-9.
21. Chomtho S, Wells JC, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;88:1040-8.
22. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32:228-35.
23. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, et al. Birth weight and muscle strength: a systematic review and meta-analysis. J Nutr Health Aging. 2012;16:609-15.
24. Narici MV, de Boer MD. Disuse of the musculo-skeletal system in space and on earth. Eur J Appl Physiol. 2011;111:403-20.
25. Jung HN, Jung CH, Hwang YC. Sarcopenia in youth. Metabolism. 2023;144:155557.
26. Benson AC, Torode ME, Fiatarone Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1:222-31.
27. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41:1361.
28. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. Nutrients. 2021;13:3519.
29. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12:2401.
30. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391:85-100.
31. Rezende IF, Conceição-Machado ME, Souza VS, Santos EM dos, Silva LR. Sarcopenia in children and adolescents with chronic liver disease. J Pediatria. 2020;96:439-46.
32. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-47.
33. Zhang G, Wang D, Chen J, Tong M, Wang J, Chang J, et al. Association of sleep duration and prevalence of sarcopenia: a large cross-sectional study. Prev Med Rep. 2024;42:102741.
34. Rubio-Arias JÁ, Rodríguez-Fernández R, Andreu L, Martínez-Aranda LM, Martínez-Rodriguez A, Ramos-Campo DJ. Effect of sleep quality on the prevalence of sarcopenia in older adults: a systematic review with meta-analysis. J Clin Med. 2019;8:2156.
35. Liu C, Cheung W, Li J, Chow SK, Yu J, Wong SH, et al. Understanding the gut microbiota and sarcopenia: a systematic review. J Cachexia Sarcopenia Muscle. 2021;12:1393-407.
36. Uptodate Free. Measurement of growth in children. 2024. [cited 31 May 2024]. Available from: https://pro.uptodatefree.ir/Show/5356.
37. Beunen GP, Rogol AD, Malina RM. Indicators of biological maturation and secular changes in biological maturation. Food Nutr Bull. 2006;27:S244-56.
38. Rogol AD. Growth, body composition and hormonal axes in children and adolescents. J Endocrinol Invest. 2003;26:855-60.
39. Narchi H, Alblooshi A, Altunaiji M, Alali N, Alshehhi L, Alshehhi H, et al. Prevalence of thinness and its effect on height velocity in schoolchildren. BMC Research Notes. 2021;14:98.
40. Li Y, Gao D, Liu J, Yang Z, Wen B, Chen L, et al. Prepubertal BMI, pubertal growth patterns, and long-term BMI: results from a longitudinal analysis in Chinese children and adolescents from 2005 to 2016. Eur J Clin Nutr. 2022;76:1432-9.
41. Marques M, Vieira F, Teles J, Baptista F. Growth and physical development of children at apparent risk of sarcopenia. Pediatr Res. 2025;97:843-50.
42. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34:771-5.
43. Kâ K, Rousseau MC, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. HRP. 2013;80:154-62.
44. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: a systematic review. Calcif Tissue Int. 2016;99:557-77.
45. Schoenau E. From mechanostat theory to development of the «functional muscle-bone-unit». J Musculoskelet Neuronal Interact. 2005;5:232-8.
46. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96:106-14.
47. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res. 2002;17:1095-101.
48. Matta PN, Baul TD, Loubeau K, Sikov J, Plasencia N, Sun Y, et al. Low sports participation is associated with withdrawn and depressed symptoms in urban, school-age children. J Affect Disord. 2021;280:24-9.
49. Bowden Davies KA, Pickles S, Sprung VS, Kemp GJ, Alam U, Moore DR, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. Ther Adv Endocrinol Metab. 2019;10:2042018819888824.

50. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32:S157-63.
51. Atlan L, Cohen S, Shiran S, Sira LB, Pratt LT, Yerushalmy-Feler A. Sarcopenia is a predictor for adverse clinical outcome in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2021;72:883-8.
52. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35:98-102.
53. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: its clinical significance. Int J Hematol. 2018;107:486-9.
54. Van Aller C, Lara J, Stephan BC, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999-2004. Clin Nutr. 2019;38:264-70.
55. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;1-8.
56. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31:583-601.
57. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4:371.
58. Trowbridge FL, Hiner CD, Robertson AD. Arm muscle indicators and creatinine excretion in children. Am J Clin Nutr. 1982;36:691-6.
59. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: a 4-year follow-up study. Muscle Nerve. 2013;47:856-63.
60. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9:249-59.
61. Lurz E, Patel H, Frimpong RG, Ricciuto A, Kehar M, Wales PW, et al. Sarcopenia in children with end-stage liver disease. J Pediatr Gastroenterol Nutr. 2018;66:222-6.
62. Ritz A, Lurz E, Berger M. Sarcopenia in children with solid organ tumors: an instrumental era. Cells. 2022;11:1278.
63. Mazahery H, von Hurst PR, McKinlay CJ, Cormack BE, Conlon CA. Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Maternal Health Neonatol Perinatol. 2018;4:12.
64. Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol. 2018;124:1-9.
65. Wang Z, Heshka S, Pietrobelli A, Chen Z, Silva AM, Sardinha LB, et al. A new total body potassium method to estimate total body skeletal musclemass in children. J Nutr. 2007;137:1988-91.
66. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN, et al. Reduced body protein in children with spastic quadriplegic cerebral palsy2. The American Journal of Clinical Nutrition.2006;83:613-8.
67. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12:654.
68. Lin S, Ling M, Chen C, Cai X, Yang F, Fan Y. Screening potential diagnostic biomarkers for age-related sarcopenia in the elderly population by WGCNA and LASSO. BioMed Res Int. 2022;2022:7483911.
69. Valášková S, Gažová A, Vrbová P, Koller T, Šalingova B, Adamičková A, et al. The severity of muscle performance deterioration in sarcopenia correlates with circulating muscle tissue-specific miRNAs. Physiol Res. 2021;70:S91-8.
70. Jativa SD, Thapar N, Broyles D, Dikici E, Daftarian P, Jiménez JJ, et al. Enhanced delivery of plasmid DNA to skeletal muscle cells using a DLC8-binding peptide and ASSLNIA-modified PAMAM dendrimer. Mol Pharm. 2019;16:2376-84.
71. Poussard S, Decossas M, Bihan OL, Mornet S, Naudin G, Lambert O. Internalization and fate of silica nanoparticles in C2C12 skeletal muscle cells: evidence of a beneficial effect on myoblast fusion. IJN. 2015;10:1479-92.
72. Michiue K, Takayama K, Taniguchi A, Hayashi Y, Kogure K. Increasing skeletal muscle mass in mice by non-invasive intramuscular delivery of myostatin inhibitory peptide by iontophoresis. Pharmaceuticals. 2023;16:397.
73. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
74. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020;11:348-65.
75. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria transplantation from stem cells for mitigating sarcopenia. Aging Dis. 2023;14:1700-13.
76. Najm A, Niculescu AG, Grumezescu AM, Beuran M. Emerging therapeutic strategies in sarcopenia: an updated review on pathogenesis and treatment advances. Int J Mol Sci. 2024;25:4300.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

A Complex Case of Koolen-De Vries Syndrome Associated with Hypopituitarism and Type 1 Diabetes Mellitus

Um Caso Complexo de Síndrome de Koolen-De Vries Associado a Hipopituitarismo e Diabetes Mellitus Tipo 1

Mafalda FÉLIX CABRAL *,1, Francisco BRANCO CAETANO *,1, Carla CONCEIÇÃO 2, Diana ANTUNES 3, Lurdes LOPES 1
Acta Med Port 2025 Dec;38(12):808-811 ▪ https://doi.org/10.20344/amp.22709

ABSTRACT

Complex diseases arise from the interplay of genetic and environmental factors. We present a case where complex diseases seem to coexist. A 12-month-old girl was referred for short stature and hypotonia. Initial evaluation revealed central hypothyroidism, growth hormone deficiency and a small pituitary gland with ectopic neurohypophysis. Replacement therapy improved growth, but developmental delay and strabismus ensued. At age 10, she experienced a first seizure treated with levetiracetam. At age 12, she presented diabetic ketoacidosis and functional insulin therapy was started; positive autoantibodies confirmed autoimmune etiology. Initial genetic testing performed by microarray analysis retrieved normal results, but exome sequencing revealed a heterozygous pathogenic variant in *KANSL1* gene, allowing for the diagnosis of Koolen-de Vries syndrome. In this patient, Koolen-de Vries syndrome presented initially as hypopituitarism and only later epilepsy. Afterwards, type 1 diabetes *mellitus* ensued, highlighting the complexity of intertwined conditions.

Keywords: Abnormalities, Multiple; Chromosomes, Human, Pair 17; Diabetes Mellitus; Hypopituitarism; Intellectual Disability/genetics

RESUMO

As doenças complexas resultam da interação entre fatores genéticos e ambientais. Apresentamos um caso de aparente coexistência de várias doenças complexas. Uma criança do sexo feminino foi referenciada aos 12 meses por má progressão estaturoponderal e hipotonia. A avaliação inicial revelou hipotiroidismo central, deficiência de hormona de crescimento e hipófise pequena com neuro-hipófise ectópica. A terapêutica de substituição melhorou o crescimento, mas foram surgindo atraso de desenvolvimento e estrabismo. Aos 10 anos, teve a primeira crise epilética sendo medicada com levetiracetam. Aos 12, apresentou-se com cetoacidose diabética iniciando insulinoterapia funcional; autoanticorpos positivos confirmaram a etiologia autoimune. O estudo inicial por *microarray* foi normal, mas a sequenciação do exoma revelou uma variante patogénica no gene *KANSL1*, levando ao diagnóstico de síndrome de Koolen-de Vries. Nesta doente, a apresentação foi inicialmente hipopituitarismo e mais tarde epilepsia. Posteriormente, surgiu diabetes *mellitus* tipo 1, ilustrando a complexidade deste caso.

Palavras-chave: Anormalidades Múltiplas; Cromossomos Humanos Par 17; Deficiência Intelectual/genética; Diabetes Mellitus; Hipopituitarismo

INTRODUCTION

Koolen-de Vries syndrome (KdVS; OMIM #610443) is a genetic syndrome characterized by congenital malformations, hypotonia, developmental delay and intellectual disability, and epilepsy.[1,2] Congenital malformations comprise structural brain anomalies, congenital heart defects, and renal and urologic anomalies. Patients can rarely present with endocrine alterations.[3] The syndrome is usually diagnosed in patients with typical clinical findings associated either with a heterozygous deletion at chromosome 17q21.31 encompassing the *KANSL1* gene in 60% of cases, a heterozygous intragenic pathogenic variant in 40% of cases, or an haploinsufficiency (whenever one of the copies of a gene is inactivated and the functional copy is not sufficient, not guaranteeing adequate production of the protein) of *KANSL1* due to chromosome rearrangements (less than 1%).[3,4]

Complex diseases are defined by the interference of different genetic and environmental factors, and the contribution of each factor is often hard to unravel.

CASE REPORT

A 12-month-old girl was referred to the outpatient clinic for growth failure and hypotonia. Family history was unremarkable. She was the first daughter of a healthy non-consanguineous couple.

Following an uneventful pregnancy, birth occurred at 40 weeks of gestation by vacuum delivery, with birth weight 3075 g (-0.35 SD), length 47 cm (-1.15 SD) and cranial perimeter 34.5 cm (+0.52 SD).

At the first visit, her weight was 8.055 kg (-1.6 SD) and her length 72 cm (-2.0 SD). Her growth chart showed a deflection of the length curve from five months on; at nine months, her growth was already at -2 SDS. Some dysmorphic features were noticed, namely a triangular face, prominent ears, as well as mild axial hypotonia.

Since a previous laboratory workup had revealed central hypothyroidism and growth hormone deficiency (IGF1 < 25 ng/mL), replacement therapy with levothyroxine had been started. In our first evaluation, she displayed normal

* Co-first authors.
1. Pediatric Endocrinology Unit. Hospital Dona Estefânia. Unidade Local de Saúde São José. Lisbon. Portugal.
2. Neuroradiology Unit. Hospital Dona Estefânia. Unidade Local de Saúde São José. Lisbon. Portugal.
3. Genetics Unit. Hospital Dona Estefânia. Unidade Local de Saúde São José. Lisbon. Portugal.
✉ **Autor correspondente:** Mafalda Félix Cabral. mafalda.cabral@ulssjose.min-saude.pt
Recebido/*Received*: 27/12/2024 - **Aceite/*Accepted*:** 17/06/2025 - **Publicado *Online*/*Published Online*:** 15/10/2025 - **Publicado/*Published*:** 02/12/2025

thyroid function. Cranial magnetic resonance imaging (MRI) showed a small pituitary gland with an ectopic neurohypophysis.

Replacement therapy with growth hormone was started at 16 months. The growth response was positive, with catch up growth from -2SDS to normal (Fig. 1); ACTH deficiency was suspected, with cortisol 3.2 ug/dL (reference range 3 - 21 ug/dL) and ACTH 11.3 pg/mL (reference range < 46 pg/mL), and as such, stress-dose hydrocortisone was prescribed.

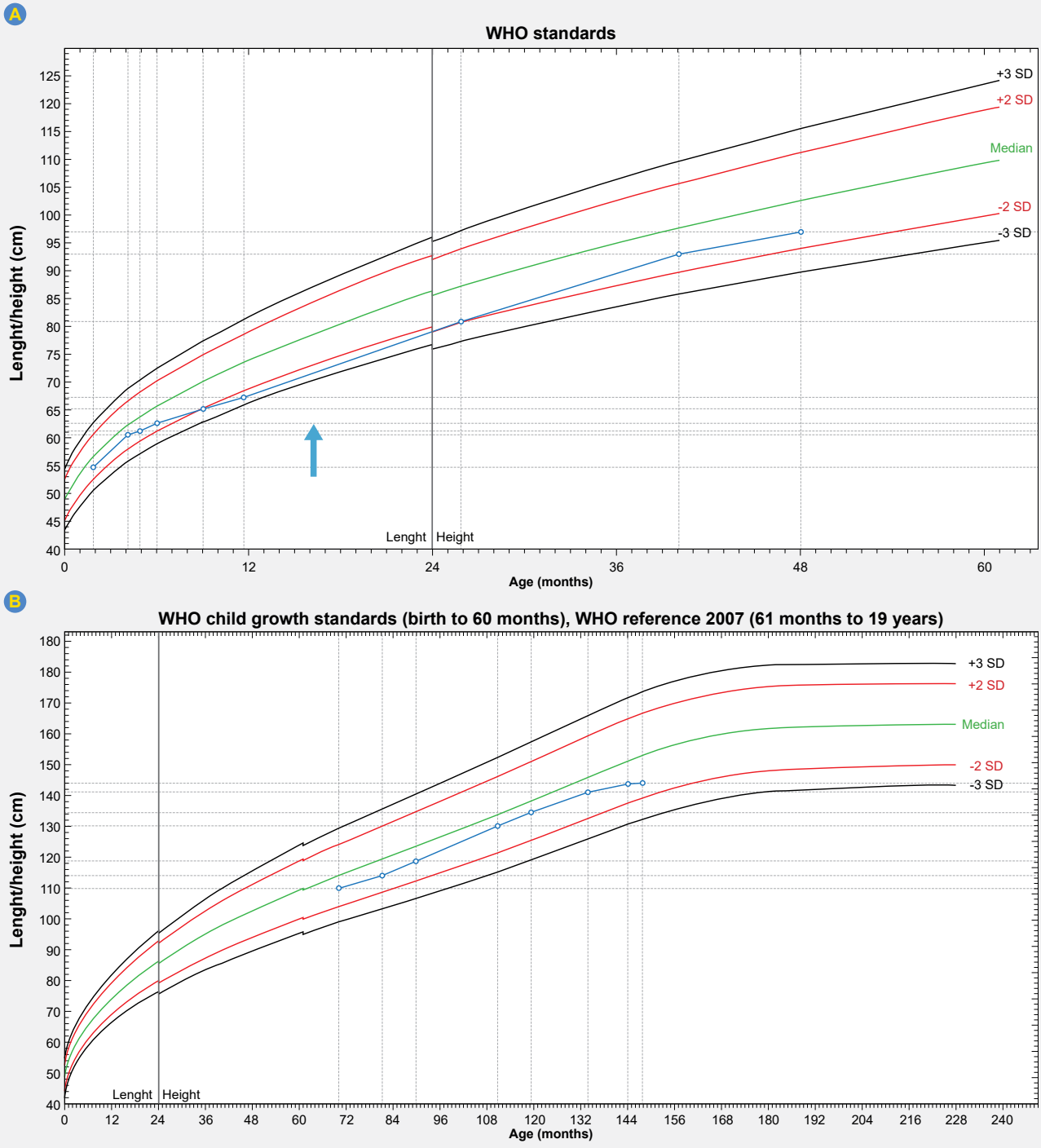


Figure 1 – Height charts showing a decline followed by catch up growth after the initiation of GH at 16 months (arrow). (A) Until 5 years (60 months). (B) From 5 years to present age.

During the third year of life, development delay and strabismus became apparent. At this time, she underwent molecular karyotyping, microarray, that did not reveal pathogenic copy number variants.

At the age of ten, she had a tonic-clonic seizure, starting anti-convulsive therapy, without further seizures. A cranial magnetic resonance imaging (MRI) was repeated, confirming a hypothalamic-pituitary malformation characterized by a thin pituitary stalk, ectopic neurohypophysis, ill-defined infundibular recess, hypertrophy of the interhypothalamic adhesion but revealing also mesencephalic-diencephalic dysplasia, corpus callosum dysgenesis, and inferior temporal dysgyria (abnormal gyral pattern in which the cortical surface is normally layered but the sulci course at unusual angles and depths) with slight alteration in hippocampal rotation (Fig. 2).

Comprehensive genetic testing through solo exome sequencing revealed a heterozygous *KANSL1* pathogenic variant which established the diagnosis of KdVS: *KANSL1* (NM_001193466.1) - c.(2666+1_2667-1)_(2724+1_2725-1) del.

Pediatric cardiology evaluation showed mitral valve prolapse with mild regurgitation, without hypertension; these findings are not usually associated with KdVS.

At the age of 12 years, she was observed at our emergency department due to vomiting, polydipsia, and polyuria. Laboratory evaluation showed: glycemia 423 mg/dL, high blood ketones, pH 7.18, bicarbonate 12.8, allowing for the diagnosis of diabetic ketoacidosis. Antibodies to glutamic acid decarboxylase, IA2 and insulin were positive, corroborating an autoimmune etiology.

Treatment with multiple daily insulin administration was started. Two months later, she changed to an automated insulin delivery pump. Now, eleven months after this diagnosis, excellent metabolic control has been achieved (time in range: 82%, HbA1c: 5.2%). The patient currently presents positive anti-thyroglobulin antibodies (294 IU/mL; Reference range < 115 IU/mL). The present height is 146.7 cm (-1.62 SD). She attends a regular school, although with an adapted curriculum.

DISCUSSION

First described in 2006, KdVS can present as early as the neonatal period, with hypotonia and feeding difficulties. While mild-to-moderate development delay is paramount, with speech and language particularly affected, progressive dysmorphic craniofacial features such as a broad nasal root and a large columella may appear. Central nervous system imaging often reveals structural abnormalities such as ventriculomegaly, corpus callosum hypoplasia, and Arnold-Chiari malformation.[3]

The present case presents not only the MRI features usually described in KdVS but also a less commonly described malformation, affecting both the pituitary and the hypothalamic region.[3,5,6] Even though very thin pituitary stalk and absent posterior neurohypophysis signal have been described by El Chehadeh-Djebbar *et al* in one case of KdVS, such a complex malformation involving the hypothalamic region has not been reported to the best of our knowledge.[7] Interestingly, while both cases display the commonly found corpus callosum hypoplasia, none featured optic nerve abnormalities that would suggest septo-optic dysplasia.

Koolen-de Vries syndrome is typically caused by a 17q21.31 deletion encompassing the NSL regulatory complex subunit 1 gene *KAT8* (*KANSL1*) or a point variant in the *KANSL1* gene. Molecular genetic testing approaches may include a combination of microarray, a multigene panel, and more comprehensive genomic testing. Penetrance is reported to be 100%.[3] The identified variant has not been previously described to the best of our knowledge. Parental segregation studies are warranted, such as genetic counseling, in order to better characterize recurrence risks.

Endocrine alterations such as hypothyroidism, hypopituitarism, primary adrenal insufficiency, and precocious

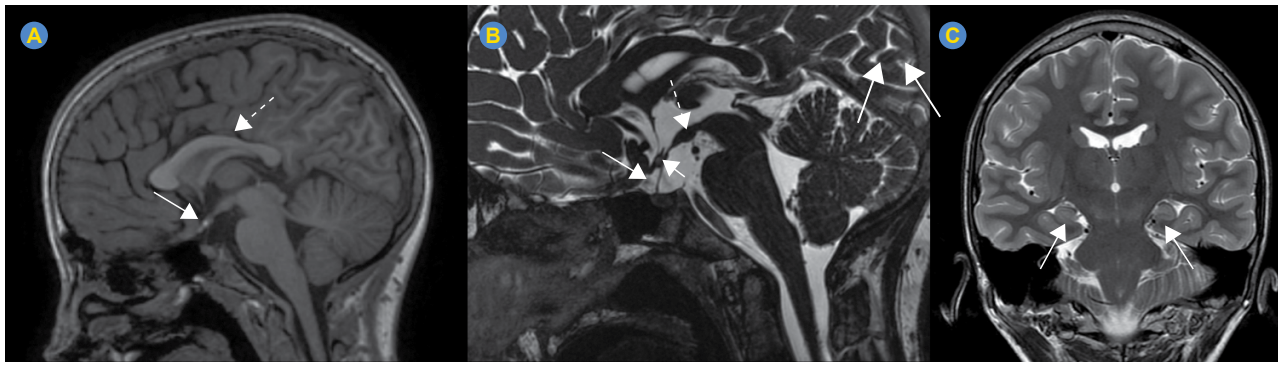


Figure 2 – Structural brain anomalies. (A) Sagittal T1 weighted image. (B) Sagittal volumetric T2 weighted image. (C) Coronal T2 weighted image. Hypothalamic-pituitary malformation characterized ectopic neurohypophysis (arrow in A), thin pituitary stalk (arrow in B), ill-defined infundibular recess (small arrow in B), hypertrophy of the interhypothalamic adhesion (dashed arrow in B); corpus callosum dysgenesis (dashed arrow in A); slight alteration in hippocampal rotation (arrows in C).

puberty have previously been described in KdVS, albeit infrequently (< 10%),[3,6] but, to our knowledge, only one patient with both type 1 diabetes and KdVS has been described.[8] Even though no causality can be established, these are not the only reports of immune disruption associated with the syndrome. *KANSL1* may be a gene that interferes in immune-response gene expression, being in a structurally complex genomic region.[9] Vitiligo, Addison and celiac diseases have also been described, and it has been hypothesized that autoimmunity may play a role in KdVS.[6,10,11]

While debate ensues on whether these diagnoses are pathogenically associated, our patient and her family face multiple difficulties, resulting from dealing with the consequences of complex diseases, namely hypopituitarism, development delay, and type 1 diabetes *mellitus*. Further investigation is warranted for a deeper understanding of the mechanisms and interactions of these entities, allowing for more precise and targeted treatment.

PREVIOUS AWARDS AND PRESENTATIONS

Presented as a poster at the 62nd Annual ESPE Meeting (ESPE 2024).

AUTHOR CONTRIBUTIONS

MFC: Writing of the manuscript.

FBC, DA, LL: Critical review of the manuscript.

CC: Data analysis, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PARENTAL CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Koolen DA, Vissers LE, Pfundt R, de Leeuw N, Knight SJ, Regan R, et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. Nat Genet. 2006;38:999-1001.
2. Colin F, Burger P, Mazzucotelli T, Strehle A, Kummeling J, Collot N, et al. GenIDA, a participatory patient registry for genetic forms of intellectual disability provides detailed caregiver-reported information on 237 individuals with Koolen-de Vries syndrome. Genet Med Open. 2023;1:100817.
3. Koolen DA, Morgan A, de Vries BBA. Koolen-de Vries syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A. GeneReviews. Seattle: University of Washington; 2023.
4. Koolen DA, Pfundt R, Linda K, Beunders G, Veenstra-Knol HE, Conta JH, et al. The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a KANSL1 sequence variant. Eur J Hum Genet. 2016;24:652-9.
5. Myers KA, Mandelstam SA, Ramantani G, Rushing EJ, de Vries BB, Koolen DA. The epileptology of Koolen-de Vries syndrome: electro-clinico-radiologic findings in 31 patients. Epilepsia. 2017;58:1085-94.
6. Karamik G, Tuysuz B, Isik E, Yilmaz A, Alanay Y, Sunamak EC, et al. The clinical phenotype of Koolen-de Vries syndrome in Turkish patients and literature review. Am J Med Genet A. 2023;191:1814-25.
7. El Chehadeh-Djebbar S, Callier P, Masurel-Paulet A, Bensignor C, Méjean N, Payet M, et al. 17q21.31 microdeletion in a patient with pituitary stalk interruption syndrome. Eur J Med Genet. 2011;54:369-73.
8. Ahmadov GA, Govender D, Atkinson MA, Sultanova RA, Eubova AA, Wasserfall CH, et al. Epidemiology of childhood-onset type 1 diabetes in Azerbaijan: Incidence, clinical features, biochemistry, and HLA-DRB1 status. Diabetes Res Clin Pract. 2018;144:252-9.
9. Fejzo MS, Chen HW, Anderson L, McDermott MS, Karlan B, Konecny GE, et al. Analysis in epithelial ovarian cancer identifies KANSL1 as a biomarker and target gene for immune response and HDAC inhibition. Gynecol Oncol. 2021;160:539-46.
10. Lobo Y, Wheller L. Vitiligo in a 9-year-old girl with Koolen-de Vries syndrome. Dermatol Online J. 2021;27:13030/qt05c1k2tc.
11. Maley AM, Spraker MK, de Vries BB, Koolen DA. Vitiligo in the Koolen-de Vries or 17q21.31 microdeletion syndrome. Clin Dysmorphol. 2015;24:86-7.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Scalloped Tongue as a Manifestation of Light Chain Amyloidosis in Multiple Myeloma

Língua Dentada como Manifestação da Amiloidose por Cadeias Leves no Mieloma Múltiplo

Javier Josue FLORES-MAMANI [1,2], Yoel David GUTIERREZ-AYALA [2], Aleida Belen FLORES-LUQUE [1,2]
Acta Med Port 2025 Dec;38(12):812-813 ▪ https://doi.org/10.20344/amp.23416

Keywords: Immunoglobulin Light-chain Amyloidosis; Macroglossia; Multiple Myeloma; Tongue Diseases
Palavras-chave: : Amiloidose de Cadeia Leve de Imunoglobulina; Doenças da Língua; Macroglossia; Mieloma Múltiplo

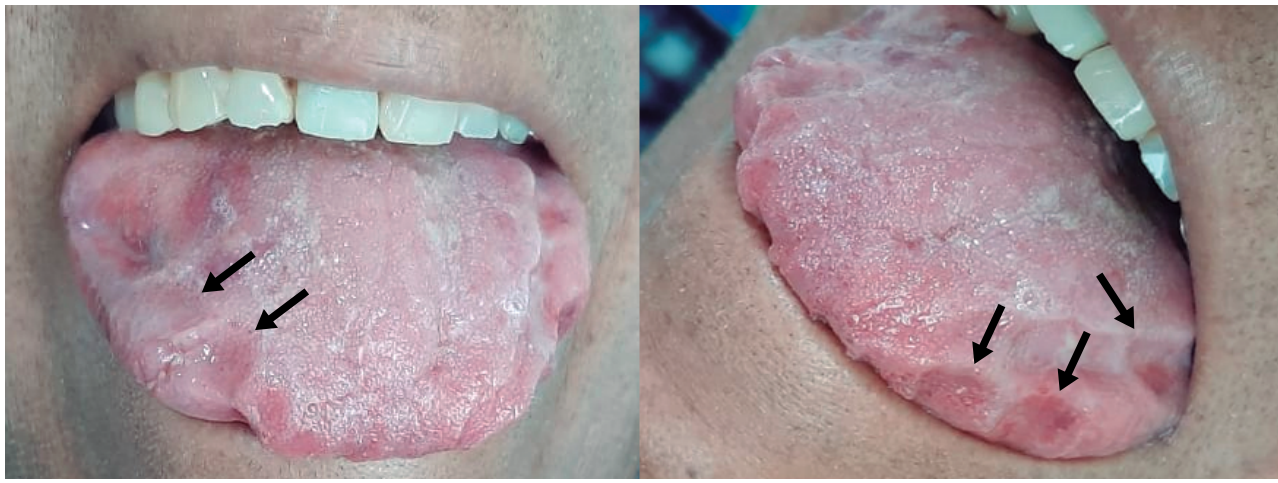


Figure 1 – Diffuse macroglossia with a dry, rough surface and scalloped lateral borders due to pressure from adjacent teeth (A). Close-up view highlighting prominent tongue indentations (arrows) and exaggerated scalloping along the edges (B).

A 58-year-old male patient with a diagnosis of multiple myeloma (MM) confirmed by bone marrow biopsy presented with a two-month history of unintentional weight loss. Physical examination revealed macroglossia with scalloped borders (Fig. 1). Given the high clinical suspicion of primary light chain amyloidosis (AL), a tongue biopsy was requested.

Amyloidosis usually presents as a systemic disease secondary to MM, which is associated with the overproduction of abnormal immunoglobulin light chain due to the presence of abnormal plasma cells.[1,2] It is a rare disease characterized by the deposition of abnormal protein (amyloid) in various organs.

Oral involvement is uncommon (< 9%), and may present with nodules, papules, plaques, macroglossia, and changes in mucosal color. Macroglossia leads to constant pressure against the inner surfaces of the teeth, creating indentations along the tongue's edges (scalloped tongue). Diagnosis is confirmed through biopsy and "Congo red" staining, which reveals amyloid deposits.[2-5]

ACKNOWLEDGEMENTS

The authors used OpenAI's ChatGPT-4 to assist with grammar and language polishing. All scientific content and conclusions are the authors' own; the authors reviewed and accept responsibility for the final text.

AUTHOR CONTRIBUTIONS

JJFM: Writing of the manuscript.
YDGA, ABFL: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

1. Instituto Académico Científico Quispe-Cornejo. La Paz. Bolivia.
2. Medical School. Universidad Mayor de San Andrés. La Paz. Bolivia.
✉ **Autor correspondente:** Javier Josue Flores-Mamani. jav00jos@gmail.com
Recebido/*Received*: 23/05/2025 - **Aceite/*Accepted*:** 14/08/2025 - **Publicado/*Published*:** 02/12/2025

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Georgin-Lavialle S, Grateau G. Aspects cliniques des amyloses systémiques en 2024. Ann Pathol. 2024;44:407-13.
2. Pontes FS, Ferreira GB, Fonseca FP, Ribeiro TF, Caldeira PC, Tavares TS, et al. Oral amyloidosis: an update. Med Oral Patol Oral Cirugia Bucal. 2023;28:e341-6.
3. Dissanayaka DW, Bandara HM, Sabesan T, Mohomed YS, Siriwardena BS. Oral manifestations of systemic amyloidosis, an aid to diagnosis of multiple myeloma – report of two cases. Braz J Otorhinolaryngol. 2022;88:146-9.
4. Tao Y, Qiu X, Ye F, Liao Z, Wu P. Amyloidosis of the tongue: a rare case report. Braz J Otorhinolaryngol. 2023;89:101286.
5. Sadaksharam J, Priya S, Subramaniam S, Muralidharan A. Oral manifestations of amyloidosis in a multiple myeloma patient: a case report. Acta Marisiensis Ser Med. 2023;69:131-4.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Recomendações de Vacinação no Doente Adulto Imunocomprometido

Vaccination Recommendations for the Immunocompromised Adult Patient

Cândida ABREU[1,2], Susana PERES[3,4], Flávia CUNHA[1], Joana MIRANDA[5], Cláudio NUNES-SILVA[1,2], André SILVA-PINTO[1,2], Lúcia RIBEIRO-DIAS[1,2], Joaquim OLIVEIRA[6]
Acta Med Port 2025 Dec;38(12):814-827 ▪ https://doi.org/10.20344/amp.22966

RESUMO

O manuscrito reúne indicações de vacinação para adultos imunocomprometidos com base nas recomendações das principais instituições de referência internacional. Estes indivíduos apresentam maior vulnerabilidade a doenças infeciosas preveníveis por vacinas e a proteção vacinal é frequentemente inferior à dos imunocompetentes. Por isso, é importante avaliar a resposta à vacina (serológica ou outra) sempre que possível. Salienta-se a importância de adaptar a vacinação ao *net state of immunosuppression* precedida por avaliação cuidadosa do risco, indicações, contraindicações e momento ideal de administração. Sempre que possível, a vacinação deve ser efetuada antes do início da imunossupressão farmacológica, antes de esplenectomia ou antes de receber um transplante de órgão sólido. Os imunocomprometidos são categorizados em grupos como: portadores de doenças inflamatórias imunomoduladas, esplenectomizados, recetores de transplantes de órgãos sólidos ou hematopoiéticos, indivíduos com infeção por HIV e aqueles com imunodeficiências congénitas (erros inatos) e são detalhadas as indicações de vacinação em diferentes situações clínicas e tipos de imunossupressão. Abordam-se as vacinas para doenças virais respiratórias como gripe, COVID-19, vírus sincicial respiratório, as vacinas da hepatite A e B, varicela-zoster e a proteção vacinal contra bactérias encapsuladas como pneumococos, meningococos e *Haemophilus influenzae*. Incluem-se ainda algumas recomendações de vacinação em contexto de viagem e profilaxia pós-exposição para situações de elevado risco. Aborda-se a vacinação dos conviventes e dos profissionais de saúde para proteção adicional. Destaca-se que a evolução das vacinas e das recomendações vacinais obriga a uma atualização constante.
Palavras-chave: Hospedeiro Imunocomprometido; Recetores de Transplante; Vacinação; Vacinas

ABSTRACT

The manuscript collates indications for vaccination in immunocompromised adults based on recommendations from leading international institutions. These individuals have increased vulnerability to vaccine-preventable infectious diseases, and their immune response to vaccination is often weaker than that of immunocompetent individuals. Therefore, whenever possible, it is important to assess vaccine response (serological or other). Emphasis is placed on adapting vaccination to the net state of immunosuppression, following a careful evaluation of risks, indications, contraindications, and the optimal timing for administration. Whenever feasible, vaccination should be carried out before the initiation of pharmacological immunosuppression, prior to splenectomy, or before receiving a solid organ transplant. Immunocompromised individuals are categorised into groups such as those with immune-mediated inflammatory diseases, individuals who have undergone splenectomy, recipients of solid organ or haematopoietic transplants, people living with HIV, and those with congenital immunodeficiencies (inborn errors). The article describes vaccination recommendations for different clinical scenarios and types of immunosuppression. Vaccines against respiratory viral diseases, including influenza, COVID-19, and respiratory syncytial virus, as well as hepatitis A and B, varicella-zoster, and vaccines protecting against encapsulated bacteria such as pneumococci, meningococci, and *Haemophilus influenzae*, are discussed. Some vaccination recommendations in the context of travel and post-exposure prophylaxis in high-risk situations are included. The article also addresses the importance of vaccinating household contacts and healthcare professionals for additional protection. Finally, it highlights that ongoing advancements in vaccines and vaccination guidelines require continuous updates.
Keywords: Immunocompromised Host; Transplant Recipients; Vaccination; Vaccines

INTRODUÇÃO

Os adultos imunocomprometidos (AIC) enfrentam um risco mais elevado de morbimortalidade por doenças infeciosas que podem ser prevenidas por vacinação. Por isso, é essencial imunizar esta população, precedida por uma avaliação cuidadosa e personalizada do risco de doença, das indicações vacinais, de eventuais contraindicações e do momento mais adequado para a sua administração. É também essencial a vacinação dos conviventes e familiares próximos.

A vacinação não substitui outras medidas preventivas não vacinais, como a evicção do contacto com o agente infecioso, onde se incluem métodos de barreira, higiene alimentar e etiqueta respiratória.

Existem algumas recomendações internacionais com indicações genéricas de vacinação em adultos com compromisso imunitário, nomeadamente dos Estados Unidos da América (EUA),[1] Canadá,[2] Austrália[3] e Nova Zelândia.[4] No entanto, a nível nacional, essas recomendações não foram desenvolvidas.

O presente documento constitui uma revisão da evidência disponível e das orientações atuais de vacinação para cada grupo de doentes com imunodisfunção, assim

1. Serviço de Doenças Infeciosas. Unidade Local de Saúde São João. Porto. Portugal.
2. RISE-Health. Departamento de Medicina. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
3. Serviço de Infecciologia e Medicina Tropical. Departamento de Medicina. Unidade Local de Saúde de Lisboa Ocidental. Lisboa. Portugal.
4. NOVA Medical School. Universidade NOVA de Lisboa. Lisboa. Portugal.
5. Serviço de Imunoalergologia. Unidade Local de Saúde São João. Porto. Portugal.
6. Serviço Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
✉ **Autor correspondente:** Cândida Abreu. candida.abreu@gmail.com
Recebido/*Received*: 13/03/2025 - **Aceite/*Accepted*:** 02/06/2025 - **Publicado *Online*/*Published Online*:** 02/12/2025

considerados pessoas:

- com patologia inflamatória imunomodulada;
- esplenectomizadas;
- recetoras de transplante de órgão sólido;
- recetoras de transplante de progenitores hematopoiéticos;
- com infeção pelo vírus da imunodeficiência humana (VIH);
- com erros inatos da imunidade.

Pretende-se que este seja um manuscrito de fácil consulta pelos médicos que acompanham os AIC, não podendo esquecer as frequentes atualizações nas indicações e introdução de novas vacinas, que requerem um conhecimento do 'estado-da-arte'.

Incluem-se ainda recomendações vacinais em situação de viagem, mas exclui-se da discussão o esquema vacinal do Programa Nacional de Vacinação (PNV), pressupondo o seu cumprimento de acordo com as recomendações da Direção-Geral da Saúde (DGS).[5]

Imunodisfunções

As imunodisfunções primárias são as que são intrínsecas ao sistema imunitário; as secundárias, as que são adquiridas por condições várias que afetam, e usualmente deprimem, a resposta imunológica.[1-3]

As imunodisfunções primárias são condições congénitas, causadas por mutações várias, que impactam linhagens de células imunitárias, como a imunodeficiência combinada grave e a imunodeficiência comum variável, que condicionam graus variáveis de hipogamaglobulinemia. As imunodisfunções secundárias afetam doentes sob o uso de medicação imunossupressora/imunomoduladora, com neoplasias hematológicas, recetores de transplante sólido e hematopoiético, doentes com asplenia funcional ou anatómica e infetados por VIH.[3]

Nas imunodeficiências primárias a alteração é usualmente vitalícia. Nas imunodeficiências secundárias a imunodisfunção pode ser reversível (no caso da infeção por VIH tratada), ou limitada no tempo (pela suspensão dos imunossupressores ou por remissão da doença hematológica, por exemplo).

Outras condições concorrem e podem impactar a imunodisfunção:

- diabetes *mellitus*,[6] particularmente quando mal controlada;
- insuficiência renal crónica[7];
- idade avançada e imuno-senescência associada[8];
- desnutrição acentuada.

No seu conjunto estes fatores englobam o conceito de '*net state of immunosuppression' – vide* Tabela 1 do Apêndice 1 (Apendice_01.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15821).[9]

Imunização em doentes imunocomprometidos

A proteção contra doenças infeciosas pode ocorrer de forma natural, pelo contacto com o agente infecioso (imunização natural), ou por administração de vacinas, imunoglobulinas ou anticorpos monoclonais.

Consideram-se dois tipos de imunização: passiva e ativa.

A imunização passiva refere-se à utilização de imunoglobulinas ou de anticorpos monoclonais, que oferecem proteção por tempo limitado[3] e são utilizadas quando o indivíduo não tem capacidade de resposta imunológica à vacina, em associação com a vacina (proteção de tétano e de raiva), ou ainda em casos de contraindicação à vacinação.

A imunização ativa implica a administração de vacinas que mimetizam a infeção natural por um agente patogénico e estimulam o desenvolvimento de uma resposta imune (com produção de anticorpos e células T de memória), que providencia proteção contra agentes infeciosos.

Vacinas vivas atenuadas e vacinas inativadas

A constituição da vacina permite a sua classificação como 'vacina viva atenuada' quando incorpora microrganismos vivos atenuados, ou 'inativada' quando esses microrganismos estão mortos ou são apenas partículas deles (vacinas subunitárias).[2]

No âmbito das vacinas inativadas consideram-se as vacinas recombinantes; estas utilizam tecnologia recombinante de DNA e permitem a constituição de um vírus atenuado para o fabrico de vacinas, tendo a vantagem de que a reversão para o vírus selvagem é virtualmente impossível. Esta tecnologia pode também ser utilizada para produzir partículas virais com potencial imunogénico, utilizadas na vacina da hepatite B e do papilomavírus humano (HPV). Consideram-se ainda as vacinas de ácido ribonucleico, as vacinas de mRNA, e as vacinas vetoriais – *vide* Tabela 1.

Vacinas no doente imunocomprometido

A administração de uma vacina viva atenuada pode permitir a multiplicação do microrganismo vacinal no indivíduo quando este tem um compromisso grave da imunidade e, por isso, é normalmente contraindicada a sua administração nestas situações. A exceção são as vacinas vivas não replicantes, (p.ex., vacina contra Mpox)[10] que não são contraindicadas nos doentes imunocomprometidos.

No caso de doentes com doença inflamatória imunomediada, não há evidência de que a administração de vacinas aumente o risco de atividade da doença de base.[11-13] Contudo, em duas séries de doentes com doença inflamatória reumatismal, foram descritas exacerbações de doença base após a vacina recombinante da zona.[14,15]

Na imunossupressão iatrogénica de baixa dose, de uma forma geral, as vacinas vivas atenuadas não são

Tabela 1 – Tipos de vacinas[1-3]

Tipologia	Exemplos
Vacinas vivas atenuadas	BCG
	Sarampo, parotidite epidémica e Rubéola
	Varicela
	Poliomielite oral
	Rotavírus Influenza (gripe) – administração nasal
	Febre amarela
	Febre tifoide oral Dengue Mpox (não replicante)
Vacinas inativadas (inativadas, mortas, subunitárias ou, recombinantes)	Poliomielite intramuscular
	Pneumocócica conjugadas (Pn13, Pn 15 e Pn20) e polissacarídica (Pn23)
	Meningocócica conjugada (C; ACYW135)
	Haemophilus influenzae
	Tétano
	Difteria
	Pertussis
	Hepatite A
	Hepatite B
	Papilomavírus humano
	Recombinante do zoster
	Influenza (gripe)
	Recombinante do vírus sincicial respiratório (bivalente)
	Recombinante do vírus sincicial respiratório (adjuvada)
	COVID-19 (mRNA, recombinante adjuvada)

Mpox: vacina contra o vírus *Monkeypox*; Pn 13 e Pn 20: vacina pneumocócica conjugada respetivamente 13 valente e 20 valente; Pn 23: vacina pneumocócica polissacarídea 23 valente; Meningococica conjugada (C, ACWY): vacina contra o serogrupo C e vacina quadrivalente contra os serogrupo ACWY; COVID-19 (mRNA e vetorial): vacina contra a COVID-19 baseada em RNA mensageiro e vacina COVID recombinante adjuvada (Nuvaxovid®)

contraindicadas, devendo ser considerada a sua administração caso a caso. São consideradas doses baixas de terapêutica imunossupressora[16]:

- prednisolona < 20 mg/dia ou equivalente, curta/longa duração ou dias alternados;
- substituição de glucocorticoides na insuficiência adrenal;
- corticoides tópicos ou injeção intra-articulares, intra-bursa ou intra-tendão;
- metotrexato < 0,4 mg/kg/semana ou < 20 mg/semana;
- azatioprina < 3 mg/kg/dia;
- mercaptopurina < 1,5 mg/kg/dia.

As vacinas inativadas não são contraindicadas, mas podem conferir menor proteção do que a infeção natural nos indivíduos com algum tipo de imunodepressão. Nalgumas circunstâncias, quando não há resposta humoral e/ou celular à estimulação imunitária (medicação com anti-CD20, défices imunitários congénitos com atingimento da imunidade humoral e celular), as vacinas podem não desencadear resposta e serem, por isso, inconsequentes ou fúteis.

As vacinas são naturalmente contraindicadas se previamente houver uma reação anafilática à sua administração ou a um dos seus componentes e, tal como nos hospedeiros não imunocomprometidos, devem ser adiadas na presença de febre.

Resposta vacinal

Os diferentes tipos de imunodepressão condicionam diferentes graus de disfunção imune e, consequentemente, de resposta às vacinas.

Recentemente, uma revisão de revisões sistemáticas sobre vacinação em imunocomprometidos[17] considerou globalmente três grandes grupos, de acordo com a resposta vacinal expectável comparada com a resposta vacinal de adultos saudáveis:

I. Regular (probabilidade de resposta de cerca de 60%): doença renal crónica sob hemodiálise ou diálise peritoneal, infeção por VIH com contagem normal de linfócitos TCD4, doenças inflamatórias imunomediadas, (sob terapêutica imunomoduladora), pós-esplenectomia e tumores sólidos;
II. Intermédia (40% - 60%): doentes a fazer terapêuticas anti-CTLA-4, neoplasias hematológicas e infeção por VIH com contagem baixa de linfócitos TCD4);
III. Fraca (≤ 40%): doentes sob agentes depletores de células B (terapêuticas anti-CD20), recetores de transplante de células hematopoiéticas, cirrose hepática e recetores de transplante de órgãos sólidos sob terapêutica imunossupressora.

Avaliação da resposta vacinal

A avaliação da resposta vacinal pode ser complexa. A resposta humoral é determinada pela deteção e quantificação de anticorpos protetores (sendo norma na vacinação da hepatite B). Contudo, essa avaliação não é generalizada a todas as vacinas e, em alguns casos, só se faz em alguns laboratórios (p. ex., na determinação de anticorpos pós vacinação da febre amarela, do tétano e da raiva). Noutros casos, não há um título de anticorpos que seja seguramente considerado protetor (p. ex., vacina da hepatite A).

Já a avaliação da imunidade celular exige mecanismos mais complexos de determinação laboratorial e habitualmente só é efetuada em estudos de investigação.[18]

Nos indivíduos mais imunodeprimidos deve considerar-se: o controle da seroconversão (se possível); doses de reforço de vacinação; ou ainda a imunização passiva convencional por anticorpos ou anticorpos monoclonais de longa duração.

Momentos de vacinação

Para majorar a resposta à vacinação e mitigar o risco de doença por estirpe vacinal associado à administração de vacinas vivas, esta deve ser efetuada, idealmente, na altura de menor imunodepressão, em fase de estabilidade clínica do doente,[19] e antes do início da terapêutica imunossupressora/imunomoduladora.

Vacina viva atenuada

Deve ser administrada pelo menos quatro semanas antes de iniciar o fármaco imunossupressor ou o transplante; nos casos em que a administração se faz após paragem do imunossupressor, devem ser respeitados os tempos que permitem garantir a sua segurança e eficácia.

No geral, é considerado adequado para vacinar, esperar o tempo de cinco semi-vidas após administração de agentes biológicos ou fármacos modificadores da doença (DMARD) para vacinar. Contudo, há fármacos cuja ação imunossupressora se estende para além disso – *vide* Tabela 2 do Apêndice 1 (Apendice_01.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15821).

Vacina inativada

Deve ser administrada, idealmente, pelo menos, duas semanas antes do início dos imunossupressores/imunomoduladores ou do transplante.[19]

Vacinas vivas atenuadas e prova de tuberculina

Estas vacinas podem interferir com a resposta à prova tuberculínica, que por isso deverá ser inoculada no mesmo dia da vacina; caso não seja possível, a prova de tuberculina deve ser realizada quatro a seis semanas depois da administração da vacina.[20]

Vacinas e administração de imunoglobulina humana normal

A imunoglobulina humana normal (IVIG) pela sua ação imunológica e antimicrobiana (com neutralização de toxinas, opsonização e lise mediada pelo complemento) pode afetar a eficácia das vacinas vivas atenuadas – como foi determinado na vacina contra o sarampo. Apesar de este efeito não ter sido estudado na vacina da rubéola, parotidite epidémica e varicela, as recomendações são idênticas. Esta interação não está prevista para outras vacinas vivas, como a vacina da febre amarela e a da tifoide oral.[1]

Desta forma, o intervalo de tempo de IVIG até à vacinação contra o sarampo, parotidite epidémica e rubéola (VASPR) é de oito a 11 meses, sendo variável de acordo com a dose de IVIG: se 400 mg/kg deve-se aguardar oito meses para vacinar, se 1000 mg/kg 10 meses e se 2000 mg/kg deve-se aguardar 11 meses.[1] Em circunstâncias em que existe um risco elevado de uma doença prevenível por vacina é aceitável a sua administração antes de completar o intervalo estabelecido. Nestas situações alguns autores sugerem determinação do título de anticorpos seis meses após a suspensão de IVIG, para avaliar a resposta à vacinação, ou, em alternativa, revacinar.[1]

A interação entre a IVIG e vacinas inativadas assume-se como reduzida, pelo que podem ser administradas antes, em simultâneo (locais anatómicos diferentes) ou depois da administração de IVIG.[1]

Profilaxia pós exposição

No caso dos doentes gravemente imunodeprimidos suscetíveis (não vacinados e sem imunidade natural), a profilaxia pós-exposição (PPE) é frequentemente recomendada.

São exemplos de PPE para os vírus: varicela-zoster,

influenza, COVID-19, hepatite B, sarampo, raiva e também para as bactérias *Clostridium tetani* e *Neisseria meningitidis*. A PPE pode ser feita com antimicrobianos, vacinação e/ou imunização passiva,[21] ou com anticorpos monoclonais (COVID-19). Nas situações em que a vacina viva de varicela é contraindicada, a imunoglobulina anti-varicela-zoster e/ou a profilaxia com aciclovir devem ser administradas.[22] Alguns peritos recomendam fazer profilaxia com aciclovir até 800 mg cada oito horas por sete dias, iniciando entre sete a 10 dias após a exposição.[23]

No caso do tétano, raiva e hepatite B a PPE a imunoglobulina associa-se à vacinação.[5]

Vacinação de familiares e conviventes próximos

Os coabitantes/contactos próximos e os profissionais de saúde que estão envolvidos nos cuidados aos AIC devem estar imunizados de acordo com o PNV, e ser vacinados anualmente contra a gripe.[5,24]

As vacinas inativadas podem ser administradas aos conviventes sem contraindicações ou precauções específicas.[5,24]

Relativamente às vacinas vivas:

- a vacina oral contra a poliomielite viva atenuada (VAP) está contraindicada;
- a vacina contra a varicela é recomendada nos conviventes não imunes de AIC, sendo que nas seis semanas após a vacinação deve ser evitado o contacto próximo com o AIC. A transmissão de vírus vacinal dos imunocompetentes para contactos próximos suscetíveis tem sido ocasionalmente documentada nos vacinados que desenvolvem exantema, mas o risco é muito baixo.[25] Se um contacto após a vacina desenvolver vesícula/bolha no local da inoculação existe risco de transmissão, devendo-se isolar o AIC e, segundo alguns autores, tratar com imunoglobulina específica profilática, (dose única 125 IU/10 kg de peso num máximo de 625 IU, idealmente nas 96 horas após exposição até aos 10 dias) e concomitantemente tratar a fonte de exposição com antivírico.[26,27] Quando a imunoglobulina especifica de varicela-zoster não existir, pode considerar-se administrar uma dose única de imunoglobulina intravenosa na dose de 400 mg/kg. Os doentes suscetíveis à varicela a fazer imunoglobulina de substituição não precisam de fazer imunoglobulina específica[25];
- a vacina contra rotavírus pode ser administrada a crianças que sejam contactos próximos de doentes transplantados ou imunodeprimidos, devendo estes evitar prestar cuidados de higiene à criança nas quatro semanas após a vacinação; os cuidadores da criança, após muda de fralda, devem higienizar as mãos com solução alcoólica a 70%;
- a VASPR e vacina do bacilo Calmette-Guérin (BCG) podem ser administradas sem contraindicações ou precauções.

PATOLOGIA INFLAMATÓRIA IMUNOMEDIADA

Os doentes com patologia imunomediada, incluindo autoimune, inflamatória e desmielinizante, apresentam risco acrescido de complicações infeciosas, maioritariamente infeções ligeiras a moderadas por agentes microbianos comuns da comunidade e, mais raramente, infeções graves e oportunistas.

O risco individual de infeção está estruturado no conceito de '*net state of immunosupression*', que engloba o regime farmacológico e fatores do próprio, como imunosenescência, comorbilidades, grau de atividade da doença de base, atingimento sistémico, pulmonar e/ou renal.[28]

O tratamento das patologias imunomediadas tem subjacente a utilização de fármacos imunomoduladores cujo mecanismo de ação está assente no conceito *'treat to target'*, por ação direta em elementos chave da normal homeostasia imunológica ou do controlo do ciclo celular, incluindo de células do sistema imunológico, envolvidos na patogenia.[29]

O impacto imunológico da terapêutica varia com fatores genéticos que condicionam a resposta inata e adaptativa, e o metabolismo do fármaco em causa.[28] Acrescenta-se que na patologia imunomediada as associações de fármacos e a sequenciação terapêutica são comuns, pelo que a mensuração do risco de infeção atribuível a determinado fármaco é difícil.

Desta forma, está recomendada a revisão e planeamento vacinal precoces, tendo em consideração a idade e comorbilidades, exposição de risco, plano de viagens, e plano previsto de tratamento imunossupressor/imunomodulador.[19]

Imunossupressão moderada/grave

É considerada imunodepressão moderada/grave a administração de[30,31]:

- terapêutica com corticosteroides sistémicos com prednisolona (ou equivalente) ≥ 20 mg/dia durante > 2 semanas;
- fármacos associados a depleção linfocitária B e/ou T (anti-CD20, fingolimod, siponimod, ozanimod, cladribina, anti-CD52);
- agentes alquilantes (ciclofosfamida);
- inibidores da calcineurina;
- micofenolato de mofetil;
- leflunomida;
- inibidores do anti-TNF alfa;
- inibidores IL-6 e da IL-1;
- inibidores das Janus cinases;
- inibidores da co-estimulação;

- antimetabolitos em dose elevada (azatioprina ≥ 3 mg/kg/dia ou metotrexato ≥ 0,4 mg/kg/semana ou ≥ 20 mg/semana).[32]

Já a imunossupressão associada a eculizumab e ravulizumab (inibidores do fator 5 do complemento) é considerada grave apenas para *N. meningitidis* e moderada para outros agentes encapsulados.[33]

Imunossupressão ligeira ou mínima

Os inibidores do eixo IL-17/IL-23, assim como omalizumab (inibidor IgE) estão associados a imunossupressão minor.[33] Sendo que alguns fármacos, como o vedolizumab, estão associados a imunossupressão seletiva por atuarem em locais anatómicos particulares.[32]

Moléculas como mepolizumab e respolizumab (inibidores da IL-5) não estão associadas a aumento do risco de infeção.[33]

Em qualquer cenário a associação de fármacos resulta no aumento de imunossupressão e risco de infeção, aspeto que deve ser considerado na decisão para administração de vacinas.[32]

Momento para vacinação – *vide* introdução

A semivida farmacológica de agentes biológicos e de DMARDS não biológicos e a farmacocinética dos fármacos são indicadores importantes para o tempo de espera recomendado para a administração de vacinas vivas atenuadas [Tabela 2 do Apêndice 1 (Apendice_01.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15821)].

A proteção vacinal desejável de acordo com o(s) fármaco(s) imunomodulador(es) e biológico(s) em utilização encontra-se detalhada na Tabela 1 do Apêndice 2 (Apendice_02.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15822) e os esquemas de vacinação preconizados para cada vacina encontram-se expressos na Tabela 2 do Apêndice 2 (Apendice_02.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15822).

ESPLENECTOMIZADOS

A ausência (asplenia) ou diminuição da função (hipossplenia) do baço leva a uma maior predisposição para infeções graves, sobretudo por bactérias encapsuladas, tais como *Streptococcus pneumoniae, Haemophilus influenzae e Neisseria meningitidis*.[34] Está ainda documentado um risco superior de infeção por bacilos gram negativo, como *Capnocytophaga canimorsus* após mordedura de animal, ou no pós-operatório imediato, e por parasitas protozoários intracelulares.[35]

A esplenectomia é o principal motivo de asplenia. Pode haver asplenia congénita ou hipossplenia secundária a condições médicas como lúpus eritematoso e doença inflamatória intestinal.[36] Para além disso, o baço tem a sua função diminuída nos extremos de idade: na infância por imaturidade do sistema imune; e nos idosos por atrofia da celularidade folicular.[37]

Nos doentes esplenectomizados, o risco de infeção é superior nos primeiros três anos após esplenectomia, mas mantém-se elevado durante toda a vida.[38] A consequência mais grave da esplenectomia é a infeção fulminante pós-esplenectomia, que pode ter uma evolução rápida em 48 horas, com uma mortalidade até 70%.[39]

Recomendações vacinais

São recomendadas as vacinas contra agentes encapsulados e vacina contra a gripe e contra a COVID-19 (Tabela 2).

Recomenda-se a revacinação contra *Haemophilus influenzae* em indivíduos com asplenia ou hipossplenia de novo, tendo em conta a baixa reatogenicidade da vacina e a não disponibilidade de testes serológicos que possam confirmar a presença de anticorpos após a vacinação. O objetivo desta estratégia é aumentar o título de anticorpos protetores.[40]

Momento de vacinação

- Esplenectomia eletiva: vacinação no mínimo duas semanas antes do procedimento[40,41];
- Esplenectomia de urgência: vacinação nos sete dias pós-operatório ou no dia da alta (o que for primeiro). Se dúvida sobre a adesão ao programa vacinal, iniciar esquema durante o internamento, assim que garantida estabilidade clínica[41];
- Asplenia ou hipossplenia funcional/anatómica: a qualquer momento, o mais rapidamente possível.[41]

É seguro administrar simultaneamente todas as vacinas do esquema inicial, desde que em locais anatómicos diferentes.

VACINAÇÃO EM RECETORES DE TRANSPLANTE DE ÓRGÃO SÓLIDO

O risco de infeção de um recetor de transplante de órgão sólido, em qualquer ponto no tempo após o transplante, depende de dois fatores:

- a exposição epidemiológica do doente e do dador do órgão, passada e presente, na comunidade e/ou nosocomial (bactérias, vírus, fungos ou parasitas, incluindo exposições distantes no tempo em relação ao transplante);
- o conceito de '*net state of immunosupression*', que inclui todos os fatores que contribuem para o risco individual de infeção do doente [Tabela 1 do

Tabela 2 – Recomendações vacinais em doentes com asplenia ou hiposplenia que vão realizar a primovacinação*

Vacina	Esquema vacinal			Comentários
	Esquema inicial	≥ 8 semanas depois	Reforço	
Haemophilus influenzae tipo B conjugada (Hib)	Dose única[a]	-	-	-
13, 15 ou 20-valente (Pn13 ou Pn15 ou Pn20)[b]	Dose única	-	-	Sempre que possível, utilizar a Pn20
Pneumocócica polissacarídica 23-valente (Pn23)[b]	-	≥ 8 semanas após Pn13/15	Aos 5 anos[c]	Máximo 2 doses de reforço durante a vida; Não aplicável se for realizada Pn20
Meningocócica tetravalente conjugada (MenACWY)	1.ª toma	2.ª toma	A cada 5 anos	Se foi administrada 1 dose prévia reiniciar o esquema de vacinação
Meningocócica B recombinante (MenB)[d]	1.ª toma	2.ª toma	Após 1 ano	Considerar repetição a cada 2 - 3 anos[e] Se foi administrada previamente 1 dose completar o esquema de vacinação
Gripe	Dose única	-	Anualmente[f]	-
COVID-19	Devem ser incluídos em grupos prioritários de vacinação			

Hib: *Haemophilus influenzae* tipo B; MenACWY: vacina meningocócica tetravalente conjugada; MenB: vacina meningocócica B; Pn13: vacina pneumocócica 13-valente; Pn15: vacina pneumocócica 15-valente; Pn20: vacina pneumocócica 20-valente; Pn23: vacina pneumocócica polisacarídica 23-valente.

*: No caso de indivíduos que fizeram vacinação pneumocócica prévia:

- apenas Pn13 - completar com a Pn23 de acordo com a Tabela ou administrar 1 dose de Pn20 após ≥ 1 ano da Pn23
- apenas Pn23 - 1 dose de Pn13 ou Pn15 ou Pn20 após ≥ 1 ano
- 1 dose de Pn13 e 1 dose de Pn23- se aplicável, completar com Pn23 de acordo com a Tabela 1; alternativa 1 dose de Pn20 após ≥ 5 anos

a) Administrar 1 dose em doentes com asplenia e com > 5 anos de idade ou em doentes com ≥ 15 meses que serão submetidos a esplenectomia eletiva. A vacinação fora dos grupos etários determinados pelo Resumo de Características do Medicamento (RCM) deve ser discutida e partilhada com os doentes ou tutores legais destes.[40]

b) Uma alternativa à vacinação com Pn13 ou Pn15 seguida de vacinação Pn23, é a vacinação única com Pn20.

c) Indicada uma repetição da dose após 5 anos da dose de reforço ou aos 65 anos (o que for mais tarde).

d) A aplicação da vacina em indivíduos com ≥ 50 anos é *off-label*, pelo que deve ser considerada caso a caso.

e) De acordo com as recomendações da ACIP.[1]

f) A vacina contra a gripe deve ser administrada anualmente, na época de outono/inverno.

Apêndice 1 (Apendice_01.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15821)].[9]

Os fármacos mais utilizados no transplante de órgãos sólidos, mecanismo de ação e principais riscos infeciosos estão sintetizados na Tabela 3 do Apêndice 1 (Apendice_01.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15821).

A resposta imune à vacinação que o indivíduo transplantado é capaz de desenvolver após o transplante está dependente do tipo e intensidade da imunossupressão instituída.

Recomendações vacinais específicas

Os dadores vivos devem ter atualizado o seu esquema vacinal de acordo com a idade, vacinação prévia e história de exposições, com base no PNV. A administração de VASPR e da vacina da varicela deve ser evitada nas quatro semanas antes da doação do órgão.[26]

O perfil vacinal do doente candidato a transplante deve ser revisto e a vacinação programada na consulta de decisão e inscrição na lista para transplante (ou consulta de avaliação de risco infecioso) e reavaliada nas consultas subsequentes.

Se o esquema vacinal for iniciado antes do transplante, mas não for completado, as doses em falta podem ser realizadas no período pós-transplante (no caso das vacinas inativadas), entre três a seis meses após o transplante, quando forem atingidos os níveis de imunossupressão basal. A vacina contra a gripe pode ser administrada um mês após o transplante.

A vacinação durante o tratamento ativo de um fenómeno de rejeição deve ser evitada.[42]

Na Tabela 3 do Apêndice 2 (Apendice_02.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15822) estão sintetizadas as recomendações vacinais no pré e pós transplante, e o respetivo esquema vacinal proposto.

RECOMENDAÇÕES VACINAIS NOS RECETORES DE TRANSPLANTE DE PROGENITORES HEMATOPOIÉTICOS

O transplante de progenitores hematopoiéticos (TPH) alogénico resulta num grau mais elevado e prolongado de imunossupressão em comparação com o TPH autólogo, devido a um regime de condicionamento mais intenso e a necessidade subsequente de imunossupressão para prevenção/tratamento da doença enxerto-contra-hospedeiro (DECH). No entanto, mesmo no TPH autólogo, há uma perda significativa de imunidade, justificando a recomendação

de vacinação pós-transplante com um esquema semelhante ao alogénico.

Diversas condições específicas podem influenciar o programa de vacinação em recetores de TPH:

- presença de DECH e terapêutica imunossupressora: em casos de diagnóstico de DECH, especialmente com aumento relevante da imunossupressão, a vacinação pode ser adiada, mas não por mais de três meses. Não há evidência robusta que demonstre que a vacinação possa ser um fator desencadeante ou agravante da DECH[43];
- hipogamaglobulinemia: doentes com hipogamaglobulinemia grave têm risco aumentado de infeções bacterianas graves e resposta vacinal diminuída; Se a recuperação for esperada em curto prazo, a vacinação pode ser adiada; caso contrário, deve ser

Tabela 3 – Recomendações vacinais para doentes após TPH

Vacinas		Meses após o transplante											
		3	4	5	6	7	8	12	13	15	18	24	26
Influenza[a]	I				X[#]								
COVID-19 (SARS-CoV-2)	I				X[#]	X			X				
Pneumo20[b]	I	X		X		X			X				
Pneumo23[b]	I									X[§]			
HiB	I				X		X				X		
Virus sincicial respiratório[c]					X								
VHB	I				X	X		X					
Tdpa[d]	I				X		X				X		
VIP	I				X		X				X		
MenACWY	I				X		X						
MenB	I				X		X						
HPV[e]	I				X		X	X					
Varicela e zoster[f]	I				X		X						
VASPR[g]	V											X[£]	X[£]
Febre amarela[h]	V											X[£]	X[£]

Pneumo20: vacina antipneumocócica conjugada 20 valente; Pneumo23: vacina antipneumocócica polissacarídica 23 valente; HiB: vacina anti-*Haemophillus influenzae* tipo b; VHB: vacina anti-Hepatite B; Tdpa: vacina anti-tétano, difteria e pertussis (acelular); VIP: vacina inativada anti-polimielite; MenACWY: vacina anti-meningococcus ACWY; MenB: vacina anti-meningococcus B; HPV: vacina anti-papilomavirus; VASPR: vacina anti-sarampo, parotidite epidémica e rubéola

#: Reforço vacinal anual;

§: Uma dose de reforço deve ser administrada 5 anos após a última dose de Pneumo23;

£: A vacinação deve ser considerada nos doentes seronegativos.

a) A vacina contra o vírus da gripe é recomendada anualmente a partir de seis meses após o transplante. Em doentes com DECH grave ou linfopenia acentuada, um reforço com uma segunda dose pode ser considerado quatro semanas após a primeira. A vacinação deve ser feita anualmente no início do outono/inverno e mantida até pelo menos seis meses após a interrupção de qualquer terapia imunossupressora. Durante um surto ou se o transplante ocorrer durante o período sazonal da gripe, a vacina pode ser antecipada para três meses após o transplante, com uma dose de reforço quatro semanas após a primeira.[45]

b) A vacina contra *Streptococcus pneumoniae* pode ser iniciada tanto aos três meses quanto aos nove meses após o TPH, sem diferenças significativas na capacidade de gerar uma resposta vacinal, permitindo adaptação ao estado clínico do doente.[46] A resposta vacinal é mais eficaz quando se inicia com a vacina antipneumocócica conjugada, preferencialmente a 20-valente, que amplia a cobertura de serotipos de *S. pneumoniae*. A primovacinação é realizada com três doses, administradas aos 3, 5 e 7 meses pós-TPH. Uma dose de reforço administrada seis meses após a primovacinação (pelo menos um ano após o TPH) aumenta a resposta imunológica, embora possa estar associada a mais reações adversas.[46,47] Posteriormente, a vacina polissacarídica é aplicada dois meses após a dose de reforço da vacina conjugada, visando aumentar a proteção contra serotipos adicionais.[48] A revacinação com a vacina pneumocócica polissacarídica pode ser feita cinco anos após a última dose em doentes com menos de 65 anos, para manter uma proteção sustentada.

c) Estão disponíveis duas novas vacinas contra o vírus sincicial respiratório (VSR), uma vacina recombinante adjuvada monovalente e uma vacina recombinante não adjuvada bivalente. Ambas demonstraram eficácia > 80% na prevenção de infeção do trato respiratório inferior pelo VSR em doentes com > 60 anos.[4,50] Apesar de não existirem estudos específicos destas vacinas nos doentes submetidos a TPH, estas poderão ser consideradas em doentes > 60 anos a partir dos 6 meses após o transplante. Caso a decisão seja pela vacinação, a vacina adjuvante poderá ter vantagem devido à sua maior imunogenicidade A vacinação contra tétano, difteria e tosse convulsa deve ser iniciada com a vacina Tdpa após o transplante. Na idade adulta, os reforços são realizados com a vacina combinada contra tétano e difteria em doses reduzidas (Td). Vacinas com altas doses de toxoide diftérico e tosse convulsa (DTPa) não são recomendadas rotineiramente em adultos saudáveis devido ao risco aumentado de efeitos adversos, embora alguns centros de transplantes possam considerar seu uso para aumentar a resposta vacinal.

d) A vacinação contra tétano, difteria e tosse convulsa deve ser iniciada com a vacina Tdpa após o transplante. Na idade adulta, os reforços são realizados com a vacina combinada contra tétano e difteria em doses reduzidas (Td). Vacinas com altas doses de toxoide diftérico e tosse convulsa (DTPa) não são recomendadas rotineiramente em adultos saudáveis devido ao risco aumentado de efeitos adversos, embora alguns centros de transplantes possam considerar seu uso para aumentar a resposta vacinal.

e) Deve ser administrada em indivíduos até aos 26 anos (pode ser considerada até aos 45 anos.

f) A vacina viva atenuada contra a varicela só deve ser administrada após completa reconstituição imunológica e ausência de imunossupressão. A vacina recombinante contra o herpes zoster pode ser administrada no pós-transplante precoce, com uma eficácia vacinal de cerca de 68% em indivíduos autotransplantados.[51] A avaliação de anticorpos IgG para varicela deve ser feita a partir de 24 meses após o transplante e após mais de um ano sem imunossupressão. Em doentes seronegativos, a vacinação com vacina viva deve ser considerada.

g) Deve realizar-se a determinação de anticorpos IgG contra sarampo, rubéola e parotidite. Em doentes seronegativos, a vacinação deve ser considerada se não houver contra-indicação para vacina viva atenuada

h) A vacina contra a febre amarela só deverá ser feita a partir dos 24 meses após o transplante (alogénico ou autólogo) e mais de 1 ano após a suspensão de imunossupressão sistémica. Até esse momento, o doente deve ser desaconselhado a viajar para áreas endémicas para a febre amarela, especialmente se houver surtos da doença.

iniciada e, se necessário, repetida após a recuperação;
- administração de fármacos anti-CD20 e de imunoglobulina (ver Introdução).

A infusão de linfócitos do dador não tem efeito negativo na resposta vacinal.

Recomendações vacinais

A vacinação com vacinas inativadas inicia-se, regra geral, seis meses após TPH; no caso específico da vacinação contra *S. pneumoniae*, a vacinação pode ser iniciada mais precocemente (a partir dos três meses)[44] – ver Tabela 3.[45-51]

No caso da vacinação com vacinas vivas atenuadas, esta só pode ocorrer 24 meses após o TPH e se não houver nenhuma contraindicação para vacinas vivas (ausência de sinais de recidiva, ausência de imunossupressão, ausência de sinais de DECH).

A Fig. 1 sumariza as recomendações de vacinação e controlo de proteção vacinal para a hepatite B em doentes submetidos a TPH. No caso dos doentes cujo doseamento de anti HBc era positivo anteriormente ao TPH devem ser sempre considerados anti HBc positivo, mesmo que negativem o anti HBc, e devem fazer quimioprofilaxia com entecavir durante o período peritransplante. A suspensão do entecavir só deve ocorrer após confirmação do título de anti-HBs ≥ 10UI/mL.

Vacinas em situações especiais

As vacinas inativadas contra a febre tifoide, cólera, encefalite japonesa, raiva e hepatite A podem ser consideradas seis meses após o TPH, e de acordo com o risco epidemiológico do doente.

VACINAÇÃO NO DOENTE COM INFEÇÃO POR VIH

O limiar para a vacinação dos doentes com infeção por VIH deve ser baixo, dado existir maior risco de infeção por agentes infeciosos preveníveis por vacinação.[45] A Tabela 4 do Apêndice 2 (Apendice_02.pdf: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22966/15822) reúne as indicações vacinais.

Particularidades da imunossupressão

A resposta imunológica à vacinação é frequentemente subótima, pois apesar de melhorar com a recuperação imunológica induzida pela terapêutica antirretrovírica combinada (TARc), esta parece decair a um ritmo mais acelerado quando comparada com a população geral. Ainda assim, muitas destas vacinas oferecem proteção e é possível melhorar a sua imunogenicidade com esquemas vacinais modificados (i.e., com doses mais elevadas ou mais frequentes), sem compromisso da segurança vacinal.[52,53]

De uma forma geral, as vacinas inativadas podem ser usadas de forma segura, enquanto as vacinas vivas atenuadas são contraindicadas.

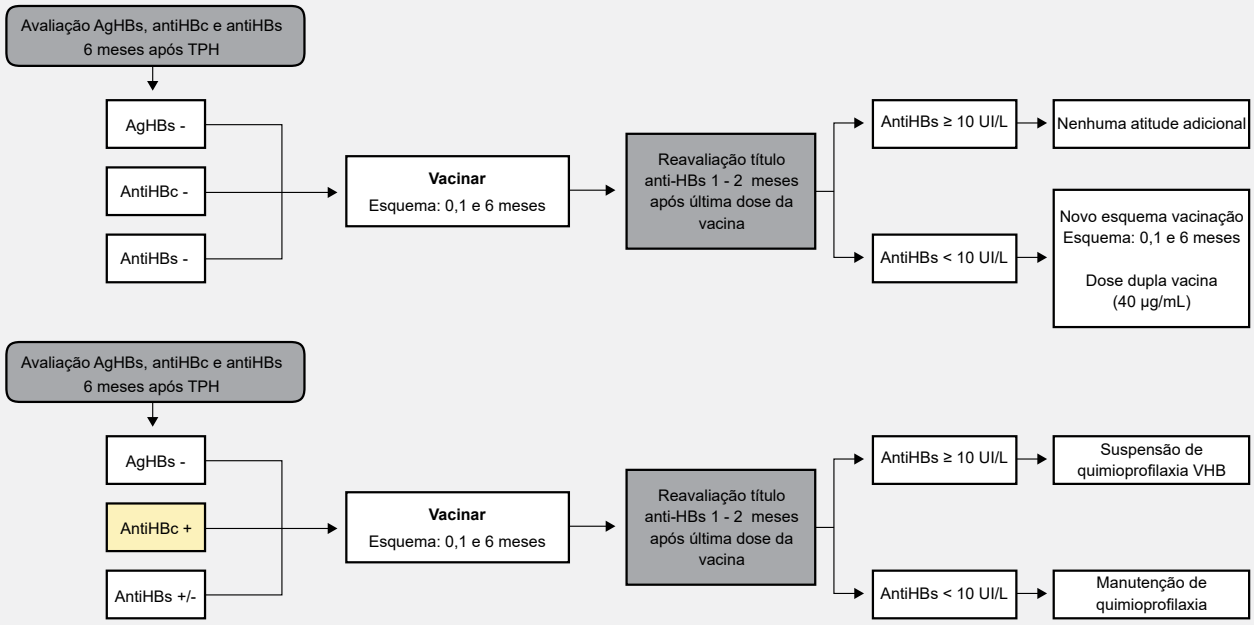


Figura 1 – Recomendações, tempos de vacinação e controlo de proteção vacinal para a hepatite B em doentes submetidos a Transplante Hematopoiético

Tabela 4 – Erros inatos da imunidade, indicações e contra-indicações vacinais

	Tdpa	Td	VIP	Hib	VHB	HPV	Influenza	Herpes zoster	Pneumococica		Meningocócica		COVID-19	VASPR	Varicela (VVZ)
									Conjug	Polissac	ACWY	B			
CID						a		b						c	c
CID com características associadas ou sindrómicas															
DiGeorge incompleto[d]														c	c
Ataxia-Telangiectasia						a								c	c
Sínd. HiperIgE AD															
Sínd. HiperIgE AR						a		b						c	c
Sind. Wiskott Aldrich						a		b							
Défices predominantes de anticorpos															
Def. minor de anticorpos[e]															
Def. major de anticorpos[f]															
Disregulação Imune														-	-
Defeitos congénitos dos fagócitos[f]															
DGC e neutropenia															
LAD e def. grânulos citotóxicos															
Defeitos da Imunidade Inata e Intrínseca a condicionar risco de:															
Infeções bacterianas				g					g		g	g			
Infeções víricas graves						a		b							
Infeções por micobactérias															
Infeções por parasitas/fungos														h	h
Doenças auto inflamatórias															
Défices do complemento[i]															
Fenocópias															
Mut. somáticas															
Autoanticorpos														j	j
Sínd. de Good															

Sem risco, recomendada;
Sem risco, benefício duvidoso;
Risco diminuto, benefício comprovado;
Risco acrescido, contraindicado.

CID: imunodeficiência combinada; AD: autossómico dominante; AR: autossómico recessivo; DGC: doença granulomatosa crónica; LAD: deficiência de adesão leucocitária

a) Especialmente recomendada no défice CD40/CD40L, AT, WAS, STK4, DOCK8, SPINK5, NEMO e defeitos da imunidade inata e intrínseca associada a suscetibilidade aumentada a infeções víricas (WHIM e défice de RHOH)[27,56,57];
b) Especialmente recomendada nos CID NK-, WAS, DOCK8, SPINK5 e defeitos da imunidade inata e intrínseca associada a suscetibilidade aumentada a infeções víricas (WHIM e défice de RHOH)[27,57];
c) Podem ser administradas apenas se: linfócitos T CD4 ≥ 500 células/uL, células T CD8 ≥ 200 células/uL e uma normal proliferação em resposta a mitogénios[27,57];
d) Síndrome de DiGeorge completa assemelha-se a uma SCID, pelo que deve seguir as mesmas orientações deste grupo[57];
e) Défice isolado de classe, subclasse ou alterações funcionais dos anticorpos;
f) Imunodeficiência comum variável, hipo/agamaglobulinemia ou síndromes de hiper-IgM;
g) É aconselhado realizar o reforço de vacinas contra agentes capsulados - pneumococo, Hib, meningococo (MenACWY e MenB) - bem como, se possível, controlar a resposta humoral às mesmas[27];
h) Reportada doença disseminada após administração de vacinas vivas atenuadas numa coorte de doentes com STAT1 GOF53[62];
i) Todas as vacinas do PNV são consideradas seguras e eficazes. As vacinas contra agentes encapsulados (Streptococcus pneumoniae, Haemophilus influenzae e Neisseria meningitidis), são altamente recomendadas. É aconselhável monitorizar as respostas vacinais sempre que possível e administrar doses de reforço consoante a durabilidade dos níveis de anticorpos protetores[56];
j) Doentes com autoanticorpos contra IFN não devem receber vacinas vivas atenuadas.[58,59]

A reconstituição imunológica no doente sob TARc reduz o risco de efeitos adversos, havendo risco-benefício a favor da vacinação com vacinas vivas. Assim, a VASPR, a vacina contra o vírus varicela zoster (VVZ) e contra a febre amarela podem ser administradas no doente com bom controlo virológico e imunológico.[52,54]

Vacinas inativadas

Devem ser efetuadas preferencialmente em doentes com supressão virológica e reconstituição imunológica (contagem de linfócitos T CD4+ ≥ 200/μL ou ≥ 15%)[55]; a vacinação deve, no entanto, ser considerada independentemente da supressão virológica e reconstituição imunológica naqueles cujo risco de aquisição de doença natural

prevenível pela vacinação é alto, com repetição do esquema vacinal após recuperação imunológica.[52]

Não são recomendados esquemas de vacinação rápidos como primeira linha e deve ser considerado o doseamento de títulos de anticorpos pós-vacinação se esta ocorreu aquando de contagem de linfócitos T CD4+ < 200/µL (< 15%) e/ou ausência de supressão virológica.[55]

Vacinas vivas atenuadas (replicantes)

A sua administração deve ser adiada até à recuperação imunológica sob TARc,[55] sendo contraindicadas com contagem de linfócitos T CD4+ < 200/µL ou < 15% (compromisso imunológico grave).

Com contagem de linfócitos T CD4+ entre 200 - 350/µL (compromisso imunológico moderado): deve ser usado o senso clínico para ajudar na decisão de administração de vacinas vivas. Se a probabilidade de exposição ao agente infecioso coberto pela vacina viva for elevada, o risco de complicações associadas à infeção natural é superior ao risco de efeitos adversos associados à vacinação. A supressão virológica do VIH num doente sob TARc aumenta a segurança e imunogenicidade da vacinação.[52]

A coadministração de múltiplas vacinas replicantes não é recomendada pela incerteza sobre imunogenicidade e eficácia. É recomendado um intervalo de, pelo menos, quatro semanas entre a administração de vacinas vivas.[52]

Efeitos da vacinação na carga vírica do VIH

Foram reportados aumentos transitórios, embora não clinicamente significativos, da carga vírica após a administração de determinadas vacinas, que por si só não constituem um obstáculo à vacinação.[52]

ERROS INATOS DA IMUNIDADE

Os erros inatos da imunidade (EII) englobam um grupo heterogéneo de doenças que comprometem o sistema imunológico, afetando tanto seu desenvolvimento quanto sua função. Este texto visa explorar as doenças cujas características exigem modificações na vacinação dos doentes afetados, estando a informação globalmente resumida na Tabela 4.[56-59] Informação adicional de recomendações e contra-indicações vacinais detalhadas por patologia encontra-se descrita na Tabela 5.[57-61]

NOTAS FINAIS

No hospedeiro adulto imunocomprometido a vacinação é relevante ao permitir reduzir o risco de infeção ou de infeção grave. As contraindicações vacinais de acordo com o conhecimento atualizado são essenciais e é fundamental aproveitar o melhor tempo de vacinação para potenciar a eficácia vacinal que pode estar diminuída, ou muito diminuída, por ação dos fármacos e pela doença. Novos fármacos no arsenal terapêutico, novas vacinas e dados de evidência científica a emergir, tornam este processo muito dinâmico e a necessitar de constante atualização.

AGRADECIMENTOS

Os autores agradecem à NOBOX o excelente apoio logístico e o suporte na formatação do manuscrito.

CONTRIBUTO DOS AUTORES

CA: Desenho e elaboração do artigo, escrita e revisão crítica do manuscrito.

SP, FC, JM, CNS, AP, LRD: Escrita e revisão crítica do manuscrito.

JO: Desenho e elaboração do artigo, revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

CONFLITOS DE INTERESSE

CA foi palestrante em reuniões da Astra-Zeneca e da Abbvie-Lda; participou em acções de formação da Pfizer e teve apoio para participação em reuniões científicas da Astra-Zeneca e Feres Farma.

SP teve apoio referente à participação como palestrante em reuniões científicas e atividades de consultoria, apoio nas deslocações a reuniões científicas e acções de formação das empresas Gilead, GSK, ViiV Healthcare, Pfizer e Amgen.

FC teve apoio da Merck Sharp and Dohme para participar em reuniões científicas.

AP teve apoio para a realização de investigação científica, organização de cursos e participação em conferências médicas e em conselhos consultivos e palestras das seguintes empresas farmacêuticas: Merck, Sharp and Dohme, ViiV Healthcare, Gilead Sciences, Pfizer, Janssen Cilag e Takeda.

JO recebeu honorários por consultadoria e/ou apoio a reuniões científicas, comunicações e ensino e/ou investigação e publicações, das seguintes empresas farmacêuticas: Gilead Sciences, Merck Sharp and Dohme, Sanofi Portugal e ViiV Healthcare.

Os restantes autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

Tabela 5 – Considerações adicionais de vacinação por classificação de erro inato

Erros inatos	Recomendações vacinais
a) SCID (Severe CID)	
Manifestam-se nos primeiros meses de vida. O TPH e a terapêutica génica são as únicas opções curativas	• Têm contraindicação absoluta para vacinas vivas. • Aquando da reconstituição imunológica pós-transplante, poderão ser introduzidas vacinas inativadas do PNV[a].[27,57]
b) CID	
Podem apresentar resposta humoral residual	• Vacinas inativadas recomendadas, mas benefício é controverso, em parte pela imunização passiva decorrente do tratamento com IgHN. • Vacinas vivas são contraindicadas, com exceção os doentes com linfócitos T funcionais [vide c), Tabela 4].[27,57] • Se diminuição das células *NK* há indicação para vacinar contra a zona.[27,57]
CID com características associadas ou sindrómicas	
Enquadrando-se maioritariamente nas CID, partilham globalmente as recomendações acima referidas. Salientam-se as exceções na coluna ao lado	• Sind hiper IgE: pode haver benefício na administração de vacinas inativadas . • NoSTAT3-LOF, vacinas de vírus vivos atenuados são seguras, mas nalgumas formas recessivas a sua administração depende da função dos linfócitos T [vide c), Tabela 4].[27,57] • Síndrome de DiGeorge incompleto, WAS e AT: são recomendadas as vacinas conjugadas contra agentes encapsulados. A administração de vacinas de vírus vivos atenuados depende da função dos linfócitos T (vide c), Tabela 4), à exceção do WAS, no qual todas as vacinas vivas atenuadas devem ser evitadas.[57] • Alguns doentes beneficiam da administração da vacina contra o VPH e a zona [vide a) e b), Tabela 4].
Défices predominantes de anticorpos	
	• Défices *minor*[b]: recomendadas todas as vacinas do PNV, sendo preferível a administração de vacinas conjugadas.[27,57] • Défices *major*[c]: vacinas inativadas são seguras, a sua eficácia é controversa. A reposição com IgHN pode colmatar alguma proteção mas não para a gripe e VPH, cujos anticorpos específicos podem estar insuficientemente representados nas formulações disponíveis.[27,57] • Vacinas vivas atenuadas são contraindicadas.[27,57]
Doenças de desregulação imune	
	• Vacinas inativadas: globalmente seguras, mas faltam estudos de eficácia.[58] • Faltam dados relativos a vacinas vivas atenuadas, devendo a sua administração ser avaliada individualmente.[27,58]
Defeitos congénitos de fagócitos	
	• Salienta-se a importância da vacina anual da gripe, pelo aumento da mortalidade por gripe nos casos de coinfecção estafilocócica.[27,58] • Vacinas de vírus vivos atenuados: contraindicadas em doentes com alterações na função citotóxica dos linfócitos, defeitos de adesão dos leucócitos ou dos grânulos citotóxicos.[27] • Vacinas de bactérias vivas atenuadas: contraindicadas em todo o grupo.[27]
Defeitos da Imunidade intrínseca e inata	
Condicionam suscetibilidade aumentada a diferentes tipos de agentes infeciosos, nomeadamente se a:	• Bactérias: contraindicadas vacinas de bactérias vivas atenuadas.[27] • Vírus: contraindicadas vacinas de vírus vivos atenuados.[58-61] • Micobactérias: contraindicadas vacinas de bactérias vivas atenuadas.[27,58] • Parasitas e fungos: vacinas vivas atenuadas devem ser administradas com precaução, por risco de doença disseminada.[62]
Défices de complemento	
	• Recomendam-se todas as vacinas do PNV, especialmente a agentes encapsulados, para os quais se deve monitorizar a resposta vacinal e, se necessário, administrar doses de reforço.
Fenocópias	
	As recomendações vacinais assemelham-se às da população geral, com exceção de doentes com: • autoanticorpos anti-IFN: vacinas vivas atenuadas são contraindicadas[58,59]; • síndrome hemolítico-urémico atípica medicados com anticorpo monoclonal anti-C5: tem as recomendações vacinais dos défices de complemento[56,57]; • síndrome de Good: tem as recomendações vacinais dos défices *major* de anticorpos.[60]

AT: síndrome ataxia-telangiectasia; CID: imunodeficiência combinada; DGC: doença granulomatosa crónica; IgHN: imunoglobulina humana normal; *NK*: *natural killer*; PNV: plano nacional de vacinação; SCID: Imunodeficiência combinada grave; TPH: transplante de progenitores hematopoiéticos; WAS: síndrome de Wiskott-Aldrich (WAS)

a) *Vide* secção "Recomendações vacinais nos recetores de transplante de progenitores hematopoiéticos"

b) Défice isolado de classe, subclasse ou alterações funcionais dos anticorpos;

c) Imunodeficiência comum variável, hipo/agamaglobulinemia ou síndromes de hiper-IgM.

REFERÊNCIAS

1. Infectious Diseases Society of America, Centers for Disease Control and Prevention. General best practice guidelines for immunization: altered immunocompetence. [consultado 2025 jan 03]. Disponível em: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html.
2. Public Health Agency of Canada. Immunization of immunocompromised persons: Canadian immunization guide. [consultado 2025 fev 05]. Disponível em: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html.
3. Australian Technical Advisory Group on Immunisation. Australian immunisation handbook: vaccination for people who are immunocompromised. 2022. [consultado 2025 fev 05]. Disponível em: https://immunisationhandbook.health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised#page-history.
4. Immunisation Advisory Centre. Vaccination of special groups. [consultado 2025 fev 05]. Disponível em: https://www.immune.org.nz/immunisation/programmes/special-groups.
5. Direção-Geral da Saúde. Norma n.º 018/2020 de 27/09/2020 - programa nacional de vacinação 2020. Lisboa: DGS; 2020.
6. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2020;16:442-9.
7. Espi M, Koppe L, Fouque D, Thaunat O. Chronic kidney disease-associated immune dysfunctions: impact of protein-bound uremic retention solutes on immune cells. Toxins. 2020;12:300.
8. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. Immun Ageing. 2019;16:25.
9. Fishman JA. Infection in organ transplantation. Am J Transplant. 2017;17:856-79.
10. Agência Europeia de Medicamentos. Resumo das características do medicamento - IMVANEX. [consultado 2025 mar 03]. Disponível em: https://ec.europa.eu/health/documents/community-register/2022/20220722156674/anx_156674_pt.pdf.
11. Leung J, Anderson TC, Dooling K, Xie F, Curtis JR. Recombinant zoster vaccine uptake and risk of flares among older adults with immune-mediated inflammatory diseases in the US. Arthritis Rheumatol. 2022;74:1833-41.
12. Nakafero G, Grainge MJ, Myles PR, Mallen CD, Zhang W, Doherty M, et al. Association between inactivated influenza vaccine and primary care consultations for autoimmune rheumatic disease flares: a self-controlled case series study using data from the Clinical Practice Research Datalink. Ann Rheum Dis. 2019;78:1122-6.
13. Machado PM, Lawson-Tovey S, Strangfeld A, Mateus E ,Hyrich KL, Gossec L, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. Ann Rheum Dis. 2022;81:695-709.
14. Lenfant T, Jin Y, Kirchner E, Hajj-Ali RA, Calabrese LH, Calabrese C. Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients. Rheumatology. 2021;60:5149-157.
15. Stevens E, Weinblatt ME, Massarotti E, Griffin F, Emani S, Desai S. Safety of the zoster vaccine recombinant adjuvanted in rheumatoid arthritis and other systemic rheumatic disease patients: a single center's experience with 400 patients. ACR Open Rheumatol. 2020;2:357-61.
16. Kroger A, Bahta L, Long S, Sanchez P. General best practice guidelines for immunization. best practices guidance of the advisory Committee on immunization practices. [consultado 2025 mar 03]. Disponível em: https://www.cdc.gov/vaccines/hcp/imz-best-practices/?CDC_AAref_Val=https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
17. See KC. Vaccination for the prevention of infection among immunocompromised patients: a concise review of recent systematic reviews. Vaccines. 2022;10:800.
18. Shapiro JR, Corrado M, Perry J, Watts TH, Bolotin S. The contributions of T cell-mediated immunity to protection from vaccine-preventable diseases: a primer. Hum Vaccin Immunother. 2024;20.
19. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. J Cutan Med Surg. 2019;23:50-74.
20. Centers for Disease Control and Prevention. Special situations. 2024. [consultado 2025 set 10]. Disponível em: https:// www.cdc.gov/vaccines/hcp/imz-best-practices/special-situations.html.
21. Bader MS, McKinsey DS. Postexposure prophylaxis for common infectious diseases. Am Fam Physician. 2013;88:25-32.
22. Lachiewicz AM, Srinivas ML. Varicella-zoster virus post-exposure management and prophylaxis: a review. Prev Med Rep. 2019;16:101016.
23. UK Health Security Agency. Guidelines on post-exposure prophylaxis (PEP) for varicella or shingles. 2025. [consultado 2025 mar 05]. Disponível em: https://khub.net/documents/135939561/1148216158/Guidelines+on+post-exposure+prophylaxis+%28PEP%29+for+varicella+or+shingles+%28February+2025%29UKHSA-guidelines-on-VZ-post-exposure-prophylaxis-February2025.pdf/e8ba9019-00a4-2546-a6a3-d83c12fd3b00?t=1740412523759.
24. Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. Am J Transplant. 2013;13:311-7
25. UK Health Security Agency. Varicella. In: Immunisation against infectious disease: the green book. 2021. [consultado 2025 mar 05]. Disponível em: https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles.
26. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44-100.
27. Martire B, Azzari C, Badolato R, Canessa C, Cirillo E, Gallo V, et al. Vaccination in immunocompromised host: recommendations of italian primary immunodeficiency network centers (IPINET). Vaccine. 2018;36:3541-54.
28. Stosor V, Zembower TR, editors. Infectious complications in cancer patients. Vol 161. Cham: Springer International Publishing; 2014.
29. Furer V, Rondaan C, Heijstek MW, Agmon-Levinet N, Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79:39-52.
30. Klotz L, Havla J, Schwab N, Hohlfeld R, Barnett M, Reddel S, et al. Risks and risk management in modern multiple sclerosis immunotherapeutic treatment. Ther Adv Neurol Disord. 2019;12:175628641983657.
31. Grebenciucova E, Pruitt A. Infections in patients receiving multiple sclerosis disease-modifying therapies. Curr Neurol Neurosci Rep. 2017;17:88.
32. Kucharzik T, Ellul P, Greuter T, Rahier J, Verstockt B, Abreu C, et al. ECCO Guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. J Crohns Colitis. 2021;15:879-913.
33. Winthrop KL, Mariette X, Silva JT, Benanu E, Calabrese LH, Dumusc A, et al. ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobuli. Clin Microbiol Infect. 2018;24:S21-40.
34. Lenti MV, Luu S, Carsetti R, Osier F, Ogwang R, Nnodu OE, et al. Asplenia and spleen hypofunction. Nat Rev Dis Primers. 2022;8:71.
35. Luu S, Spelman D, Woolley IJ. Post-splenectomy sepsis: preventative strategies, challenges, and solutions. Infect Drug Resist. 2019;12:2839-51.
36. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. Lancet. 2011;378:86-97.
37. Lizamma A, Merlin R, Bency X, Princy J, Kumari R, Gaddam L. Microscopic study of human spleen in different age groups. Int J Res Med Sci. 2017;3:1701-6.
38. Chong J, Jones P, Spelman D, Leder K, Cheng AC. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: a retrospective cohort study. Epidemiol Infect. 2017;145:397-400.
39. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. J Br Surg. 1991;78:1031-8.

40. Bonanni P, Grazzini M, Niccolai G, Paolini D, Varone O, Bartoloni A, et al. Recommended vaccinations for asplenic and hyposplenic adult patients. Hum Vaccin Immunother. 2017;13:359-68.
41. South Australian Expert Advisory Group on Antimicrobial Resistance. Splenectomy vaccination and antimicrobial prophylaxis (adult) clinical guideline. 2019. [consultado 2024 jan 10]. Disponível em: https://www.sahealth.sa.gov.au/wps/wcm/connect/7d9c4800412ad856b9d6bfe8f09fe17d/Clinical_Guideline_Splenectomy_Vaccination%2B%26%2BAntimicrobial_Prophylaxis_v1.2.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-7d9c4800412ad856b9d6bfe8f09fe17d-p4gFnEL.
42. Danziger-Isakov L, Kumar D. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33:e13563.
43. Hilgendorf I, Freund M, Jilg W, Einsele H, Gea-Banacloche J, Greinix H, et al. Vaccination of allogeneic haematopoietic stem cell transplant recipients: report from the International Consensus Conference on Clinical Practice in chronic GVHD. Vaccine. 2011;29:2825-33.
44. Cordonnier C, Labopin M, Chesnel V, Ribaud P, De La Camara R, Martino R, et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis. 2009;48:1392-401.
45. Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. Blood. 2016;127:2824-32
46. Cordonnier C, Ljungman P, Juergens C, Maertens J, Selleslag D, Sundaraiyer V, et al. Immunogenicity, safety, and tolerability of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged ≥2 years: an open-label study. Clin Infect Dis. 2015;61:313-23.
47. Langedijk AC, van Aalst M, Meek B, van Leeuwen EM, Zeerleder S, Meijer E, et al. Long-term pneumococcal vaccine immunogenicity following allogeneic hematopoietic stem cell transplantation. Vaccine. 2019;37:510-5.
48. Cordonnier C, Labopin M, Chesnel V, Ribaud P, Camara Rde L, Martino R, et al. Immune response to the 23-valent polysaccharide pneumococcal vaccine after the 7-valent conjugate vaccine in allogeneic stem cell transplant recipients: results from the EBMT IDWP01 trial. Vaccine. 2010;28:2730-4.
49. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, et al. Respiratory syncytial virus prefusion f protein vaccine in older adults. New Eng J Med. 2023;388:595-608.
50. Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, et al. Efficacy and safety of a bivalent RSV prefusion f vaccine in older adults. New Eng J Med. 2023;388:1465-77.
51. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, López-Jiménez J, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation. JAMA. 2019;322:123.
52. Geretti AM, Brook G, Cameron C, Chadwick D, French N, Heyderman R, et al. British HIV association guidelines on the use of vaccines in HIV - positive adults 2015. HIV Med. 2016;17:S2-81.
53. National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, Infectious Diseases Society of America. AIDS info immunizations for preventable diseases in adults and adolescents with HIV. 2023. [consultado 2025 fev 24]. Disponível em: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/immunizations.
54. Thompson MA, Horberg MA, Agwu AL, Colasanti JA, Jain MK, Short WR, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73:e3572-605.
55. European AIDS Clinical Society. EACS Guidelines version 12.0. 2023. [consultado 2025 set 23]. Disponível em: https://www.eacsociety.org/media/guidelines-12.0.pdf.
56. Brodszki N, Frazer-Abel A, Grumach AS, Kirschfink M, Litzman J, Perez E, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) complement guideline: deficiencies, diagnosis, and management. J Clin Immunol. 2020;40:576-91.
57. American Academy of Pediatrics. Immunization and other considerations in immunocompromised children. In: Red Book: 2024–2027 Report of the Committee on Infectious Diseases. 33rd ed. Illinois: American Academy of Pediatrics; 2024.
58. Bonilla FA. Update: vaccines in primary immunodeficiency. J Allerg Clin Immunol. 2018;141:474-81.
59. Bastard P, Michailidis E, Hoffmann HH, Chbihi M, Le Voyer T, Rosain J, et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. J Experiment Med. 2021;218:e20202486
60. Kabir A, Alizadehfar R, Tsoukas CM. Good's syndrome: time to move on from reviewing the past. Front Immunol. 2022;12:815710.
61. Markowitz LE, Dunne EF, Saraiya M, Chesson HW, Curtis CR, Gee J, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2014;63:1-30.
62. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood. 2016;127:3154-64.

Palisaded Neutrophilic Granulomatous Dermatitis as the Initial Manifestation of Rheumatoid Arthritis

Dermatite Granulomatosa Neutrofílica em Paliçada como Manifestação Inicial de Artrite Reumatoide

Keywords: Autoimmune Diseases; Dermatitis; Granuloma; Neutrophils; Rheumatoid Arthritis
Palavras-chave: Artrite Reumatoide; Dermatite; Doenças Autoimunes; Granuloma; Neutrófilos

Rheumatoid arthritis (RA) is an autoimmune disease that can be associated with cutaneous manifestations, most commonly rheumatoid nodules. Other dermatological findings include vasculitis, pyoderma gangrenosum, Sweet syndrome, and reactive granulomatous dermatitis, which encompasses both palisaded neutrophilic granulomatous dermatitis (PNGD) and interstitial granulomatous dermatitis.[1]

Palisaded neutrophilic granulomatous dermatitis is a rare neutrophilic dermatosis often linked to autoimmune disease (notably RA and systemic lupus erythematosus) and less frequently to hematologic malignancy, infection, or drugs.[2,3] Although its clinical spectrum is broad, PNGD typically appears as symmetrical papules, plaques, or nodules on the extensor limbs, with central ulceration or crust.[4] Histopathological examination is essential to establish the diagnosis. Response to treatment is variable and focuses on controlling the underlying systemic disease; reported options include corticosteroids, dapsone, or hydroxychloroquine.[1]

We present a case of PNGD with an unusual clinical pattern that represented the initial manifestation of RA.

A 71-year-old woman with a history of arterial hypertension, atrial fibrillation, and dyslipidemia – on long-standing therapy – was referred to Dermatology for asymptomatic lesions evolving over six months, with a progressive increase in number and size. The eruption began on the right upper limb and later spread to the face and left upper limb. She denied systemic symptoms. Approximately three months after the cutaneous onset, she developed bilateral inflammatory-type polyarthralgia. Examination revealed polyarthritis of metacarpophalangeal joints, proximal and distal interphalangeal joints of the hands, and metatarsophalangeal joints. The diagnosis of RA was established, supported by positive rheumatoid factor (34.2 U/mL) and anti-cyclic citrullinated peptide antibodies (82.0 U/mL), despite the atypical distal interphalangeal involvement.

A dermatologic examination revealed multiple symmetric violaceous nodules (2 - 5 cm) on the elbows, a solitary lesion on the right arm and wrist, and another on the glabellar region (Fig. 1). Additionally, a reticulated erythema was observed on the extensor surfaces of the upper limbs, along with urticaria-like lesions on the anterior forearms. Palisaded neutrophilic granulomatous dermatitis was suspected and skin biopsies were performed. Histopathology showed a

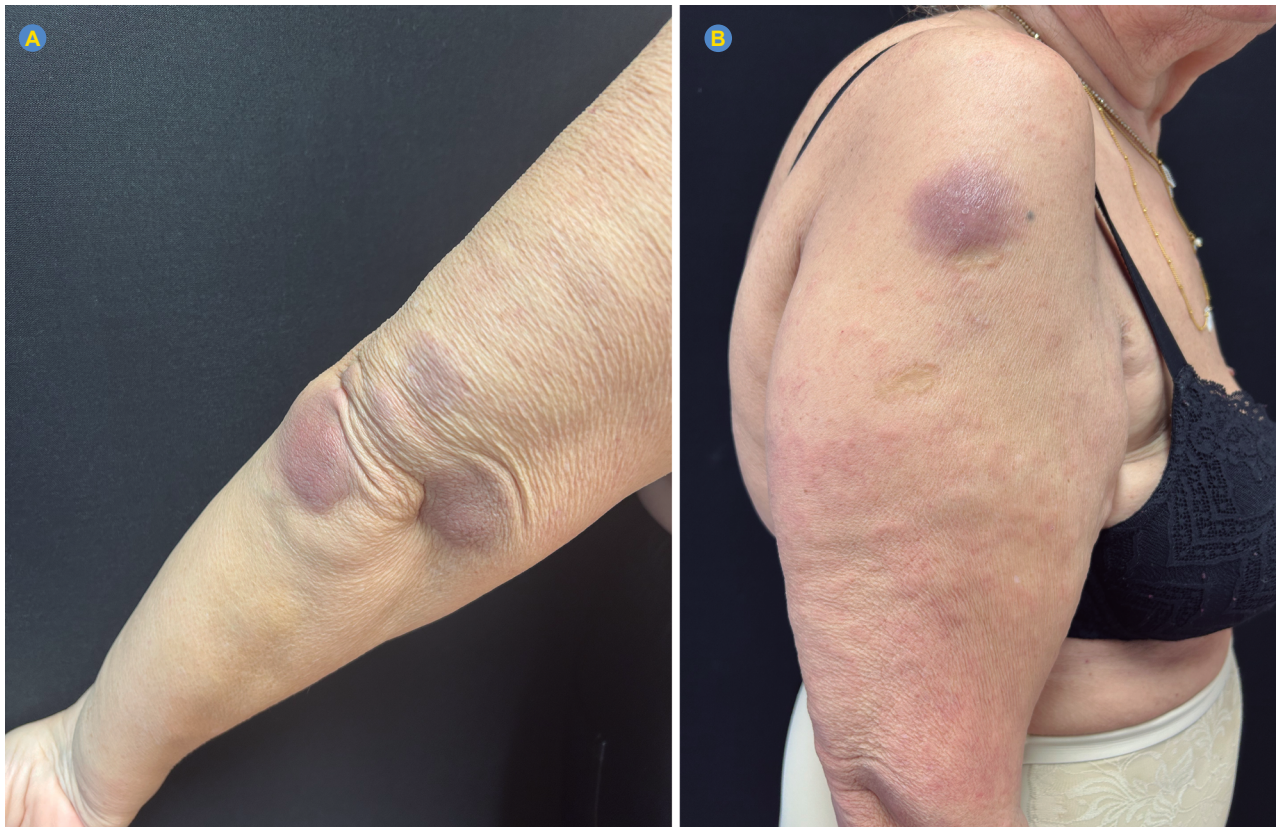


Figure 1 – Violaceous nodules on the right elbow and anterolateral aspect of the right arm (A); reticulated erythema on the distal half of the extensor surface of the right upper limb (B)

lympho-histioplasmacytic and neutrophilic infiltrate in the dermis extending into the hypodermis, with large areas of necrobiosis surrounded by histiocytes, focally arranged in a palisaded pattern, confirming PNGD. A targeted work-up to exclude other causes (connective-tissue disease, malignancy, and drug-related etiologies) was negative; given the temporal relationship, the dermatosis was considered associated with RA.

The patient was initially treated with prednisolone, followed by methotrexate. Due to persistent cutaneous lesions, hydroxychloroquine was later added to the treatment.

Palisaded neutrophilic granulomatous dermatitis is a rare dermatological entity often associated with systemic autoimmune disease. In this patient, it preceded the clinical manifestations of RA, highlighting the need to include PNGD among the possible cutaneous presentations of RA and to recognize its variable morphology – including multiple large nodules and facial involvement.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

JR: Collection of clinical data, literature review, drafting of the manuscript.

RR: Collection of clinical data, critical review of the manuscript.

JN, JA: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Diaz MJ, Natarelli N, Wei A, Rechdan M, Botto E, Tran JT, et al. Cutaneous manifestations of rheumatoid arthritis: diagnosis and treatment. J Pers Med. 2023;13:1479.
2. Yang C, Tang S, Li S, Ying S, Zhu D, Liu T, et al. Underlying systemic diseases in interstitial granulomatous dermatitis and palisaded neutrophilic granulomatous dermatitis: a systematic review. Dermatology. 2023;239:287-98.
3. Bangalore Kumar A, Lehman JS, Johnson EF, Cantwell HM, Sartori Valinotti JC, Sokumbi O, et al. Reactive granulomatous dermatitis as a clinically relevant and unifying term: a retrospective review of clinical features, associated systemic diseases, histopathology and treatment for a series of 65 patients at Mayo Clinic. J Eur Acad Dermatol Venereol. 2022;36:2443-50.
4. Sarıkaya Tellal E, Ilhan Erdil D, Gore Karaali M, Aksu AE, Erdemir VA, Polat AK, et al. Interstitial granulomatous dermatitis and palisaded neutrophilic granulomatous dermatitis: retrospective clinicopathological analysis of 16 cases. Dermatol Pract Concept. 2023;13:e2023129.

José RAMOS [1], Rodrigo REI [2], Joana NOGUEIRA[3], João ALVES [1]
1. Dermatovenereology Department. Unidade Local de Saúde Almada-Seixal. Almada. Portugal.
2. Rheumatology Department. Unidade Local de Saúde Almada-Seixal. Almada. Portugal.
3. Pathology Department. Unidade Local de Saúde Almada-Seixal. Almada. Portugal.
✉ **Autor correspondente:** José Ramos. jalramos@campus.ul.pt
Recebido/*Received*: 18/06/2025 - **Aceite/*Accepted*:** 19/09/2025 - **Publicado *Online*/*Published Online*:** 08/10/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23552

A Rare Case of Multidermatomal Herpes Zoster

Um Caso Raro de Herpes Zoster Multidermatomal

Keywords: Herpes Zoster/diagnosis; Herpes Zoster/drug therapy
Palavras-chave: Herpes Zoster/diagnóstico; Herpes Zoster/tratamento farmacológico

Dear Editor,

Herpes zoster (HZ) is a common condition, typically diagnosed based on clinical history and physical examination, allowing early treatment without the need for additional diagnostic testing.[1,2]

In addition to the classic clinical presentation, rare cases have been described, mostly in immunocompromised and/or elderly patients, in which the rash spreads across two or more contiguous dermatomes on one hemibody, without crossing the midline and without known disseminated disease, termed multidermatomal herpes zoster (MHZ).[3,4]

We report the case of a 60-year-old woman who presented to her family doctor with a vesicular rash on the right posterior cervical region and right upper limb, along with complaints of allodynia and paresthesias in the affected dermatomes, with onset two days prior. She reported prodromal paresthesias, describing a "burning sensation" at the affected sites for the eight days preceding the onset of the rash. Her medical history was significant for hypertension, major depressive disorder, and cervical spondyloarthrosis, and her daily medications included lisinopril 20 mg and sertraline 100 mg. Physical examination revealed multiple clusters of vesicular lesions with serous content on an erythematous base, distributed across the right posterolateral cervical region and right shoulder, corresponding to the C3, C4, and C5 dermatomes (Fig. 1). A diagnosis of MHZ was made, and treatment was initiated with 125 mg brivudine (daily, for seven days), given the simplicity of the therapeutic regimen compared to other antivirals, along with 50 mg tramadol (twice daily), and 75 mg pregabalin (twice daily). Laboratory tests, including complete blood count, HIV-1 and -2 antibodies, and serum immunoglobulins G and M, revealed no significant abnormalities. Four weeks after diagnosis, the patient was asymptomatic and discontinued all ongoing therapy. Vaccination against herpes zoster was recommended for recurrence prevention, with an interval of one year after symptom resolution.

This case underscores an atypical presentation of herpes zoster, emphasizing the need to avoid diagnostic delays. Timely recognition is crucial, as early treatment is well established to reduce symptom duration and severity, and to prevent potential complications.[2] As one of the few cases reported in an immunocompetent patient, this presentation challenges current etiopathogenic hypotheses centered on states of immunosuppression. However, the patient's age cannot be ruled out as a contributing factor, given the expected progressive decline in T cell–mediated immunity following primary varicella-zoster virus infection.[1] Finally, the authors consider the excellent clinical response to guideline-based therapy for classic HZ to be noteworthy, as there are no specific guidelines for MHZ to date.

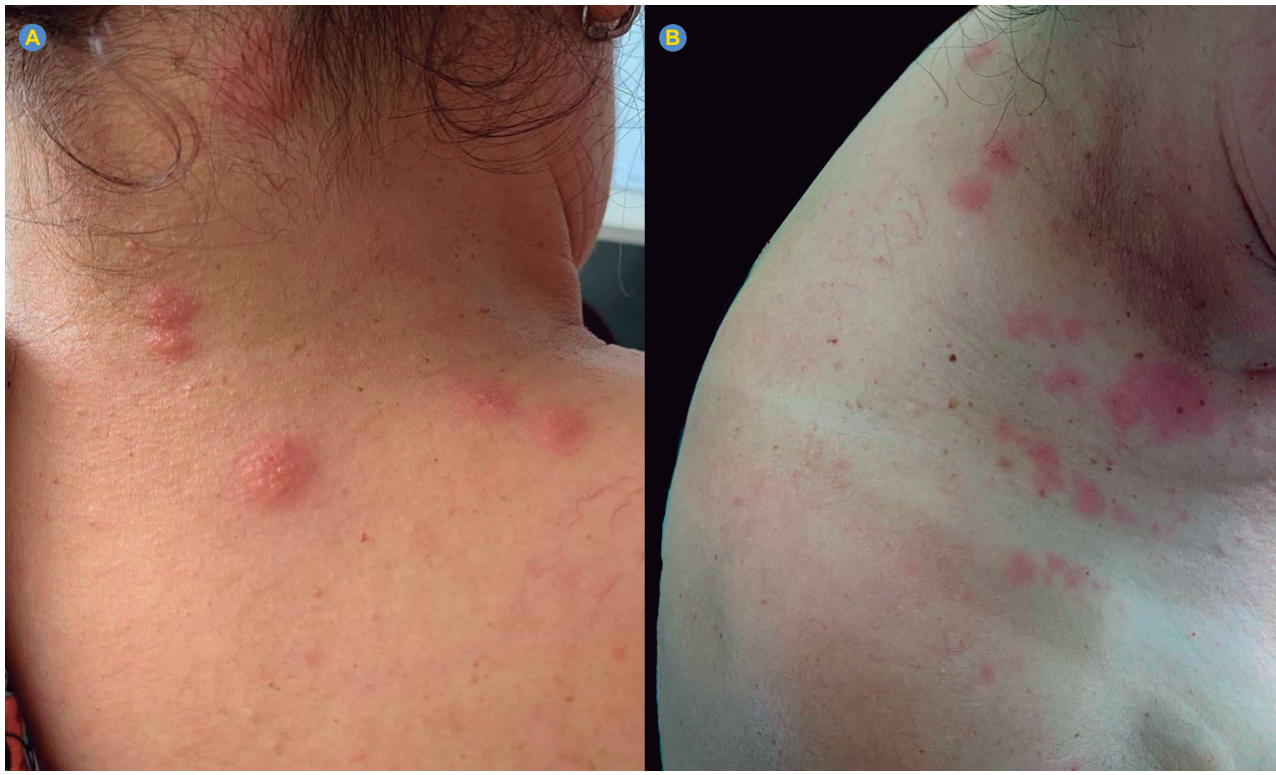


Figure 1 – Physical examination showing multiple clusters of vesicular lesions with serous content on an erythematous base (A), distributed across the C3, C4, and C5 dermatomes of the right hemibody (B), prior to initiation of treatment

PREVIOUS AWARDS AND PRESENTATIONS

The reported case was presented at the *VI Jornadas do Núcleo do Internato AceS Gerês/Cabreira*, having been awarded 2nd place.

ACKNOWLEDGMENTS

The authors would like to thank Álvaro Reis and Diana Carneiro, from USF Terras do Ave, for their support and valuable contributions to this work.

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

SRF, AM: Study design, data acquisition and analysis, image collection, writing and critical review.

SVS: Study design, data acquisition and analysis, writing and critical review of the manuscript.

RF, JVRF: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Cohen JI. Clinical practice: herpes zoster. N Engl J Med. 2013;369:255-63.
2. Werner RN, Nikkels AF, Marinović B, Schäfer M, Czarnecka-Operacz M, Agiuset AM, et al. European consensus-based (S2k) Guideline on the management of herpes zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), part 2: treatment. J Eur Acad Dermatol Venereol. 2017;31:20-9.
3. Beuerlein KG, Strowd LC. Multidermatomal herpes zoster: a pain in the neck? Dermatol Online J. 2019;25:13030/qt9kz407dx.
4. Vaz TR, Pinto CS. Quando a atipia desafia o diagnóstico: relato de um caso de herpes zoster. Rev Port Med Geral Fam. 2023;39:149-54.

Soraia RIBEIRO FERNANDES✉[1], Albino MARTINS[1], Susana VILAR SANTOS[1], Rita de FARIA[1], João VILA REAL FERNANDES[1]

1. Serviço de Medicina Geral e Familiar. Unidade de Saúde Familiar Terras do Ave. Unidade Local de Saúde do Médio Ave. Braga. Portugal.

✉ **Autor correspondente:** Soraia Ribeiro Fernandes. soraiaribfernandes@gmail.com

Recebido/*Received*: 02/07/2025 - **Aceite/*Accepted*:** 24/09/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23613

Atypical Scrotal Manifestation of Madelung's Disease

Manifestação Escrotal Atípica da Doença de Madelung

Keywords: Lipomatosis, Multiple Symmetrical; Scrotum
Palavras-chave: Escroto; Lipomatose Simétrica Múltipla

Madelung's disease (MD) is a rare and benign disorder of lipid metabolism, with an estimated incidence of 1:25 000. It predominantly affects middle-aged men of Mediterranean origin, typically associated with a history of chronic alcohol abuse.[1,2]

The disease is characterized by the progressive and symmetric accumulation of non-encapsulated adipose tissue, primarily involving the proximal upper body regions. Its etiology and pathogenesis remain poorly understood.[2,3]

Currently, there are no established diagnostic criteria. Diagnosis relies on clinical and imaging evaluation, with magnetic resonance imaging (MRI) considered the gold standard.[1-3]

We report the case of a 64-year-old male patient diagnosed with MD, with a past medical history of alcohol-related chronic liver disease, active smoking, and a recent diagnosis of squamous cell carcinoma of the mid-esophagus (stage uT1bN1M0). He presented to the emergency department with a progressively enlarging right inguinoscrotal swelling that had been developing over three years, with significant worsening in size and pain over the preceding week.

Physical examination revealed a large bilateral scrotal mass, soft in consistency, non-tender to palpation, irreducible, and without signs of local inflammation (Fig. 1A). Given the clinical presentation and a presumptive diagnosis of inguinal hernia, a scrotal ultrasound (US) was performed for further characterization. It revealed marked bilateral scrotal enlargement, predominantly composed of polylobulated, hyperechoic adipose tissue, without clear anatomical continuity with the inguinal canal (Fig. 1B). The imaging findings were similar to the patient's cervicofacial fat accumulation due to MD, raising the suspicion of scrotal involvement. A dedicated pelvic MRI was subsequently performed, confirming the presence of fat signal intensity tissue throughout all sequences, without suspicious contrast enhancement, consistent with scrotal involvement by MD.

Despite its typically insidious and asymptomatic progression, lipomatous masses in MD may exert compressive effects on adjacent structures. Involvement of the scrotal region is particularly relevant due to its proximity to the external genitalia, potentially leading to complications such as testicular atrophy and hidden penis syndrome, which were observed in this case.[4-6] However, at the time of writing, the patient remains under follow-up in the General Surgery outpatient clinic, with conservative management until symptoms justify surgical intervention.

To the best of our knowledge, scrotal involvement in MD is exceedingly rare, with only a few cases described in the literature.[6] Given this uncommon presentation, we believe this report is of particular interest, as it underscores the importance of including MD in the differential diagnosis of atypical scrotal masses – especially in chronic alcohol users with compatible phenotypic features – potentially avoiding unnecessary invasive procedures.

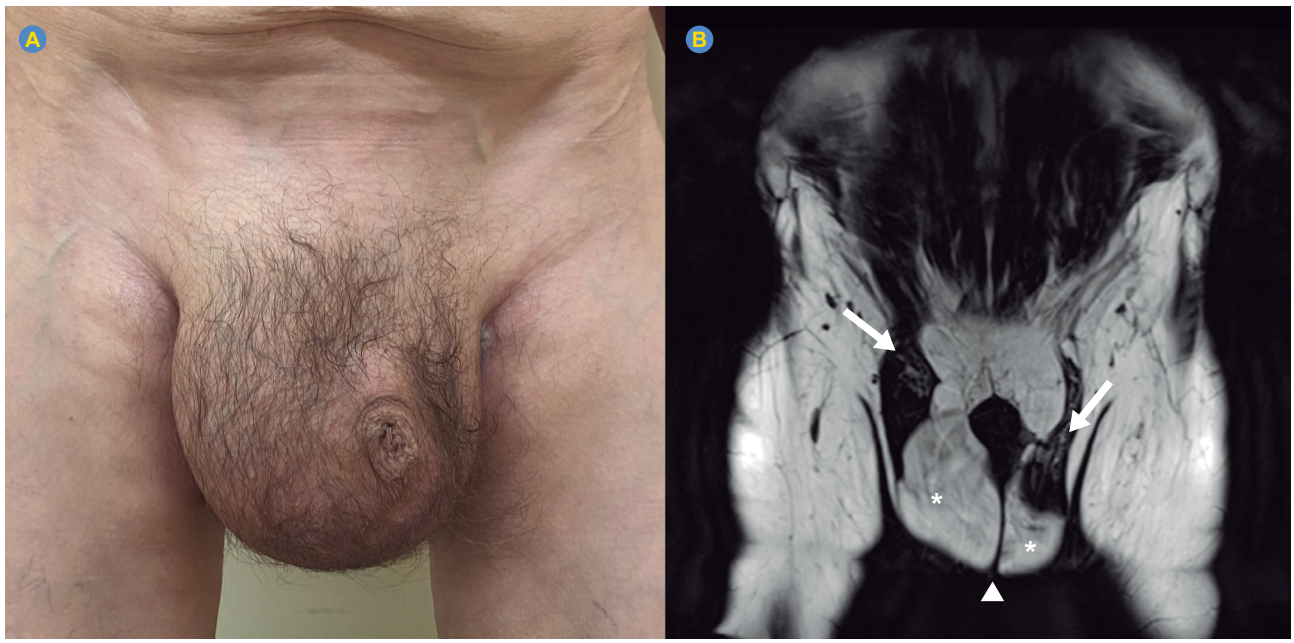


Figure 1 – Patient's photo of the genital area view showing marked bilateral scrotal enlargement, more prominent on the right side, causing a deformity aptly named hidden penis syndrome (A). Coronal T2-weighted MRI image of the scrotum, demonstrating large masses with high-signal intensity for fat deposition (asterisks), that causes a leftward shift of the scrotal septum (arrowhead) and superolateral displacement of the testis (arrows).

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

PA: Writing of the manuscript.

DG, IP: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Lee BH, Lee YM, Park SO, Chang LS, Kim YH. A case report of Madelung's disease. Arch Plast Surg. 2023;50:463-7.
2. Cucu AI, Sava A, Bobu AM, Costea CF, Hartie VL, Patrascanu E, et al. A case report of Madelung's disease in Romania. Diagnostics. 2025;15:459.
3. Szewc M, Sitarz R, Moroz N, Maciejewski R, Wierzbicki R. Madelung's disease – progressive, excessive, and symmetrical deposition of adipose tissue in the subcutaneous layer: case report and literature review. Diabetes Metab Syndr Obes. 2018;11:819-25.
4. Dung PT, Son TT, Son TQ, Tuan NM. Giant scrotal lipoma in Madelung's disease: a case report. Int J Surg Case Rep. 2023;106:108151.
5. Szychta P, Witmanowski H. Multiple symmetrical scrotal lipomatosis: diagnosis and treatment with comprehensive summary of the entity. Plast Reconstr Surg Glob Open. 2024;12:e5701.
6. da Costa JN, Gomes T, Matias J. Madelung disease affecting scrotal region. Ann Plast Surg. 2017;78:73-7.

Paulo André VIANA DE ARAÚJO [1], Diogo José GOMES GARRIDO [1], Isabel Cristina da Silva Basto SIMÕES DE PAIVAS [1]

1. Department of Radiology. Hospital Divino Espírito Santo. Ponta Delgada. Portugal.

✉ **Autor correspondente:** Paulo André Viana de Araújo. paulo.av.araujo@gmail.com

Recebido/*Received*: 29/07/2025 - **Aceite/*Accepted*:** 26/09/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23743

Patients with Substance Use Disorders: Challenges During Non-Psychiatric Inpatient Care

Doentes com Perturbação Por Uso de Substâncias: Desafios em Contexto de Internamento Não Psiquiátrico

Keywords: Inpatients; Patient Discharge; Substance-Related Disorders
Palavras-chave: Alta do Doente; Doentes Internados; Perturbações Relacionadas com Uso de Substâncias

Patients with substance use disorders (SUD) represent a vulnerable population in general hospital wards, where medical staff often face significant challenges in their care. These patients face a substantially higher risk of medical complications (infectious, hepatic, neurological, and oncological disorders) directly related to their substance use – notably, nearly one in five inpatients in general hospital wards has an SUD.[1]

Research indicates that individuals with SUD are up to three times more likely to leave against medical advice (AMA) compared with patients without SUD, particularly those with opioid use disorder, intravenous drug use, or recent psychiatric admissions.[1] Leaving AMA is strongly associated with higher rates of hospital readmission, 30-day mortality, and overdose risk.[2] One study reported a tenfold increase in overdose rates within the first month following an AMA discharge.[1]

Qualitative studies provide valuable insight into the factors driving early discharge and patient dissatisfaction.[1] Negative interactions with healthcare professionals, perceived stigma, and lack of trust are frequently reported. Patients often report feeling judged or labelled, with many describing dismissive attitudes toward their medical concerns. Inadequate pain management is another critical issue: fear of undertreatment and withdrawal symptoms often drives patients to self-discharge and resume substance use to alleviate discomfort. Withdrawal management and detoxification present further obstacles. Not all clinicians are familiar with evidence-based guidelines for opioid or polysubstance withdrawal, leading to inconsistent care and worsening of withdrawal symptoms. In some cases, the discontinuation of prescribed psychiatric or maintenance medications further compounds distress and contributes to premature hospital departure. Based on previous negative detoxification experiences, some patients even increase their substance use before admission, anticipating the discomfort and inadequate symptom management they may face in the hospital.[3]

Hospital policies regarding SUD remain highly variable. Punitive approaches – restricting visitation, or heightened surveillance – can worsen mistrust and provoke disengagement. Conversely, patient-centred policies that emphasize evidence-based addiction treatment, harm reduction, and neutral, non-stigmatizing language have been shown to improve outcomes. The establishment of dedicated inpatient addiction consultation teams significantly reduces AMA discharges, increases abstinence days, and lowers post-discharge emergency visits.[3,4]

To improve care for hospitalized patients with SUD, hospitals should adopt standardized protocols for withdrawal management, ensure adequate pain control, implement staff training to reduce stigma, and provide dedicated inpatient addiction consultation teams, which evidence suggests can play a pivotal role in ensuring comprehensive and equitable treatment.[5] Ongoing attention to these challenges is essential in general hospital care, reinforcing the need to consistently approach addiction as a medical condition.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Simon R, Snow R, Wakeman S. Understanding why patients with substance use disorders leave the hospital against medical advice: a qualitative study. Subst Abuse. 2019;40:503-9.
2. Choi M, Kim H, Qian H, Palepu A. Readmission rates of patients discharged against medical advice: a matched cohort study. PLoS One. 2011;6:e24459.
3. Wickremsinhe M, Holland A, Scott J, Gittins R, Brown M, Noctor A, et al. Improving hospital care for people who use drugs: deliberative process development of a clinical guideline for opioid withdrawal management. Harm Reduct J. 2024;21:201.
4. D'Orazio JD, Bares SH, Glancey C, Hibberd PL, Mathew TA. The impact of addiction medicine consultation on discharges against medical advice in patients with opioid use disorder and Staphylococcus aureus bacteremia. Open Forum Infect Dis. 2020;7:S152.
5. Wakeman SE, Metlay JP, Chang Y, Herman GE, Rigotti NA. Inpatient addiction consultation for hospitalized patients increases post-discharge abstinence and reduces addiction severity. J Gen Intern Med. 2017;32:909-16.

Marta RIBEIRO [1], Ana LOURENÇO [1]
1. Psychiatry and Mental Health Department. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
Autor correspondente: Marta Loureiro Ribeiro. martail.ribeiro@gmail.com
Recebido/*Received*: 07/08/2025 - **Aceite/*Accepted*:** 01/10/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23793

Minimally Symptomatic Primary Hyperparathyroidism with Brown Tumor in a Young Adult

Hiperparatiroidismo Primário Minimamente Sintomático com Tumores Castanhos num Adulto Jovem

Keywords: Hyperparathyroidism; Osteitis Fibrosa Cystica
Palavras-chave: Hiperparatiroidismo; Osteíte Fibrosa Quística

To the Editor,

We present a rare case of primary hyperparathyroidism (pHPT) presenting as lytic bone lesions. This is a late, rare, and severe manifestation whose incidence has markedly declined due to earlier biochemical screening.

A 23-year-old man presented with a mandibular mass, initially suspected to be odontogenic. Histopathology suggested a giant cell granuloma, and surgical excision was proposed. Preoperative labs showed hypercalcemia (14.5 mg/dL), very high parathyroid hormone (iPTH) levels (676 pg/mL), hypophosphatemia, and vitamin D deficiency. Neck ultrasonography and a Sestamibi scan identified a parathyroid lesion, and the patient underwent successful parathyroidectomy, with histology confirming an adenoma. Complete evaluation of primary hyperparathyroidism was performed postoperatively during endocrinology follow-up.

This case is noteworthy due to the absence of significant symptoms despite severe biochemical and skeletal involvement at two distinct sites: the mandible and the proximal tibia. Notably, the tibial lesion had been evaluated months earlier for mild knee pain, which was attributed to mechanical causes. As prior evaluations did not include serum calcium or iPTH measurements, this case underscores how easily pHPT can be underestimated in young patients when clinical suspicion is low.

Brown tumors, or osteitis fibrosa cystica, are benign lytic bone lesions resulting from excessive osteoclastic activity driven by persistently elevated iPTH levels. These lesions are non-neoplastic but potentially destructive complications of prolonged, untreated hyperparathyroidism. Histologically, they consist of fibrous stroma, multinucleated giant cells, and hemosiderin deposits, which account for their characteristic brown coloration. Radiographically, they appear as well-circumscribed radiolucent lesions and can mimic malignancies or metastatic disease.[1-3] As histopathology alone cannot distinguish giant cell granulomas from brown tumors, the biochemical profile is essential for diagnosis.

Before the advent of routine biochemical screening, osteitis fibrosa cystica were considered a hallmark of pHPT. Today, they occur in fewer than 3% of cases due to earlier diagnosis and treatment. When present, they most commonly appear as solitary lesions in older women. Multifocal involvement is extremely rare, particularly in young male patients.[4]

This case highlights important clinical considerations:

1. Primary hyperparathyroidism may present with minimal symptoms, and brown tumors remain a possible manifestation when diagnosis is delayed;
2. In young patients with lytic bone lesions or persistent osteoarticular pain, serum calcium and iPTH should be considered;
3. Parathyroidectomy is the definitive treatment and usually leads to regression of brown tumors;

At one-year follow-up, our patient remained asymptomatic, required no supplementation and showed regression of the lesions.

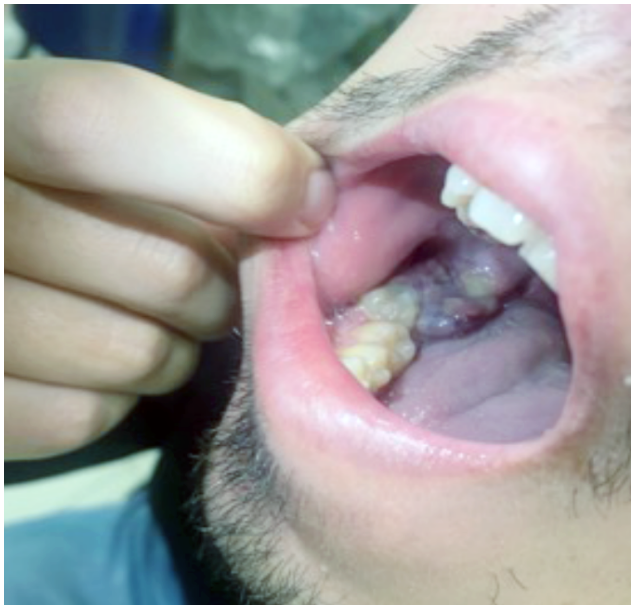


Figure 1 – Brown tumor in the right mandibular zygomatic quadrant

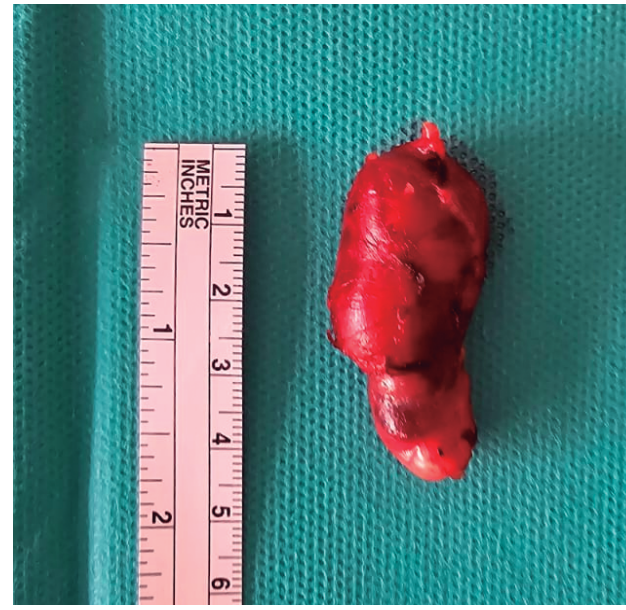


Figure 2 – Surgical specimen of targeted parathyroidectomy. Right inferior parathyroid gland measuring 4.0 × 2.0 × 1.5 cm and weighing 6.2 g (normal size: ~3 - 7 mm; normal weight: 30 - 50 mg).

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

EB: Conceptualization, data collection, writing of the manuscript.

VS, DA: Critical review of the manuscript.

JG, JR: Supervision, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Fraser WD. Hyperparathyroidism. Lancet. 2009;374:145-58.
2. Aldosari S, Alghamdi EA, Alragea A. Multiple brown tumors in primary hyperparathyroidism causing pathological fracture: a case report of a 21-year-old adult male. Cureus. 2023;15:e35979.
3. Lou I, Schneider DF, Sippel RS, Chen H, Elfenbein DM. The changing pattern of diagnosing primary hyperparathyroidism in young patients. Am J Surg. 2017;213:146-50.
4. Majumdar S, Uppala D, Kotina S, Alekhya B. Brown tumor of hyperparathyroidism with multiple lesions. J Oral Maxillofac Pathol. 2022;26:S111-5.

Eva BORGES [1,2], Vanessa REBELO SANTOS [1,2], David APARÍCIO [1,2], José GIRÃO [1,2], José ROCHA [1,2]

1. Department of Surgery. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
2. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.

✉ **Autor correspondente:** Eva Borges. evagomes@fm.ul.pt

Recebido/*Received*: 06/07/2025 - **Aceite/*Accepted*:** 01/10/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23646

Strongyloides stercoralis Hyperinfection in Pemphigus Vulgaris: A Neglected Preventable Fatality

Hiperinfeção por *Strongyloides stercoralis* em Pênfigo Vulgar: Uma Fatalidade Prevenível e Negligenciada

Keywords: Immunosuppressive Agents/adverse effects; Pemphigus/drug therapy; Strongyloides stercoralis; Strongyloidiasis/chemically induced; Strongyloidiasis/diagnosis; Strongyloidiasis/drug therapy; Superinfection
Palavras-chave: Estrongiloidíase/diagnóstico; Estrongiloidíase/induzida quimicamente; Estrongiloidíase/tratamento farmacológico; Imunossupressores/efeitos adversos; Pênfigo/tratamento farmacológico; Strongyloides stercoralis; Superinfecção

Dear Editor,

We read with great interest the recent case report by Tribolet de Abreu *et al* describing *Strongyloides stercoralis* hyperinfection syndrome in a patient with pemphigus vulgaris under immunosuppressive therapy.[1] "This case highlights critical lessons that extend beyond dermatology, offering valuable insights into general internal medicine, tropical medicine, and the safety of immunosuppressive therapy.".

While *S. stercoralis* is endemic to tropical and subtropical regions, its chronic indolent course often remains asymptomatic, allowing for silent persistence for decades via autoinfection.[2] "The use of corticosteroids has been identified as the most significant risk factor for precipitating hyperinfection or disseminated disease, due to their immunomodulatory effect that inhibits eosinophil function and accelerates parasite replication.[3] In the patient described, intermittent eosinophilia preceded the life-threatening complication, underscoring the need to integrate absolute eosinophil count monitoring into routine pre-immunosuppressive assessment, especially in at-risk populations.

Moreover, this case raises an urgent call to re-evaluate current screening strategies. Stool microscopy, despite being widely available, lacks sensitivity due to irregular larval shedding.[2] Although serological assays offer superior sensitivity, their availability remains inconsistent in lower-income and endemic regions. Enzyme-linked immunosorbent assay (ELISA)-based methods have demonstrated high sensitivity but may be limited by cross-reactivity with other helminths. Moreover, molecular assays, although highly specific, are often inaccessible in resource-constrained settings.[2,3] In this context, expert groups explicitly recommend that, in endemic regions with limited diagnostic capacity, empirical ivermectin administration before initiating immunosuppressive therapy should be considered a pragmatic and feasible preventive strategy.[3-5]

For migrant populations originating from endemic regions, pre-emptive screening or treatment is particularly important, as infection may persist for decades after leaving endemic areas.[6] Importantly, autochthonous cases have also been reported in non-endemic countries through risk factors such as agricultural work and prolonged soil contact.[7] Therefore, current guidelines emphasize risk-based approaches that combine epidemiological history, occupational exposure, and immune status in clinical decision-making.[3,6] Such a pre-emptive approach could prevent catastrophic outcomes, as mortality for untreated hyperinfection approaches 75%.[2]

This case also underscores an often-overlooked aspect of pemphigus management protocols. While baseline tuberculosis screening is routinely performed prior to initiating rituximab or high-dose corticosteroids, screening for *Strongyloides stercoralis* remains infrequently implemented—despite posing comparable morbidity risks. Dermatologists, rheumatologists, and oncologists managing immunosuppressive regimens should integrate *S. stercoralis* risk assessment into treatment algorithms, particularly in endemic or migrant populations from endemic areas.

We commend the authors for presenting this clinically and epidemiologically relevant case. We advocate for a paradigm shift from reactive diagnosis to proactive prevention of *S. stercorali* hyperinfection in all immunosuppressed patients at risk. This will require interdisciplinary awareness, updated guidelines, and health policy adaptation to prioritize accessible screening or empirical treatment. By integrating screening options, proposed guidelines, and context-specific strategies for both endemic and non-endemic regions, healthcare systems can significantly reduce preventable fatalities. Only through such measures can we mitigate this silent but preventable cause of mortality in immunocompromised patients.

ACKNOWLEDGMENTS

The authors declare that ChatGPT was used to improve language clarity and organization.

AUTHOR CONTRIBUTIONS

NKR: Conceptualization, literature review, manuscript drafting.

SKR: Supervision, validation, critical revision of the manuscript.

NC: Literature review, critical revision of the manuscript.

KLS: Critical revision of the manuscript.

All authors approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Tribolet de Abreu I, de Vasconcelos P, Moiteiro da Cruz R, Soares-Almeida L, Filipe P. Nonfatal strongyloides stercoralis hyperinfection secondary to pemphigus vulgaris immunosuppressant treatment: case report and brief literature review. Acta Med Port. 2025;38:427-32.
2. Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *strongyloides stercoralis*. Curr Opin Infect Dis. 2012;25:458-63.
3. Requena-Méndez A, Buonfrate D, Gomez-Junyent J, Zammarchi L, Bisoffi Z, Muñoz J. Evidence-based guidelines for screening and management of strongyloidiasis in non-endemic countries. Am J Trop Med Hyg. 2017;97:645-52.
4. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. Clin Microbiol Rev. 2004;17:208-17.
5. Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, Van Den Ende J, et al. Severe strongyloidiasis: a systematic review of case reports. BMC Infect Dis. 2013;13:78.
6. Schär F, Trostdorf U, Giardina F, Khieu V, Muth S, Marti H, et al. *Strongyloides stercoralis*: global distribution and risk factors. PLoS Negl Trop Dis. 2013;7:e2288.
7. Román-Sánchez P, Pastor-Guzmán A, Moreno-Guillén S, Igual-Adell R, Suñer-Generoso S, Tornero-Estébanez C. High prevalence of Strongyloides stercoralis among farm workers on the Mediterranean coast of Spain: analysis of the predictive factors of infection in developed countries. Am J Trop Med Hyg. 2003;69:336-40.

Nathkapach KAEWPITOON RATTANAPITOON [1] ✉, Natthawut CHAROENPHON [2], Khristine LAGUADOR SANDOVAL [3], Schawanya KAEWPITOON RATTANAPITOON [1]

1. Parasitic Disease Research. FMC Medical Center. Nakhon Ratchasima. Thailand.
2. Faculty of Medical Science. Naresuan University. Pitsanulok. Thailand.
3. School of Arts and Sciences. National University. Philippines. Pasay City. Philippines.

✉ **Autor correspondente:** Nathkapach Kaewpitoon Rattanapitoon. nathkapach.ratt@gmail.com

Recebido/*Received*: 24/07/2025 - **Aceite/*Accepted*:** 06/10/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23728

Healthy Life Years After 65: Building on Portugal's Progress with Stronger Geriatric Medicine

Anos de Vida Saudável Após os 65: Consolidar os Progressos de Portugal com uma Medicina Geriátrica mais Forte

Keywords: Geriatricians/education; Geriatrics/education
Palavras-chave: Geriatras/educação; Geriatria/educação

Recent demographic reports from Eurostat and the Portuguese Centre for Planning and Policy Evaluation (PLANAPP) highlight the growing relevance of population aging.[1,2] Portugal stands out among the three European countries with the largest increase in perceived healthy life years (HLY) at age 65 over the last decade, with a gain of 2.3 years.[3]

Data show that at age 65, HLY is approximately 7.3 years for women and 9.1 years for men. This is a positive indicator for the health of the Portuguese population. Nevertheless, two points merit attention. First, HLY after age 65 remains below the European average, especially for women (9.6 years for women and 9.2 years for men) and well below the 14 years of HLY observed in some Nordic countries. Second, this phenomenon occurs despite overall life expectancy in Portugal (82.5 years) being above the European average (81.4 years), including some of the Nordic countries.[3] As a result, by age 74, the average older adult in Portugal is expected to live with functional limitations, which suggests that further improvements in HLY are still needed.

The gender gap in HLY is notable: women, despite living longer than men, spend a greater proportion of their later years with functional limitations. This discrepancy likely reflects a higher burden of chronic disease, lower education levels, differences in occupational history and variations in symptom reporting.[1]

Portugal's gains in HLY at age 65 coincide with the development of the field of geriatric medicine,[4] which remains essential to sustain and expand these improvements. The development of orthogeriatric and oncogeriatric units, outpatient clinics, and acute care units has promoted active aging and has been progressively implemented over the last 10 to 15 years.[4] However, geriatrics is still not formally recognized as a specialty in Portugal, and only 113 physicians currently hold the official competency in geriatrics awarded by the Portuguese Medical Association (0.16% of all specialists), underscoring the need for further investment in specialized training.[1]

Moreover, population aging throughout the country is highly uneven, with sharper trends in inner regions and the autonomous regions, such as the Azores. This geographic variability calls for a strategic allocation of geriatric services to areas with the greatest aging pressures.[1]

Geriatric medicine, centered on preserving functionality and autonomy, aligns with the World Health Organization´s ICOPE (integrated care for older people) strategy to optimize intrinsic capacity. Its comprehensive approach – including multidimensional assessment, prevention of decline, frailty and fall management, and medication optimization – requires effective coordination across hospital, community, and post-discharge care.[5]

While the recent achievements are encouraging, sustaining progress in Portugal requires expanding programs promoting active aging and frailty prevention, improving health literacy, implementing the specialty of geriatrics and, investing in undergraduate and postgraduate training.

ACKNOWLEDGMENTS

The authors have declared that GPT-4 was used for language polishing. After using this tool, the work was reviewed and edited by the author, who assumes full responsibility for its content.

AUTHOR CONTRIBUTIONS

CC: Data collection and analysis, critical review of the manuscript.

FFR, AMS, HF: Critical review of the manuscript.

MA: Study design, data analysis, writing and critical review of the manuscript.

All authors approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Centro de Planeamento e de Avaliação de Políticas Públicas. Envelhecimento na população: perceções, recursos de saúde e respostas sociais. 2025. [cited 2025 Aug 20]. Available from: https://planapp.gov.pt/wp-content/uploads/2025/05/PLANAPP-NA-EnvelhecimentoPopulacao.pdf.
2. Eurostat. Population structure and ageing - statistics explained. [cited 2025 Jul 05]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing.
3. Eurostat. Healthy life years statistics - statistics explained. [cited 2025 Aug 12]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Healthy_life_years_statistics.
4. Alves M, Marques L, Bohn L, Osório F, Sarmento G, Bekerman C, et al. Value-based geriatric care: good news from Portugal. Acta Med Port. 2025;38:441-5.
5. Cesari M, Amuthavalli Thiyagarajan J, Cherubini A, Acanfora MA, Assantachai P, et al. Defining the role and reach of a geriatrician. Lancet Healthy Longev. 2024;5:100644.

Catarina CABRITA [1], Filipa FIALHO REIS [2,3], Ana Margarida SILVA [2,4], Hugo Alexandre FERREIRA [2], Mariana ALVES [2,3]

1. Medicina 2 (Polo da Ilha Do Pico). Hospital da Horta. Horta. Portugal.
2. Unidade de Ortogeriatria. Unidade Local de Saúde Santa Maria. Lisboa. Portugal.
3. Faculdade de Medicina. Universidade de Lisboa. Lisboa. Portugal.
4. Serviço de Ortopedia. Unidade Local de Saúde Santa Maria. Lisboa. Portugal.

✉ **Autor correspondente:** Mariana Alves. mariana.alves@medicina.ulisboa.pt

Revisto por/*Reviewed by*: Céu Rocha

Recebido/*Received*: 26/08/2025 - **Aceite/*Accepted*:** 08/10/2025 - **Publicado/*Published*:** 02/12/2025

https://doi.org/10.20344/amp.23872

Correction to the Article "Pediatric Sarcopenia: What do We Know?"

Errata ao Artigo "Sarcopenia Pediátrica: O que Sabemos?"

Following publication of the original article, the authors identified errors in the content. The corrected text is presented below. The original article has also been corrected.

Após a publicação do artigo original, os autores identificaram erros no conteúdo. O texto corrigido é apresentado abaixo. O artigo original também foi corrigido.

On page 801, in the fifth paragraph of the left column, a reference has been added, and the subsequent references have been renumbered. Thus, where it reads (in red):

"Although initially focused on the elderly, sarcopenia has emerged as a growing concern among pediatric populations, particularly in children with chronic diseases. Recently, some studies have suggested that it may also be present in asymptomatic children.[17]"

It should read (**in bold**):

"Although initially focused on the elderly, sarcopenia has emerged as a growing concern among pediatric populations, particularly in children with chronic diseases. Recently, some studies have suggested that it may also be present in asymptomatic children.**[18]**"

On page 805, in the second paragraph of the '**FUTURE PERSPECTIVES**' section, the last sentence has been removed (in red). Thus, where it reads:

"Due to the multifactorial nature of sarcopenia, there is an urgent need to develop validated biomarker panels for clinical use in both children and adults. Currently, inflammatory markers like TNF-alpha and IL-6 and others like testosterone, GH, creatinine, and carnitine are used.[65]

It should read:

"Due to the multifactorial nature of sarcopenia, there is an urgent need to develop validated biomarker panels for clinical use in both children and adults."

On page 805, in the third paragraph of the '**FUTURE PERSPECTIVES**' section, where it reads:

Genomic studies have identified certain sequences linked to an increased risk of sarcopenia, such as the *rs34415150* variant of *HLA-DQA1*, *rs143384* of *GDF5*, and *rs62102286* of DYM.[66] Additionally, in sarcopenic patients, genes like *MT1X* and ARHGAP36 have shown higher diagnostic precision compared to *FAM171A1, GPCPD1, ZNF415*, and *RXRG*, indicating their potential as predictive markers for early screening.[67] Circulating microRNAs (e.g., microRNA-1, microRNA-29a, microRNA-29b) have also been observed in patients with reduced physical performance.[68]"

It should read (**in bold**):

Genomic studies have identified certain sequences linked to an increased risk of sarcopenia **in older men and women**, such as the *rs34415150* variant of *HLA-DQA1*, *rs143384* of *GDF5*, and *rs62102286* of DYM.[67] Additionally, in sarcopenic patients, genes like *MT1X* and ARHGAP36 have shown higher diagnostic precision compared to *FAM171A1, GPCPD1, ZNF415*, and *RXRG*, indicating their potential as predictive markers for early screening.[68] Circulating microRNAs (e.g., microRNA-1, microRNA-29a, microRNA-29b) have also been observed in **adult** patients with reduced physical performance.[69]"

In the '**REFERENCES**' section, all references following reference 18 have been renumbered.

Thus, where it reads:

19. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol. 2008;586:2371-9.
20. Chomtho S, Wells JC, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;88:1040-8.
21. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32:228-35.
22. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, et al. Birth weight and muscle strength: a systematic review and meta-analysis. J Nutr Health Aging. 2012;16:609-15.
23. Narici MV, de Boer MD. Disuse of the musculo-skeletal system in space and on earth. Eur J Appl Physiol. 2011;111:403-20.
24. Jung HN, Jung CH, Hwang YC. Sarcopenia in youth. Metabolism. 2023;144:155557.

25. Benson AC, Torode ME, Fiatarone Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1:222-31.
26. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41:1361.
27. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. Nutrients. 2021;13:3519.
28. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12:2401.
29. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391:85-100.
30. Rezende IF, Conceição-Machado ME, Souza VS, Santos EM dos, Silva LR. Sarcopenia in children and adolescents with chronic liver disease. J Pediatria. 2020;96:439-46.
31. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-47.
32. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
33. Rubio-Arias JÁ, Rodríguez-Fernández R, Andreu L, Martínez-Aranda LM, Martínez-Rodriguez A, Ramos-Campo DJ. Effect of sleep quality on the prevalence of sarcopenia in older adults: a systematic review with meta-analysis. J Clin Med. 2019;8:2156.
34. Liu C, Cheung W, Li J, Chow SK, Yu J, Wong SH, et al. Understanding the gut microbiota and sarcopenia: a systematic review. J Cachexia Sarcopenia Muscle. 2021;12:1393-407.
35. Uptodate Free. Measurement of growth in children. 2024. [cited 31 May 2024]. Available from: https://pro.uptodatefree.ir/Show/5356.
36. Beunen GP, Rogol AD, Malina RM. Indicators of biological maturation and secular changes in biological maturation. Food Nutr Bull. 2006;27:S244-56.
37. Rogol AD. Growth, body composition and hormonal axes in children and adolescents. J Endocrinol Invest. 2003;26:855-60.
38. Narchi H, Alblooshi A, Altunaiji M, Alali N, Alshehhi L, Alshehhi H, et al. Prevalence of thinness and its effect on height velocity in schoolchildren. BMC Research Notes. 2021;14:98.
39. Li Y, Gao D, Liu J, Yang Z, Wen B, Chen L, et al. Prepubertal BMI, pubertal growth patterns, and long-term BMI: results from a longitudinal analysis in Chinese children and adolescents from 2005 to 2016. Eur J Clin Nutr. 2022;76:1432-9.
40. Marques M, Vieira F, Teles J, Baptista F. Growth and physical development of children at apparent risk of sarcopenia. Pediatr Res. 2025;97:843-50.
41. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34:771-5.
42. Kâ K, Rousseau MC, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. HRP. 2013;80:154-62.
43. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: a systematic review. Calcif Tissue Int. 2016;99:557-77.
44. Schoenau E. From mechanostat theory to development of the «functional muscle-bone-unit». J Musculoskelet Neuronal Interact. 2005;5:232-8.
45. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96:106-14.
46. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res. 2002;17:1095-101.
47. Matta PN, Baul TD, Loubeau K, Sikov J, Plasencia N, Sun Y, et al. Low sports participation is associated with withdrawn and depressed symptoms in urban, school-age children. J Affect Disord. 2021;280:24-9.
48. Bowden Davies KA, Pickles S, Sprung VS, Kemp GJ, Alam U, Moore DR, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. Ther Adv Endocrinol Metab. 2019;10:2042018819888824.
49. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32:S157-63.
50. Atlan L, Cohen S, Shiran S, Sira LB, Pratt LT, Yerushalmy-Feler A. Sarcopenia is a predictor for adverse clinical outcome in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2021;72:883-8.
51. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35:98-102.
52. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: its clinical significance. Int J Hematol. 2018;107:486-9.
53. Van Aller C, Lara J, Stephan BC, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999-2004. Clin Nutr. 2019;38:264-70.
54. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;1-8.
55. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31:583-601.
56. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4:371.
57. Trowbridge FL, Hiner CD, Robertson AD. Arm muscle indicators and creatinine excretion in children. Am J Clin Nutr. 1982;36:691-6.
58. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: a 4-year follow-up study. Muscle Nerve. 2013;47:856-63.
59. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9:249-59.
60. Lurz E, Patel H, Frimpong RG, Ricciuto A, Kehar M, Wales PW, et al. Sarcopenia in children with end-stage liver disease. J Pediatr Gastroenterol Nutr. 2018;66:222-6.
61. Ritz A, Lurz E, Berger M. Sarcopenia in children with solid organ tumors: an instrumental era. Cells. 2022;11:1278.
62. Mazahery H, von Hurst PR, McKinlay CJ, Cormack BE, Conlon CA. Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Maternal Health Neonatol Perinatol. 2018;4:12.
63. Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol. 2018;124:1-9.
64. Wang Z, Heshka S, Pietrobelli A, Chen Z, Silva AM, Sardinha LB, et al. A new total body potassium method to estimate total body skeletal muscle mass in children. J Nutr. 2007;137:1988-91.
65. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN, et al. Reduced body protein in children with spastic quadriplegic cerebral palsy2. Am J Clin Nutr. 2006;83:613-8.
66. Curcio F, Ferro G, Basile C, Liguori I, Parrella P, Pirozzi F, et al. Biomarkers in sarcopenia: a multifactorial approach. Exp Gerontol. 2016;85:1-8.
67. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12:654.
68. Gadher SJ, Jarkovska K, Kovarova H. Reproductive therapies and a need for potential biomarkers for prognostic and diagnostic screening of women desperate to conceive. Expert Rev Proteomics. 2009;6:591-3.
69. Valášková S, Gažová A, Vrbová P, Koller T, Šalingova B, Adamičková A, et al. The severity of muscle performance deterioration in sarcopenia correlates with circulating muscle tissue-specific miRNAs. Physiol Res. 2021;70:S91-8.
70. Jativa SD, Thapar N, Broyles D, Dikici E, Daftarian P, Jiménez JJ, et al. Enhanced delivery of plasmid DNA to skeletal muscle cells using a DLC8-binding peptide and ASSLNIA-modified PAMAM dendrimer. Mol Pharm. 2019;16:2376-84.
71. Poussard S, Decossas M, Bihan OL, Mornet S, Naudin G, Lambert O. Internalization and fate of silica nanoparticles in C2C12 skeletal muscle cells:

evidence of a beneficial effect on myoblast fusion. IJN. 2015;10:1479-92.
72. Michiue K, Takayama K, Taniguchi A, Hayashi Y, Kogure K. Increasing skeletal muscle mass in mice by non-invasive intramuscular delivery of myostatin inhibitory peptide by iontophoresis. Pharmaceuticals. 2023;16:397.
73. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
74. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020;11:348-65.
75. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria transplantation from stem cells for mitigating sarcopenia. Aging Dis. 2023;14:1700-13.

It should read:

19. Kwon EJ, Kim YJ. What is fetal programming? a lifetime health is under the control of in utero health. Obstet Gynecol Sci. 2017;60:506-19.
20. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol. 2008;586:2371-9.
21. Chomtho S, Wells JC, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;88:1040-8.
22. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32:228-35.
23. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, et al. Birth weight and muscle strength: a systematic review and meta-analysis. J Nutr Health Aging. 2012;16:609-15.
24. Narici MV, de Boer MD. Disuse of the musculo-skeletal system in space and on earth. Eur J Appl Physiol. 2011;111:403-20.
25. Jung HN, Jung CH, Hwang YC. Sarcopenia in youth. Metabolism. 2023;144:155557.
26. Benson AC, Torode ME, Fiatarone Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1:222-31.
27. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41:1361.
28. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. Nutrients. 2021;13:3519.
29. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12:2401.
30. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391:85-100.
31. Rezende IF, Conceição-Machado ME, Souza VS, Santos EM dos, Silva LR. Sarcopenia in children and adolescents with chronic liver disease. J Pediatria. 2020;96:439-46.
32. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-47.
33. Zhang G, Wang D, Chen J, Tong M, Wang J, Chang J, et al. Association of sleep duration and prevalence of sarcopenia: a large cross-sectional study. Prev Med Rep. 2024;42:102741.
34. Rubio-Arias JÁ, Rodríguez-Fernández R, Andreu L, Martínez-Aranda LM, Martínez-Rodriguez A, Ramos-Campo DJ. Effect of sleep quality on the prevalence of sarcopenia in older adults: a systematic review with meta-analysis. J Clin Med. 2019;8:2156.
35. Liu C, Cheung W, Li J, Chow SK, Yu J, Wong SH, et al. Understanding the gut microbiota and sarcopenia: a systematic review. J Cachexia Sarcopenia Muscle. 2021;12:1393-407.
36. Uptodate Free. Measurement of growth in children. 2024. [cited 31 May 2024]. Available from: https://pro.uptodatefree.ir/Show/5356.
37. Beunen GP, Rogol AD, Malina RM. Indicators of biological maturation and secular changes in biological maturation. Food Nutr Bull. 2006;27:S244-56.
38. Rogol AD. Growth, body composition and hormonal axes in children and adolescents. J Endocrinol Invest. 2003;26:855-60.
39. Narchi H, Alblooshi A, Altunaiji M, Alali N, Alshehhi L, Alshehhi H, et al. Prevalence of thinness and its effect on height velocity in schoolchildren. BMC Research Notes. 2021;14:98.
40. Li Y, Gao D, Liu J, Yang Z, Wen B, Chen L, et al. Prepubertal BMI, pubertal growth patterns, and long-term BMI: results from a longitudinal analysis in Chinese children and adolescents from 2005 to 2016. Eur J Clin Nutr. 2022;76:1432-9.
41. Marques M, Vieira F, Teles J, Baptista F. Growth and physical development of children at apparent risk of sarcopenia. Pediatr Res. 2025;97:843-50.
42. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34:771-5.
43. Kâ K, Rousseau MC, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. HRP. 2013;80:154-62.
44. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: a systematic review. Calcif Tissue Int. 2016;99:557-77.
45. Schoenau E. From mechanostat theory to development of the «functional muscle-bone-unit». J Musculoskelet Neuronal Interact. 2005;5:232-8.
46. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96:106-14.
47. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res. 2002;17:1095-101.
48. Matta PN, Baul TD, Loubeau K, Sikov J, Plasencia N, Sun Y, et al. Low sports participation is associated with withdrawn and depressed symptoms in urban, school-age children. J Affect Disord. 2021;280:24-9.
49. Bowden Davies KA, Pickles S, Sprung VS, Kemp GJ, Alam U, Moore DR, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. Ther Adv Endocrinol Metab. 2019;10:2042018819888824.
50. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32:S157-63.
51. Atlan L, Cohen S, Shiran S, Sira LB, Pratt LT, Yerushalmy-Feler A. Sarcopenia is a predictor for adverse clinical outcome in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2021;72:883-8.
52. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35:98-102.
53. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: its clinical significance. Int J Hematol. 2018;107:486-9.
54. Van Aller C, Lara J, Stephan BC, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999-2004. Clin Nutr. 2019;38:264-70.
55. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;1-8.
56. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31:583-601.
57. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4:371.
58. Trowbridge FL, Hiner CD, Robertson AD. Arm muscle indicators and creatinine excretion in children. Am J Clin Nutr. 1982;36:691-6.
59. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: a 4-year follow-up study. Muscle Nerve. 2013;47:856-63.

60. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9:249-59.
61. Lurz E, Patel H, Frimpong RG, Ricciuto A, Kehar M, Wales PW, et al. Sarcopenia in children with end-stage liver disease. J Pediatr Gastroenterol Nutr. 2018;66:222-6.
62. Ritz A, Lurz E, Berger M. Sarcopenia in children with solid organ tumors: an instrumental era. Cells. 2022;11:1278.
63. Mazahery H, von Hurst PR, McKinlay CJ, Cormack BE, Conlon CA. Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Maternal Health Neonatol Perinatol. 2018;4:12.
64. Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol. 2018;124:1-9.
65. Wang Z, Heshka S, Pietrobelli A, Chen Z, Silva AM, Sardinha LB, et al. A new total body potassium method to estimate total body skeletal musclemass in children. J Nutr. 2007;137:1988-91.
66. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN, et al. Reduced body protein in children with spastic quadriplegic cerebral palsy2. The American Journal of Clinical Nutrition.2006;83:613-8.
67. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12:654.
68. Lin S, Ling M, Chen C, Cai X, Yang F, Fan Y. Screening potential diagnostic biomarkers for age-related sarcopenia in the elderly population by WGCNA and LASSO. BioMed Res Int. 2022;2022:7483911.
69. Valášková S, Gažová A, Vrbová P, Koller T, Šalingova B, Adamičková A, et al. The severity of muscle performance deterioration in sarcopenia correlates with circulating muscle tissue-specific miRNAs. Physiol Res. 2021;70:S91-8.
70. Jativa SD, Thapar N, Broyles D, Dikici E, Daftarian P, Jiménez JJ, et al. Enhanced delivery of plasmid DNA to skeletal muscle cells using a DLC8-binding peptide and ASSLNIA-modified PAMAM dendrimer. Mol Pharm. 2019;16:2376-84.
71. Poussard S, Decossas M, Bihan OL, Mornet S, Naudin G, Lambert O. Internalization and fate of silica nanoparticles in C2C12 skeletal muscle cells: evidence of a beneficial effect on myoblast fusion. IJN. 2015;10:1479-92.
72. Michiue K, Takayama K, Taniguchi A, Hayashi Y, Kogure K. Increasing skeletal muscle mass in mice by non-invasive intramuscular delivery of myostatin inhibitory peptide by iontophoresis. Pharmaceuticals. 2023;16:397.
73. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
74. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020;11:348-65.
75. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria transplantation from stem cells for mitigating sarcopenia. Aging Dis. 2023;14:1700-13.
76. Najm A, Niculescu AG, Grumezescu AM, Beuran M. Emerging therapeutic strategies in sarcopenia: an updated review on pathogenesis and treatment advances. Int J Mol Sci. 2024;25:4300.

Original article:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23301/15785
Updated article:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23301/15836

Na página 801, no quinto parágrafo da coluna da esquerda, foi acrescentada uma referência e as referências seguintes foram renumeradas. Assim, onde se lê (a vermelho):

"Although initially focused on the elderly, sarcopenia has emerged as a growing concern among pediatric populations, particularly in children with chronic diseases. Recently, some studies have suggested that it may also be present in asymptomatic children.[17]"

Deverá ler-se (**a negrito**):

"Although initially focused on the elderly, sarcopenia has emerged as a growing concern among pediatric populations, particularly in children with chronic diseases. Recently, some studies have suggested that it may also be present in asymptomatic children.[18]"

Na página 805, no segundo parágrafo da secção '***FUTURE PERSPECTIVES***', a última frase foi removida (a vermelho). Assim, onde se lê:

"*Due to the multifactorial nature of sarcopenia, there is an urgent need to develop validated biomarker panels for clinical use in both children and adults. Currently, inflammatory markers like TNF-alpha and IL-6 and others like testosterone, GH, creatinine, and carnitine are used.[65]"*

Deverá ler-se:

"Due to the multifactorial nature of sarcopenia, there is an urgent need to develop validated biomarker panels for clinical use in both children and adults."

Na página 805, no terceiro parágrafo da secção '***FUTURE PERSPECTIVES***', onde se lê:

"Genomic studies have identified certain sequences linked to an increased risk of sarcopenia, such as the rs34415150 *variant of* HLA-DQA1*,* rs143384 *of* GDF5*, and* rs62102286 *of DYM.[66] Additionally, in sarcopenic patients, genes like* MT1X *and* ARHGAP36 *have shown higher diagnostic precision compared to* FAM171A1*,* GPCPD1*,* ZNF415*, and* RXRG*,*

indicating their potential as predictive markers for early screening.[67] Circulating microRNAs (e.g., microRNA-1, microRNA-29a, microRNA-29b) have also been observed in patients with reduced physical performance.[68]"

Deverá ler-se (**a negrito**):

"Genomic studies have identified certain sequences linked to an increased risk of sarcopenia ***in older men and women****, such as the* rs34415150 *variant of* HLA-DQA1, rs143384 *of* GDF5*, and* rs62102286 *of DYM.[67] Additionally, in sarcopenic patients, genes like* MT1X *and* ARHGAP36 *have shown higher diagnostic precision compared to* FAM171A1, GPCPD1, ZNF415*, and* RXRG*, indicating their potential as predictive markers for early screening.[68] Circulating microRNAs (e.g., microRNA-1, microRNA-29a, microRNA-29b) have also been observed in* ***adult*** *patients with reduced physical performance.[69]"*

Na secção '***REFERENCES***', todas as referências após a referência 18 foram renumeradas.

Assim, onde se lê:

19. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol. 2008;586:2371-9.
20. Chomtho S, Wells JC, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;88:1040-8.
21. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32:228-35.
22. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, et al. Birth weight and muscle strength: a systematic review and meta-analysis. J Nutr Health Aging. 2012;16:609-15.
23. Narici MV, de Boer MD. Disuse of the musculo-skeletal system in space and on earth. Eur J Appl Physiol. 2011;111:403-20.
24. Jung HN, Jung CH, Hwang YC. Sarcopenia in youth. Metabolism. 2023;144:155557.
25. Benson AC, Torode ME, Fiatarone Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1:222-31.
26. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41:1361.
27. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. Nutrients. 2021;13:3519.
28. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12:2401.
29. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391:85-100.
30. Rezende IF, Conceição-Machado ME, Souza VS, Santos EM dos, Silva LR. Sarcopenia in children and adolescents with chronic liver disease. J Pediatria. 2020;96:439-46.
31. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-47.
32. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
33. Rubio-Arias JÁ, Rodríguez-Fernández R, Andreu L, Martínez-Aranda LM, Martínez-Rodriguez A, Ramos-Campo DJ. Effect of sleep quality on the prevalence of sarcopenia in older adults: a systematic review with meta-analysis. J Clin Med. 2019;8:2156.
34. Liu C, Cheung W, Li J, Chow SK, Yu J, Wong SH, et al. Understanding the gut microbiota and sarcopenia: a systematic review. J Cachexia Sarcopenia Muscle. 2021;12:1393-407.
35. Uptodate Free. Measurement of growth in children. 2024. [cited 31 May 2024]. Available from: https://pro.uptodatefree.ir/Show/5356.
36. Beunen GP, Rogol AD, Malina RM. Indicators of biological maturation and secular changes in biological maturation. Food Nutr Bull. 2006;27:S244-56.
37. Rogol AD. Growth, body composition and hormonal axes in children and adolescents. J Endocrinol Invest. 2003;26:855-60.
38. Narchi H, Alblooshi A, Altunaiji M, Alali N, Alshehhi L, Alshehhi H, et al. Prevalence of thinness and its effect on height velocity in schoolchildren. BMC Research Notes. 2021;14:98.
39. Li Y, Gao D, Liu J, Yang Z, Wen B, Chen L, et al. Prepubertal BMI, pubertal growth patterns, and long-term BMI: results from a longitudinal analysis in Chinese children and adolescents from 2005 to 2016. Eur J Clin Nutr. 2022;76:1432-9.
40. Marques M, Vieira F, Teles J, Baptista F. Growth and physical development of children at apparent risk of sarcopenia. Pediatr Res. 2025;97:843-50.
41. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34:771-5.
42. Kâ K, Rousseau MC, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. HRP. 2013;80:154-62.
43. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: a systematic review. Calcif Tissue Int. 2016;99:557-77.
44. Schoenau E. From mechanostat theory to development of the «functional muscle-bone-unit». J Musculoskelet Neuronal Interact. 2005;5:232-8.
45. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96:106-14.
46. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res. 2002;17:1095-101.
47. Matta PN, Baul TD, Loubeau K, Sikov J, Plasencia N, Sun Y, et al. Low sports participation is associated with withdrawn and depressed symptoms in urban, school-age children. J Affect Disord. 2021;280:24-9.
48. Bowden Davies KA, Pickles S, Sprung VS, Kemp GJ, Alam U, Moore DR, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. Ther Adv Endocrinol Metab. 2019;10:2042018819888824.
49. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32:S157-63.
50. Atlan L, Cohen S, Shiran S, Sira LB, Pratt LT, Yerushalmy-Feler A. Sarcopenia is a predictor for adverse clinical outcome in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2021;72:883-8.
51. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35:98-102.
52. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: its clinical significance. Int J Hematol. 2018;107:486-9.
53. Van Aller C, Lara J, Stephan BC, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999-2004. Clin Nutr. 2019;38:264-70.
54. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;1-8.

55. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31:583-601.
56. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4:371.
57. Trowbridge FL, Hiner CD, Robertson AD. Arm muscle indicators and creatinine excretion in children. Am J Clin Nutr. 1982;36:691-6.
58. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: a 4-year follow-up study. Muscle Nerve. 2013;47:856-63.
59. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9:249-59.
60. Lurz E, Patel H, Frimpong RG, Ricciuto A, Kehar M, Wales PW, et al. Sarcopenia in children with end-stage liver disease. J Pediatr Gastroenterol Nutr. 2018;66:222-6.
61. Ritz A, Lurz E, Berger M. Sarcopenia in children with solid organ tumors: an instrumental era. Cells. 2022;11:1278.
62. Mazahery H, von Hurst PR, McKinlay CJ, Cormack BE, Conlon CA. Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Maternal Health Neonatol Perinatol. 2018;4:12.
63. Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol. 2018;124:1-9.
64. Wang Z, Heshka S, Pietrobelli A, Chen Z, Silva AM, Sardinha LB, et al. A new total body potassium method to estimate total body skeletal muscle mass in children. J Nutr. 2007;137:1988-91.
65. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN, et al. Reduced body protein in children with spastic quadriplegic cerebral palsy2. Am J Clin Nutr. 2006;83:613-8.
66. Curcio F, Ferro G, Basile C, Liguori I, Parrella P, Pirozzi F, et al. Biomarkers in sarcopenia: a multifactorial approach. Exp Gerontol. 2016;85:1-8.
67. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12:654.
68. Gadher SJ, Jarkovska K, Kovarova H. Reproductive therapies and a need for potential biomarkers for prognostic and diagnostic screening of women desperate to conceive. Expert Rev Proteomics. 2009;6:591-3.
69. Valášková S, Gažová A, Vrbová P, Koller T, Šalingova B, Adamičková A, et al. The severity of muscle performance deterioration in sarcopenia correlates with circulating muscle tissue-specific miRNAs. Physiol Res. 2021;70:S91-8.
70. Jativa SD, Thapar N, Broyles D, Dikici E, Daftarian P, Jiménez JJ, et al. Enhanced delivery of plasmid DNA to skeletal muscle cells using a DLC8-binding peptide and ASSLNIA-modified PAMAM dendrimer. Mol Pharm. 2019;16:2376-84.
71. Poussard S, Decossas M, Bihan OL, Mornet S, Naudin G, Lambert O. Internalization and fate of silica nanoparticles in C2C12 skeletal muscle cells: evidence of a beneficial effect on myoblast fusion. IJN. 2015;10:1479-92.
72. Michiue K, Takayama K, Taniguchi A, Hayashi Y, Kogure K. Increasing skeletal muscle mass in mice by non-invasive intramuscular delivery of myostatin inhibitory peptide by iontophoresis. Pharmaceuticals. 2023;16:397.
73. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
74. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020;11:348-65.
75. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria transplantation from stem cells for mitigating sarcopenia. Aging Dis. 2023;14:1700-13.

Deverá ler-se:

19. Kwon EJ, Kim YJ. What is fetal programming? a lifetime health is under the control of in utero health. Obstet Gynecol Sci. 2017;60:506-19.
20. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol. 2008;586:2371-9.
21. Chomtho S, Wells JC, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;88:1040-8.
22. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32:228-35.
23. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, et al. Birth weight and muscle strength: a systematic review and meta-analysis. J Nutr Health Aging. 2012;16:609-15.
24. Narici MV, de Boer MD. Disuse of the musculo-skeletal system in space and on earth. Eur J Appl Physiol. 2011;111:403-20.
25. Jung HN, Jung CH, Hwang YC. Sarcopenia in youth. Metabolism. 2023;144:155557.
26. Benson AC, Torode ME, Fiatarone Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1:222-31.
27. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41:1361.
28. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. Nutrients. 2021;13:3519.
29. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12:2401.
30. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391:85-100.
31. Rezende IF, Conceição-Machado ME, Souza VS, Santos EM dos, Silva LR. Sarcopenia in children and adolescents with chronic liver disease. J Pediatria. 2020;96:439-46.
32. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27:335-47.
33. Zhang G, Wang D, Chen J, Tong M, Wang J, Chang J, et al. Association of sleep duration and prevalence of sarcopenia: a large cross-sectional study. Prev Med Rep. 2024;42:102741.
34. Rubio-Arias JÁ, Rodríguez-Fernández R, Andreu L, Martínez-Aranda LM, Martínez-Rodriguez A, Ramos-Campo DJ. Effect of sleep quality on the prevalence of sarcopenia in older adults: a systematic review with meta-analysis. J Clin Med. 2019;8:2156.
35. Liu C, Cheung W, Li J, Chow SK, Yu J, Wong SH, et al. Understanding the gut microbiota and sarcopenia: a systematic review. J Cachexia Sarcopenia Muscle. 2021;12:1393-407.
36. Uptodate Free. Measurement of growth in children. 2024. [cited 31 May 2024]. Available from: https://pro.uptodatefree.ir/Show/5356.
37. Beunen GP, Rogol AD, Malina RM. Indicators of biological maturation and secular changes in biological maturation. Food Nutr Bull. 2006;27:S244-56.
38. Rogol AD. Growth, body composition and hormonal axes in children and adolescents. J Endocrinol Invest. 2003;26:855-60.
39. Narchi H, Alblooshi A, Altunaiji M, Alali N, Alshehhi L, Alshehhi H, et al. Prevalence of thinness and its effect on height velocity in schoolchildren. BMC Research Notes. 2021;14:98.
40. Li Y, Gao D, Liu J, Yang Z, Wen B, Chen L, et al. Prepubertal BMI, pubertal growth patterns, and long-term BMI: results from a longitudinal analysis in Chinese children and adolescents from 2005 to 2016. Eur J Clin Nutr. 2022;76:1432-9.
41. Marques M, Vieira F, Teles J, Baptista F. Growth and physical development of children at apparent risk of sarcopenia. Pediatr Res. 2025;97:843-50.

42. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34:771-5.
43. Kâ K, Rousseau MC, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. HRP. 2013;80:154-62.
44. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: a systematic review. Calcif Tissue Int. 2016;99:557-77.
45. Schoenau E. From mechanostat theory to development of the «functional muscle-bone-unit». J Musculoskelet Neuronal Interact. 2005;5:232-8.
46. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96:106-14.
47. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res. 2002;17:1095-101.
48. Matta PN, Baul TD, Loubeau K, Sikov J, Plasencia N, Sun Y, et al. Low sports participation is associated with withdrawn and depressed symptoms in urban, school-age children. J Affect Disord. 2021;280:24-9.
49. Bowden Davies KA, Pickles S, Sprung VS, Kemp GJ, Alam U, Moore DR, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. Ther Adv Endocrinol Metab. 2019;10:2042018819888824.
50. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32:S157-63.
51. Atlan L, Cohen S, Shiran S, Sira LB, Pratt LT, Yerushalmy-Feler A. Sarcopenia is a predictor for adverse clinical outcome in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2021;72:883-8.
52. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35:98-102.
53. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: its clinical significance. Int J Hematol. 2018;107:486-9.
54. Van Aller C, Lara J, Stephan BC, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999-2004. Clin Nutr. 2019;38:264-70.
55. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;1-8.
56. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31:583-601.
57. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4:371.
58. Trowbridge FL, Hiner CD, Robertson AD. Arm muscle indicators and creatinine excretion in children. Am J Clin Nutr. 1982;36:691-6.
59. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: a 4-year follow-up study. Muscle Nerve. 2013;47:856-63.
60. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9:249-59.
61. Lurz E, Patel H, Frimpong RG, Ricciuto A, Kehar M, Wales PW, et al. Sarcopenia in children with end-stage liver disease. J Pediatr Gastroenterol Nutr. 2018;66:222-6.
62. Ritz A, Lurz E, Berger M. Sarcopenia in children with solid organ tumors: an instrumental era. Cells. 2022;11:1278.
63. Mazahery H, von Hurst PR, McKinlay CJ, Cormack BE, Conlon CA. Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Maternal Health Neonatol Perinatol. 2018;4:12.
64. Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol. 2018;124:1-9.
65. Wang Z, Heshka S, Pietrobelli A, Chen Z, Silva AM, Sardinha LB, et al. A new total body potassium method to estimate total body skeletal musclemass in children. J Nutr. 2007;137:1988-91.
66. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN, et al. Reduced body protein in children with spastic quadriplegic cerebral palsy2. The American Journal of Clinical Nutrition.2006;83:613-8.
67. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12:654.
68. Lin S, Ling M, Chen C, Cai X, Yang F, Fan Y. Screening potential diagnostic biomarkers for age-related sarcopenia in the elderly population by WGCNA and LASSO. BioMed Res Int. 2022;2022:7483911.
69. Valášková S, Gažová A, Vrbová P, Koller T, Šalingova B, Adamičková A, et al. The severity of muscle performance deterioration in sarcopenia correlates with circulating muscle tissue-specific miRNAs. Physiol Res. 2021;70:S91-8.
70. Jativa SD, Thapar N, Broyles D, Dikici E, Daftarian P, Jiménez JJ, et al. Enhanced delivery of plasmid DNA to skeletal muscle cells using a DLC8-binding peptide and ASSLNIA-modified PAMAM dendrimer. Mol Pharm. 2019;16:2376-84.
71. Poussard S, Decossas M, Bihan OL, Mornet S, Naudin G, Lambert O. Internalization and fate of silica nanoparticles in C2C12 skeletal muscle cells: evidence of a beneficial effect on myoblast fusion. IJN. 2015;10:1479-92.
72. Michiue K, Takayama K, Taniguchi A, Hayashi Y, Kogure K. Increasing skeletal muscle mass in mice by non-invasive intramuscular delivery of myostatin inhibitory peptide by iontophoresis. Pharmaceuticals. 2023;16:397.
73. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
74. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020;11:348-65.
75. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria transplantation from stem cells for mitigating sarcopenia. Aging Dis. 2023;14:1700-13.
76. Najm A, Niculescu AG, Grumezescu AM, Beuran M. Emerging therapeutic strategies in sarcopenia: an updated review on pathogenesis and treatment advances. Int J Mol Sci. 2024;25:4300.

Artigo original:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23301/15785

Artigo corrigido:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23301/15836

https://doi.org/10.20344/amp.24225

www.actamedicaportuguesa.com