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Huntington's Disease and Psychiatric Comorbidities: A Retrospective Study in Portugal

Doença de Huntington e Comorbilidade Psiquiátrica: Um Estudo Retrospectivo em Portugal

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ABSTRACT

Introduction: Huntington's disease is a progressive neurodegenerative disorder characterized by motor, cognitive, and behavioral symptoms. While psychiatric comorbidity is common and may influence disease outcomes, there is a lack of data on its prevalence and impact in Portugal. This study aimed to analyze the frequency and impact of a diagnosis of psychiatric comorbidities among Huntington's disease hospitalized patients in Portugal.

Methods: A retrospective observational study was conducted using administrative data from Portuguese public hospitals within the National Health Service between 2000 and 2016. All hospitalization episodes of patients with a diagnosis of Huntington's disease (International Classification of Diseases, Ninth Revision, Clinical Modification code 333.4) were analyzed. Comorbid psychiatric diagnoses registered as primary or secondary diagnoses were identified and defined using the Clinical Classification Software codes 650-670. Age at admission, length of hospital stay, admission type, in-hospital mortality, and estimated hospital charges were analyzed according to psychiatric comorbidity categories and adjusting for age and sex.

Results: A total of 1667 hospitalizations with a diagnosis of Huntington's disease occurred between 2000 and 2016, of which 28.97% had a psychiatric comorbidity. These patients were more likely to be younger (adjusted odds ratio = 1.32, 95% confidence interval 1.07 - 1.64; $p = 0.011$) and to have longer hospitalizations (adjusted odds ratio = 1.88, 95% confidence interval 1.52 - 2.34; $p < 0.001$) than those with no psychiatric comorbidity. No association was found between psychiatric comorbidity in general and in-hospital mortality, admission type or hospitalization costs. An upward trend was observed in Huntington's disease admissions and the percentage of those with psychiatric comorbidity over the study period.

Conclusion: Psychiatric comorbidity in Huntington's disease was associated with younger age at admission and longer hospitalizations. These results highlight the importance of psychiatric care in the management of these patients. Early screening and intervention could improve outcomes and optimize healthcare resource allocation.

Keywords: Comorbidity; Hospitalization; Huntington Disease; Mental Disorders; Portugal; Routinely Collected Health Data

RESUMO

Introdução: A doença de Huntington é uma doença neurodegenerativa progressiva, caracterizada por sintomas motores, cognitivos e comportamentais. Embora a comorbilidade psiquiátrica seja comum e possa influenciar *outcomes*, há falta de dados sobre a sua prevalência e impacto em Portugal. O objetivo deste estudo foi analisar a frequência e o impacto do diagnóstico de comorbilidades psiquiátricas entre os doentes internados com doença de Huntington em Portugal.

Métodos: Um estudo observacional retrospetivo foi conduzido utilizando dados administrativos de hospitais públicos do Serviço Nacional de Saúde em Portugal continental entre 2000 e 2016. Todos os episódios de hospitalizações com diagnóstico de doença de Huntington (código 333.4 do *International Classification of Diseases, Ninth Revision, Clinical Modification*) foram analisados. Comorbilidades psiquiátricas registadas como diagnósticos primários ou secundários foram identificadas e definidas utilizando os códigos 650-670 do *Clinical Classification Software*. Idade à admissão, tempo de internamento, tipo de admissão, mortalidade intrahospitalar e custos de internamento estimados foram analisados de acordo com a presença de comorbilidade psiquiátrica e ajustados para idade e sexo.

Resultados: Houve um total de 1667 internamentos com diagnóstico de doença de Huntington entre 2000 e 2016, dos quais 28,97% tinham comorbilidade psiquiátrica. Estes doentes tinham maior probabilidade de serem mais jovens (*adjusted odds ratio* = 1,32, intervalo de confiança de 95% 1,07 - 1,64; $p = 0,011$) e de terem um internamento mais longo (*adjusted odds ratio* = 1,88, intervalo de confiança de 95% 1,52 - 2,34; $p < 0,001$) do que os doentes sem comorbilidade psiquiátrica. Não foi encontrada associação entre comorbilidade psiquiátrica em geral e mortalidade intra-hospitalar, tipo de admissão ou custos de internamento. Foi observada uma tendência crescente de internamentos com doença de Huntington e percentagem destes com comorbilidade psiquiátrica ao longo do tempo do estudo.

Conclusão: Comorbilidade psiquiátrica na doença de Huntington associou-se a idade mais jovem à admissão e a hospitalizações mais longas. Estes resultados destacam a importância de cuidados psiquiátricos nestes doentes. Rastreios precoces e intervenções poderiam melhorar *outcomes* e otimizar a alocação de recursos em saúde.

Palavras-chave: Comorbilidade; Dados de Saúde Recolhidos Rotineiramente; Doença de Huntington; Hospitalização; Perturbações Mentais; Portugal

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KEY MESSAGES

- From the total of 1667 hospitalizations with a diagnosis of Huntington's disease, 28.97% had a psychiatric comorbidity, higher than the prevalence of psychiatric disease in the general Portuguese population.
- Patients with a psychiatric comorbidity had significantly higher length of stay and were significantly younger than those without.
- Strengths include being the first of its kind study in Portugal and the use of a large nationwide database over 17 years.
- Limitations include difficulty when generalizing results to the present and to the general Huntington's disease population, as only hospitalization episodes between 2000 and 2016 were studied; and those associated with retrospective observational studies and databases not primarily collected for research.

INTRODUCTION

Huntington's disease (HD) is a progressive, autosomal-dominant neurodegenerative disease characterized by motor, cognitive and behavioral symptoms. It is caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin gene (HTT) on chromosome 4.[1,2]

The worldwide prevalence of HD is estimated at 4.88 per 100 000 with an incidence of 0.48 cases per 100 000 person-years, with the prevalence being significantly higher in Europe. The distribution of normal CAG repeat length, which is associated with HD prevalence, in the Portuguese population (mode of 17 CAGs) is similar to others of Western European origin.[1,3]

The diagnosis of HD is made by genetic testing for the CAG expansion. Clinical diagnosis is based on established signs that appear long after the start of the disease process. The typical age of onset occurs in the prime of adult life (mean 45 years old), which, combined with the autosomal dominant inheritance, progressive course, and combination of symptoms, proves to be devastating for patients and their families.[1,4] The progression of HD is inexorable, commonly leading to death within 15 to 20 years of onset.

When it comes to motor symptoms, chorea usually predominates in the beginning of the disease course, being later overshadowed by parkinsonism. Neurocognitive decline caused by HD is described as a subcortical dementia, impairing executive function, attention and concentration, and causing erosion of personality, while keeping memory relatively intact.[5]

Psychiatric comorbidities are common in the course of HD, with patients being more than twice as likely to suffer from anxiety and attention deficit and more than three times as likely to suffer from depression, suicidality and obsessive-compulsive disorder when compared to the general population.[6] Historical estimates range from 33% to 76% for the lifetime prevalence of psychiatric disorders in HD patients.[7,8]

Mood disturbances may precede motor onset by 4 - 10 years and are some of the earliest manifestations of HD. The progression of HD does not seem to correlate with the severity of depression, suggesting that neurons involved in mood regulation and motor or cognitive skills are affected by different mechanisms. Apathy also increases in frequency and intensity as HD progresses, which differs from apathy in major depression in the general population.[9-12]

Lifetime suicide attempts were reported in 7% - 10% of HD patients, compared to 1% - 3% of the world population.[13] Suicidal ideation has also been found to be increased in asymptomatic at-risk individuals, increasing further in the prediagnostic phase, decreasing in recently diagnosed patients, but then increasing again in later stages of the disease.[14] Anxiety, depression, and substance use have been shown to increase the risk of suicidality in HD patients.[15-17]

Psychosis in HD seems to be more prevalent than previously reported, being found in 13% - 18% of patients. Its presence correlates with cognitive and functional deficits, as well as behavioral disturbances,[18,19] including higher rates of suicidal ideation/attempt, depression, irritability, violent/aggressive behavior, apathy, perseverative/obsessive behavior and alcohol/drug abuse.[19]

Other psychiatric conditions found in patients with HD include mania, executive dysfunction syndrome, apathy, irritability, perseveration, delirium, demoralization, sexual problems, and sleep problems.[5]

Considering the lack of data on the relation of HD and psychiatric comorbidities in Portugal, this study aimed to analyze the frequency and impact of a diagnosis of psychiatric comorbidities among HD hospitalized patients in Portugal between 2000 and 2016.

METHODS

Study design and reporting

A retrospective observational study was carried out using administrative data from all hospitalizations from 2000 to 2016 in Portuguese mainland public hospitals within the National Health Service (SNS), a universally accessible health system. The episodes were organized anonymously in a

national database provided by the Central Administration of the Health System (ACSS) of the Portuguese Ministry of Health. Data analysis, reporting and manuscript formatting respected the Reporting of studies Conducted using Observational Routinely-collected health data (RECORD) checklist.[20]

Data source

The database contained administrative information, diagnoses, and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) regarding all inpatient episodes. Data from autonomous administrations of Azores and Madeira or private hospitals, was not included in this database.

Sample selection

All inpatient episodes, discharged between 2000 and 2016 with a diagnosis of HD in Portuguese mainland public hospitals were included using ICD-9-CM code 333.4: Huntington's chorea. Associated, primary or secondary, psychiatric diagnoses were identified and grouped into categories using the HCUP Clinical Classification Software (CCS) category codes 650 - 670.

Variables

Data extracted included sex, age at admission, type of admission (unscheduled/urgent or scheduled), length of stay (LoS), primary and secondary diagnosis defined by the ICD-9-CM, and discharge destination. Outcome variables analyzed included in-hospital mortality, LoS, type of admission, and estimated hospital charges. Hospital charges were estimated based on the expenditure tables for the Portuguese National Health Service hospital reimbursement as defined by governmental decree in 2009 (*in Diário da República*).[21]

Data cleaning

Due to potential misclassification or input error, a low frequency (0.30%), nonsensical value in the type of admission variable was recoded into the most common value. For the same reason, two low-frequency values (1.80% and 0.84%) in the discharge destination variable were recoded into the most common value. Sensitivity analyses were conducted, excluding these cases.

Bias

Selection and information bias, as well as confounders, were considered. Selection bias was limited as all data was anonymized, and the authors had no involvement in data collection and clinical coding. Furthermore, the data comes from a universally accessible health system to the Portuguese population.

Information bias could arise from the use of administrative data and diagnosis classification systems – the ICD-9-CM code 333.4: Huntington's chorea used has been validated in a prior external study, showing a PPV of 75.5% and sensitivity of 50.0% for the identification of Huntington's disease. However, during that study, the code was combined with a Spanish modification (ICD-10-ES) for two of the 18 years of analysis.[22]

Age and sex were assumed to be likely confounders, and adjusted models (aOR) were calculated for each outcome.

Statistical analysis

Descriptive statistics were used to describe all inpatient episodes. Categorical variables were described as absolute (n =) and relative (%) frequencies. Continuous variables were presented as medians and quartiles (Q1;Q3).

Results were presented for the total number of HD hospitalizations, presence of any comorbid psychiatric diagnosis and presence of specific psychiatric diagnosis. The Mann Whitney-U test was used for non-normally distributed continuous variables and the chi-square test was used for categorical variables. Odds ratios (OR) were calculated to quantify associations between psychiatric comorbidities and age at admission, LoS, type of admission, in-hospital mortality and estimated hospital charges. Adjusted odds ratios (aOR) for age and sex were computed using logistic regression to explore the associations with LoS, type of admission, in-hospital mortality, estimated hospital charges, as well as age at admission (adjusted only for sex). Outcomes for categorical variables were dichotomized as present or absent. Age at admission, LoS and estimated hospital charges were dichotomized by median split.

All analyses were two-tailed, considering a *p*-value of less than 0.05 as statistically significant. Statistical analysis was performed using IBM SPSS Statistics® v.28.0.1.0. for Windows (Armonk, NY: IBM Corp).

Ethical considerations

The data used in this study was anonymized and approved by ACSS for secondary data research analysis. No primary data on human subjects or identifiable protected information was accessed by the authors.

RESULTS

There were a total of 1667 hospitalization episodes for patients with a Huntington's disease (HD) diagnosis over the 17-year (2000 - 2016) study period.

Characteristics of the study population are shown in Table 1. Age of patients at admission had a median age (Q1;Q3) of 58.00 (45.00; 70.00) years and 51.47% (858) of hospitalizations were of male patients. When it comes to

Table 1 – Episode characterization and outcomes in hospitalizations of patients with Huntington's disease, with and without psychiatric comorbidity

Variable	Estimate			*p*-value
	Total hospitalization episodes (n = 1667)	Without psychiatric comorbidity (n = 1184)	With psychiatric comorbidity (n = 483)	
Age at admission, years, median (Q1; Q3)	58.00 (45.00; 70.00)	58.00 (46.00; 70.00)	56.00 (44.00; 68.00)	**0.022**[a]
Sex, n (%)				0.148[b]
Female	809 (48.53)	588 (49.66)	221 (45.76)	
Male	858 (51.47)	596 (50.34)	262 (54.24)	
Admission type, n (%)				0.089[b]
Scheduled	366 (21.96)	273 (23.06)	93 (19.25)	
Unscheduled / urgent	1301 (78.04)	911 (76.94)	390 (80.75)	
Length of stay, days, median (Q1; Q3)	8.00 (4.00; 16.00)	7.00 (3.00; 14.00)	10.00 (6.00; 20.00)	**< 0.001**[a]
In-hospital mortality, n (%)	147 (8.80)	112 (9.46)	35 (7.25)	0.148[b]
Place after discharge, n (%)				0.273[b]
Home/self-care (routine discharge)	1408 (84.46)	994 (83.95)	414 (85.71)	
Against medical advice	7 (0.42)	3 (0.25)	4 (0.83)	
Another short-term general hospital	91 (5.46)	64 (5.41)	27 (5.59)	
Posterior specialized observation	14 (0.84)	11 (0.93)	3 (0.62)	
Estimated charges, €, median (Q1; Q3)	1762.68 (1704.93; 3048.99)	1781.61 (1683.84; 2878.62)	1762.68 (1762.68; 3060.73)	0.568[a]

Significant *p*-values < 0.05
n: number of hospitalization episodes; Q1: 1st quartile; Q3: 3rd quartile.
a: Mann-Whitney *U* test
b: chi-square test

admission type, 78.04% (1301) were unscheduled/urgent admissions. Most patients, 84.46% (1408) had a routine discharge to home/self-care and the median (Q1;Q3) for estimated hospitalization charges was €1762.68 (1704.93; 3048.99).

Of the total of hospitalizations (1667), 28.97% (483) had a registered psychiatric diagnosis. These patients were significantly younger, with a median (Q1;Q3) age at admission of 56.00 (44.00; 68.00) years, compared to a median (Q1;Q3) age at admission of 58.00 (46.00; 70.00) years in the group without psychiatric comorbidities ($p = 0.022$). Patients with psychiatric comorbidities were also significantly more likely to have a longer LoS, with a median (Q1;Q3) LoS of 10.00 (6.00; 20.00) days, in contrast with a median (Q1;Q3) LoS of 7.00 (3.00; 14.00) days for those without psychiatric comorbidities ($p < 0.001$).

During the study period, there was a general upward trend in both the number of total hospitalizations with HD and the percentage of those with psychiatric comorbidities (Table 2, Fig.1).

The prevalence of groups of comorbid psychiatric disorders is shown in Table 3. The most prevalent comorbidity groups were delirium, dementia and amnestic and other cognitive disorders [n = 173 (10.38%)] and mood disorders [n = 145 (8.70%)].

Outcomes depending on the presence of any psychiatric comorbid disorder are shown in Table 4 and Fig. 2. Patients with any psychiatric comorbidity were more likely to be younger (OR = 1.30, 95% CI 1.05 - 1.60; $p = 0.017$), even after adjusting for sex (aOR = 1.32, 95% CI 1.07 - 1.64; $p = 0.011$). Compared to episodes without psychiatric comorbidity, those with any psychiatric comorbidity were more likely to have a longer hospitalization duration (OR = 1.90, 95% CI 1.53 - 2.36; $p < 0.001$). After adjusting for age and sex, the association remained significant (aOR = 1.88, 95% CI 1.52 - 2.34; $p < 0.001$). No significant association was found between the presence of psychiatric comorbidity and in-hospital mortality, type of admission or hospitalization costs.

Characteristics and outcomes based on the presence of specific psychiatric comorbid disorder groups are shown in Table 5. Adjusting for sex, patients with developmental disorders were the most likely to be admitted at a younger age (aOR = 4.87, 95% CI 1.85 - 12.76; $p = 0.001$), followed by schizophrenia and other psychotic disorders (aOR = 3.57, 95% CI 1.76 - 7.27; $p < 0.001$), alcohol-related disorders

Table 2 – Trends in Huntington's disease hospitalizations with psychiatric comorbidity during the study period (2000 - 2016)

Year	Total hospitalizations, n =	Hospitalizations with psychiatric comorbidity, n =	Hospitalizations with psychiatric comorbidity, %
2000	44	5	11.36
2001	54	10	18.52
2002	52	14	26.92
2003	77	17	22.08
2004	54	19	24.68
2005	72	17	23.61
2006	87	22	26.29
2007	85	20	23.53
2008	100	29	29.00
2009	103	25	24.27
2010	111	32	28.83
2011	132	41	31.06
2012	140	48	34.29
2013	155	43	27.74
2014	124	46	37.10
2015	113	39	34.51
2016	164	56	34.15
Total	1667	483	28.97

n: number of hospitalization episodes

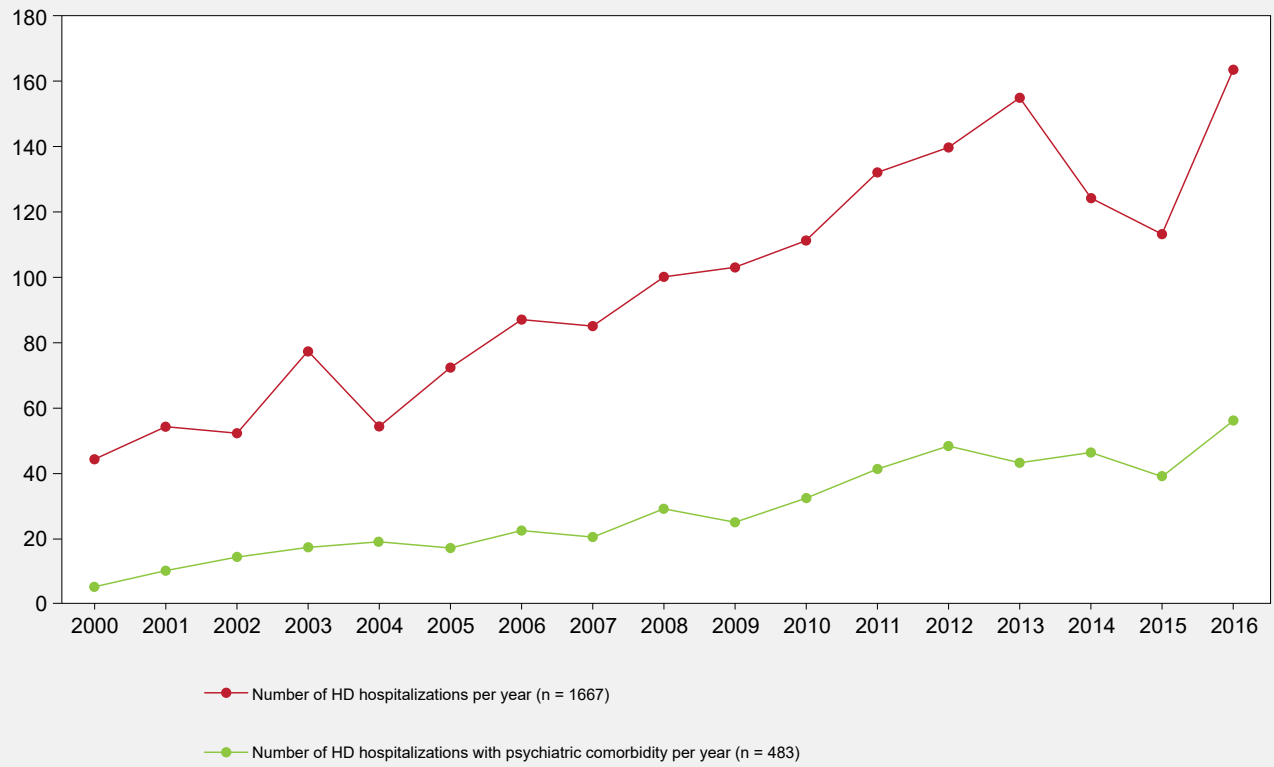

Figure 1 – Trends in Huntington's disease hospitalizations with psychiatric comorbidity during the study period (2000 - 2016)

Table 3 – Psychiatric comorbidities in hospitalizations of patients with Huntington's disease. Comorbidities classified using the Clinical Classification Software (CCS) for ICD-9-CM

Psychiatric comorbidities	n = (%)
Adjustment disorders	9 (0.54)
Anxiety disorders	30 (1.80)
Attention-deficit, conduct and disruptive behavior disorders	14 (0.84)
Delirium, dementia and amnestic and other cognitive disorders	173 (10.38)
Developmental disorders	31 (1.86)
Disorders usually diagnosed in infancy, childhood, or adolescence	0 (0.00)
Impulse control disorders, NEC	2 (0.12)
Mood disorders	145 (8.70)
Personality disorders	8 (0.50)
Schizophrenia and other psychotic disorders	46 (2.76)
Alcohol-related disorders	35 (2.10)
Substance-related disorders	5 (0.30)
Suicide and intentional self-inflicted injury	15 (0.90)
Screening and history of mental health and substance abuse codes	53 (3.18)
Miscellaneous mental health disorders	13 (0.78)

n: number of hospitalization episodes

(aOR = 2.16, 95% CI 1.06 - 4.39; p = 0.034) and mood disorders (aOR = 1.45, 95% CI 1.02 - 2.05; p = 0.039), whereas patients with delirium, dementia, and amnestic and other cognitive disorders were more likely to be older (aOR = 0.55, 95% CI 0.40-0.76; p < 0.001) than those with no psychiatric comorbidity.

The odds ratio for statistically significant longer LoS was highest in the anxiety disorders group (aOR = 2.53, 95% CI 1.15 - 5.57; p = 0.021), followed by delirium, dementia, and amnestic and other cognitive disorders (aOR = 2.20, 95% CI 1.57 - 3.06; p < 0.001) and mood disorders (aOR = 1.52, 95% CI 1.08 - 2.16; p = 0.017).

Patients within the screening and history of mental health and substance abuse codes group had a lower chance of being admitted in an unscheduled/urgent manner (aOR = 0.43, 95% CI 0.23 - 0.79; p = 0.007) than those with no psychiatric comorbidity.

No association was found between in-hospital mortality and any specific comorbid psychiatric disorder.

When it comes to hospitalization costs, schizophrenia and other psychotic disorders group (aOR = 2.86, 95% CI 1.12-7.31, p = 0.028) was the most likely to have higher estimated hospitalization charges, followed by delirium, dementia, and amnestic and other cognitive disorders (aOR = 1.52, 95% CI 1.02 - 2.25; p = 0.039). Patients with adjustment disorders were more likely to incur lower costs (aOR = 0.09, 95% CI 0.02 - 0.43; p = 0.003).

Results of sensitivity analyses, excluding cases with variable recoding due to nonsensical values, were similar to the primary results, as shown in the Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23438/15789).

DISCUSSION

This study provides an analysis of hospitalization patterns and outcomes in patients with HD over a 17-year period (2000 - 2016) in Portugal. There were a total of 1667 hospitalizations identified, with a median age at admission of 58.00 years, a slight predominance of men (51.47%) and a median LoS of 8.00 days. A study in Austria reported a younger median age at admission (50.08 years), a shorter median LoS (7 days) and a predominance of female patient admissions (67.9%). However, in that study, only 32.9% of patients required hospitalization, the rest being treated in a specialized outpatient department, indicating a potentially less severe disease population.[23] Most admissions in our study (78.04%) were unscheduled or urgent, possibly reflecting the acute nature of HD-related complications.

The prevalence of psychiatric comorbidities among HD hospitalized patients was 28.97%, which is higher than the point prevalence of psychiatric disease in the general population in Portugal (estimated at 22.9% according to a large study)[24] but lower than lifetime prevalence estimates in HD cohorts, which range from 33% to 76%.[7,8] This difference likely reflects the nature of our data, which captures diagnoses registered during hospitalizations, not representing cumulative lifetime morbidity.

There was a general upward trend in the number of HD

Table 4 – Outcomes in hospitalizations of patients with Huntington's disease according to the presence of any comorbid psychiatric disorder

	Age at admission ≤ 58 years		Length of stay > 8.00 days		Unscheduled / Urgent admission		In-hospital mortality		Estimated hospitalization charges > €1762.68	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Any comorbid psychiatric disorder	1.30 (1.05 - 1.60)	**0.017**	1.90 (1.53 - 2.36)	**< 0.001**	1.26 (0.97 - 1.64)	0.089	0.75 (0.50 - 1.10)	0.149	1.23 (1.00 - 1.64)	0.051
	aOR[a] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value
	1.32 (1.07 - 1.64)	**0.011**	1.88 (1.52 - 2.34)	**< 0.001**	1.27 (0.97 - 1.66)	0.082	0.79 (0.53 - 1.17)	0.235	1.28 (1.00 - 1.64)	0.052

Significant *p*-values < 0.05
a: adjusted for sex
b: adjusted for age and sex
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

hospitalizations and in the proportion with psychiatric comorbidities over the years, which could be due to increasing recognition and classification of HD and psychiatric disease or better coding in general. In fact, the amount of comorbidities reported in hospitalizations in Portuguese hospitals was shown to have increased between 2000 and 2010, attributed to better coding.[25]

The most common psychiatric comorbid disorders identified were delirium, dementia and amnestic and other cognitive disorders (10.38%), and mood disorders (8.70%). Comparing these figures with other studies is challenging due to differences in methods and data sources. For example, a German study reported substantially higher frequencies: depression in 42.9% of HD patients, anxiety in 12.3% and dementia in over a third.[26] However, that study included all insured HD patients, not just hospitalizations, which likely captured a different clinical picture. Similarly, the Austrian study mentioned found worsening of psychiatric symptoms to be the cause of admission in 43% of cases (46.6% of those relating to depression and 24.1% to psychotic behavior with delusions) and a primary psychiatric discharge diagnosis was registered in 13.3% of patients. However, only the primary reasons for admission were considered in that study, and a wider HD cohort was included (only 32.9% requiring hospital admission),[23] suggesting a population that may differ from the one in our study.

Patients with any kind of psychiatric comorbidity were found to have significantly higher length of stay (LoS), even after adjusting for age and sex. They were also more likely to be younger at admission, even when controlling for sex, suggesting higher complexity and/or disease severity.

When looking at specific psychiatric comorbidity disorders, only anxiety disorders, mood disorders and delirium, dementia, and amnestic and other cognitive disorders groups showed an association with LoS, all being associated with higher LoS. Patients with developmental disorders, schizophrenia and other psychotic disorders, alcohol-related disorders and mood disorders were likely to be admitted at a younger age. These results are coherent with the literature, as mood disturbances are recognized to be some of the earliest manifestations of HD,[9-12] psychosis has been found to have a mean age of onset of 48.34 years (mirroring HD onset)[19] and the onset of alcohol dependence in general peaks at 18 - 19 years old.[27] Patients with delirium, dementia, and amnestic and other cognitive disorders were likely to be older, which is consistent with disease progression.[28] No significant association was found between psychiatric comorbidity and in-hospital mortality, suggesting that although contributing to hospitalization burden, psychiatric comorbidities might not influence short-term in-hospital survival directly. The presence of any type of psychiatric comorbidity in general was not associated with type of admission. However, when looking specifically at the screening and history of mental health and substance abuse codes group, a reduced likelihood of urgent admissions was found, which could indicate a protective role for urgent admissions or acute events of these documented screenings or psychiatric history. Regarding hospitalization costs, while no association was found when analyzing psychiatric comorbidity overall, schizophrenia and other psychotic disorders, as well as delirium, dementia, and amnestic and other cognitive disorders groups were associated with higher costs, which could be related to the complexity of these patients and their required care, especially since dementia is associated with later stages of HD.[28] In contrast, adjustment disorders were associated with lower costs, which could be associated with milder disease presentations closer to initial diagnosis.

Limitations

This study has several limitations inherent to its design and source of data.

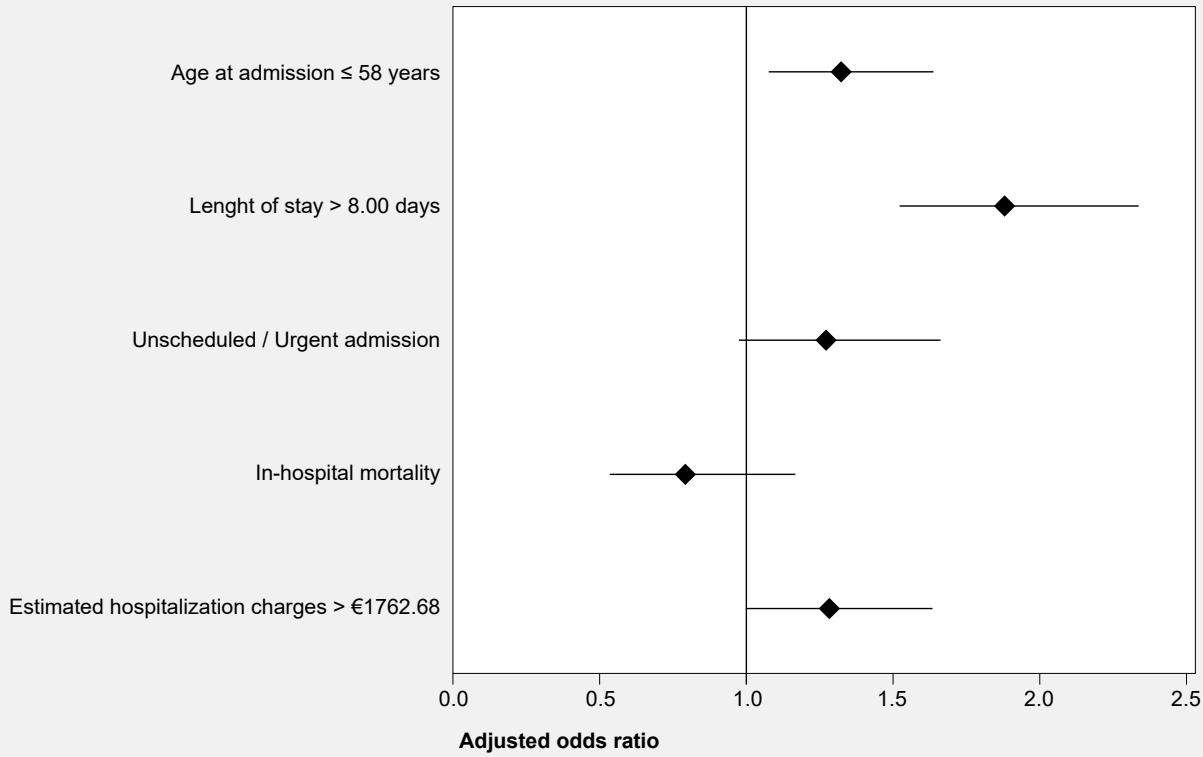

Figure 2 – Outcomes in Huntington's disease hospitalizations with any comorbid psychiatric disorder. Odds ratios adjusted for age and sex.

The database used was not collected primarily for research purposes, which may lead not only to coding inaccuracies, misclassification or potential missing data that could affect the results, but also to the lack of extra clinical detail which limit the authors' ability to account for disease severity and other unmeasured confounders. The reported sensitivity of the ICD-9-CM code 333.4 for Huntington's disease (50%)[22] suggests a substantial proportion of actual HD cases might have been missed. Since only primary and secondary diagnosis were considered, the number of HD patients with psychiatric comorbidity might be underestimated.

Furthermore, the database covers hospitalizations between 2000 and 2016, which may impact the generalizability of the results to the present. In addition, hospitalization costs were estimated using a single 2009 governmental decree, which might not reflect actual costs across the entire period.

Also, since the sample used consists only of hospitalized patients, leaving out those who did not require hospitalization (with presumably lower disease severity), it might not represent the general HD population.

Beyond that, due to being a retrospective observational study, unidentified confounders might be present and unadjusted for.

Strengths

This study uses a large nationwide database covering nearly all hospitalizations in Portugal over 17 years, allowing for a significant sample size considering the rarity of Huntington's disease and permitting a comprehensive analysis of hospitalization trends and outcomes.

Also, to the authors' knowledge, this study is the first of its kind in Portugal.

CONCLUSION

Psychiatric comorbidity in Huntington's disease was associated with younger age at admission and longer hospitalizations. These findings highlight the need for integrated care strategies that include the psychiatric needs of this population, since the extra complexity added by psychiatric comorbidities seems to lead to longer hospitalizations. Early psychiatric screening and intervention could prove useful to improve patient outcomes and reduce the burden on healthcare resources. Further research may provide more information, especially on the effects of specific psychiatric disorders which might benefit from larger sample sizes.

Table 5 – Outcomes in hospitalizations of patients with Huntington's disease according to the presence of specific psychiatric disorders

Specific comorbid psychiatric disorders	Age at admission ≤ 58 years		Length of stay > 8.00 days		Unscheduled/ Urgent admission		In-hospital mortality		Estimated hospitalization charges > €1762.68	
	aOR[a] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value
Adjustment disorders	1548693600.56 (0.00 – ∞)	0.999	2.08 (0.51 – 8.40)	0.306	1.51 (0.31 – 7.40)	0.609	0.00 (0.00 – ∞)	0.999	0.09 (0.02 – 0.43)	**0.003**
Anxiety disorders	2.16 (0.98 – 4.76)	0.056	2.53 (1.15 – 5.57)	**0.021**	2.11 (0.73 – 6.13)	0.170	0.43 (0.06 – 3.16)	0.403	0.79 (0.36 – 1.74)	0.556
Attention-deficit, conduct, and disruptive behavior disorders	1524270913.12 (0.00 – ∞)	0.998	1.05 (0.36 – 3.01)	0.934	2.26 (0.50 – 10.28)	0.292	0.00 (0.00 – ∞)	0.999	545250638.54 (0.00 – ∞)	0.999
Delirium, dementia, and amnestic and other cognitive disorders	0.55 (0.40 – 0.76)	**< 0.001**	2.20 (1.57 – 3.06)	**< 0.001**	1.27 (0.83 – 1.95)	0.272	1.13 (0.68 – 1.91)	0.633	1.52 (1.02 – 2.25)	**0.039**
Developmental disorders	4.87 (1.85 – 12.76)	**0.001**	1.30 (0.63 – 2.69)	0.474	1.98 (0.74 – 5.26)	0.173	1.56 (0.46 – 5.29)	0.475	1.15 (0.49 – 2.69)	0.753
Impulse control disorders, NEC	1224804456.02 (0.00 – ∞)	0.999	2002687573.31 (0.00 – ∞)	0.999	0.56 (0.03 – 9.19)	0.682	0.00 (0.00 – ∞)	0.999	501276718.11 (0.00 – ∞)	0.999
Mood disorders	1.45 (1.02 – 2.05)	**0.039**	1.52 (1.08 – 2.16)	**0.017**	1.07 (0.70 – 1.62)	0.765	0.56 (0.26 – 1.23)	0.149	0.89 (0.61 – 1.30)	0.548
Personality disorders	1241027031.59 (0.00 – ∞)	0.999	0.74 (0.17 – 3.11)	0.677	1.45 (0.29 – 7.48)	0.637	0.00 (0.00 – ∞)	0.999	2.23 (0.27 – 18.26)	0.455
Schizophrenia and other psychotic disorders	3.57 (1.76 – 7.27)	**< 0.001**	1.78 (0.96 – 3.27)	0.066	1.90 (0.83 – 4.34)	0.128	0.60 (0.14 – 2.54)	0.490	2.86 (1.12 – 7.31)	**0.028**
Alcohol-related disorders	2.16 (1.06 – 4.39)	**0.034**	1.08 (0.55 – 2.13)	0.826	0.89 (0.38 – 2.09)	0.785	0.66 (0.15 – 2.80)	0.571	0.90 (0.42 – 1.89)	0.772
Substance-related disorders	1693962908.17 (0.00 – ∞)	0.999	1557703383.84 (0.00 – ∞)	0.999	1.43 (0.16 – 13.13)	0.752	4.63 (0.50 – 42.85)	0.177	544950998.54 (0.00 – ∞)	0.999
Suicide and intentional self-inflicted injury	12.10 (1.58 – 92.43)	**0.016**	0.99 (0.35 – 2.75)	0.979	2.95 (0.66 – 13.32)	0.159	1.15 (0.15 – 9.00)	0.897	0.48 (0.17 – 1.36)	0.166
Screening and history of mental health and substance abuse codes	0.79 (0.45 – 1.37)	0.400	1.60 (0.91 – 2.82)	0.106	0.43 (0.23 – 0.79)	**0.007**	0.98 (0.38 – 2.53)	0.960	1.25 (0.65 – 2.41)	0.503
Miscellaneous mental health disorders	3.27 (0.89 – 11.96)	0.074	2.30 (0.70 – 7.52)	0.170	4.14 (0.53 – 32.45)	0.177	0.00 (0.00 – ∞)	0.999	1.13 (0.31 – 4.14)	0.852

Significant *p*-values < 0.05
a: adjusted for sex
b: adjusted for age and sex
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

AUTHOR CONTRIBUTIONS

JR: Conceptualization, methodology, formal analysis, writing – original draft, writing – review & editing.

CS: Data curation, methodology, writing– review & editing.

MGP: Supervision, methodology, data curation, formal analysis, writing – review & editing.

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.

COMPETING INTERESTS

CS received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Medtronic, Boston Scientific, BIAL, Zambon and Abbvie; participated on BIAL and Zambon advisory boards; is the secretary of the Portuguese Movement Disorders Society.

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