**Table 3. Hypercoagulability evaluation on SARS-CoV2 infection using Viscoelastic Testing**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical Trial 2020** | | **n** | **Age**  (mean) | **Sex**  **M/F** | **Study Local** | **Clinical**  **Status** | **Standard**  **Laboratory** | **ROTEM**  **Profile** | **Study Conclusion,**  **AC Therapy** |
| ***Raval***  ***et al* 32**  clinical case | | 1 | 63  years | M | USA. | ARDS, ICU Shock, MV, vasopressor support (VS) | -↑↑ DD  -↑ Fibrinogen  -NV: PT, APTT | Hypercoagulable profile:  -↑MCF-EXT,INT,FIB  -↓CFT-EXT  -↑α angle EXTEM | -7.500 IU UFH 8/8h for prophylaxis  -None TE or HE; ↓DD.  -VET may have a role in rapidly identifying severe SARS-CoV2. |
| ***Iwasaki***  ***et al* 33**  clinical case | | 1 | 53  years | F | Japan | ARDS, ICU  Severe pneumonia | -↑↑ DD, CRP  -NV: PT, APTT,  Platelet. | *Hypercoagulability:*  -↑ MCF-EXT/INTEM  -↓CFT-FIBTEM | -UFH(10.000IU/day)  Hypercoagulability not seen with SCT, but detected with Rotem. Robust anticoagulation might be needed to prevent TE in a subset of COVID-19 pts. |
| ***Spieza et al*** **30** Single-centre, prospective, observational Study | | 22  Versus Healthy Control | 68 ± 8  years | M: 20  F: 2 | Padova Univ. Hospital  Italy | Acute respiratory failure (ARF)  ICU | Significantly:  -↑↑ DD  -↑↑Fibrinogen  Both: p<0,0001 | *Marked Hypercoagulability*  (vs healthy controls):  ↓CFT-INT (p=0,0002)  ↓CFT-EXT (p=0,001))  ↑MCF-INT/EXT/FIB (All: p<0,001) | -SARS-CoV2 with ARF present a severe hypercoagulability rather than a CC.  -Fibrin formation/polymerization may predispose to TE and correlate with worse outcome. |
| ***Madathil et al*** **34**  Single-centre, retrospective, observational study | | 11 | 53  (45,5-65,5)  years | M: 64% | Maryland  USA | ARDS, ICU  MV  AH:54,5%  Diab:45,5% | Significantly (sig.):  ↑↑ DD  ↑↑ Fibrinogen  ↑↑ CRP | Despite significantly high CRP+ DD, systemic fibrinolysis (SF) was not seen on EXT or FIB (ML=0%). SF is thus unlikely to occur in SARS-CoV2 with cytokine storm | Critically ill SARS-CoV2 pts demonstrate significantly ↑↑ in DD consistent with microvascular thrombosis, but only small fractions of fibrin seem to be locally broken down, and no SF was observed.  - *Fibrinolysis shutdown* |
| ***Ibañez et al* 35**  Single-centre, prospective, observational study | | 19 | 61  (55-73) | M:  10  (53%) | Hospital  Clinic  Barcelona  Spain | ARDS, ICU  MV  AH:47%  Diab:19%  SOFA:4  DIC/SIC:1/1.8 | SCT,DD plus ROTEM:24-48h after ICU admission: | | -All pts under thromboprophylaxis  ***Conclusion***:  ROTEM showed hypercoagulability  with decreased fibrinolytic capacity  despite increased DD, which main source could be the lungs |
| Significantly (sig.):  ↑↑ DD  ↑↑ Fibrinogen  -NV: Platelet, PT, APTT | *-Hypercoagulability:*  ↑clot firmness: MCF-EXT/FIB  -*Fibrinolysis shutdown:*↓clot lysis:LI30/LI60-EXT/FIB:100-99%  -No sig. correlation between Rotem, DD and SOFA score |
| ***Nougier***  ***et al* 36**  Single-centre, prospective, observational study | | 78 | 60.2  ±14.4  years | M:51  F:27 | Hospital  EdouardHerriot  Lyon  France | ICU: ARDS  MV-66.7%  KRT-14.6%  ICU: 48 Wards:30 | Significantly (sig.):  ↑↑ DD, (++ICU)  ↑↑ Fibrinogen  ↑↑Peak Thrombin (++ICU)  ↑ FVIII, ETP  ↑ α2antiplamin  ↑↑t-PA,PAI-1  ↑↑TAFIa/i  -NV: AT | *-Hypercoagulability:*  ↑↑MCF  ↑↑TEM t-PA MCF  ↑↑TEM t-PA α angle  -*Fibrinolysis shutdown:* ↓↓clot lysis:LI30 (++ ICU) | -All under thromboprophylaxis  29%-ICU: thrombosis-8 PE,5DVT,1aortic  ***Conclusion:*** ↑↑ thrombin generation capacity which remained within NV despite heparin, and hypofibrinolysis mainly associated with ↑↑PAI-1 levels. Both contribute to thrombosis risk despite adequate AC therapy.  Modified ROTEM (TEM-t-PA) is able to detect HS+ hypofibrinolysis at the same time in COVID-19 with thrombosis |
| ***Pavoni et al*** **2**  Single-centre, retrospective, observational study | | 40 | 61 ±13  years | M: 60%  F: 40% | Florence  Italy | ARDS, ICU  Severe pneumonia  15% DVT  5% TE  30% CRT | SCT,DD+ROTEM tests performed at admission (T0) and 5 (T5) and 10 (T10) days after hospital admission | | -ROTEM analysis showed that an inflammatory state was associated with a severe hypercoagulability profile, rather than a CC, that persisted over time. Not found hyperfibrinolysis on ROTEM or SIC  -SCT fail to highlight the severity of prothrombotic profile, where ROTEM can help/be very useful. |
| -PT- slightly ↓ T0 and sig. ↑↑ at T10 (p=0,002)  -APTT/Fibrinogen, were higher at T0 than T10 (p=0,017, p=0,002,respectively)  -NV: AT | *Hypercoagulability*:  -↓CFT: INT-40%; EXT-50%pts,  - Sig. higher CS: ↑MCF: INT-50%, EXT-70%, FIB-72,5% pts  -This HS persist in the first 5 days, but it ↓ 10 days after, without returning to NV. |
| ***Almskog***  ***et al* 27**  Single-centre, prospective, observational study | | 60  (>18y)  Versus Healthy Control | Ward 61 y  51-74  ICU: 62 y  55-66 | Male  Ward  70%  ICU: 60% | Stockholm , Sweden  Wards/ ICU | ARDS  Severe pneumonia  Ward/ICU  AH:48%  Diab:28%  AC:80%  (LMWH) | SCT, DD, AT+ ROTEM, just after hosp. admission and compared with healthy controls: | | -ROTEM variables (MCF-EXT, MCF-FIB, CT-EXT, CFT-EXT) were significantly different in SARS-CoV2 pts early after hospital admission compared with healthy controls.  -This pattern was more pronounced in patients with increased disease severity, suggesting that ROTEM analysis could be potentially useful predictor of thrombotic complications and mortality in these pts. |
| -No correlation between DD and MCF-EXTEM (C=0,02; p=0,9)  -Significant correlation between fibrinogen and MCF-FIBTEM (C=0,84; p<0,001) | -MCF EXT/FIB were sig. higher in both groups (Ward/ ICU) (p<0,001),and higher in severely ill compared with those at wards(p<0,05)  -CT EXT was sig. longer and  -CFT EXT sig. shorter.  *Hypercoagulability* is present in mild to severe COVID-19\*\*  Fibrinolysis (LI30),wasn`t sig.↑ |
| ***Corrêa***  ***et al* 38**  Single-centre,  prospective,  observational  study | 30 | | 61  (52-83)  years | M:  50% | Hosp.  Israelita  Albert  Einstein  São Paulo  Brazil | ARDS, ICU  MV/VS:90%  KRT:33%  AH:40%  Diab.:36.7%  Obesity:41%  80%of pts:≥1 comorbidity | SCT, Rotem, Rotem Platelet (ARA/ADPTEM), Plasma fibrinolysis (DD, Plasminogen, α2-AP), AT, PC, PS, at baseline and D1,D3,D7,D14 analysis according SOFA score >10 or ≤10 | | -22/30 pts (73.3%) prophylactic and  7/30 pts (23.3%) therapeutic heparin.  -TE in 20% and HE in10% of pts.  -Most COVID-19 pts have a pronounced HS and ↓fibrinolysis, detected by ROTEM, but not with SCT  -The magnitude of coagulation abnormalities seems to correlate with the severity of organ dysfunction. |
| -↑ Fibr. (++SOFA>10)  ↑↑DD;↑PC; ↓PS  -N/↑: AT  -NV:PT, APTT, Plat. Rotem Platelet, α2-AP, Plasminogen, | *Hypercoagulable state* (HS):  -↑MCF-INT/EXT from D0-D14  -↑MCF-FIB (++ SOFA>10)  -↓ML-INT/EXT  -↓ML-INT (++ SOFA>10) (p=0.004) |
| ***Collett***  ***et al* 39**  Single-centre,  cohort,  retrospective  observational  study | 6 | | 69  (64-73) | M:5  F:1 | Royal  Adelaide  Hospital  Adelaide  Australia | ARDS, ICU  MV:83%  KRT:33%  ECMO:0% | -↑ Fibr., ↑DD  -N: PT,INR, APTT, Platelet,  AT, PC, PS  -LA: absent | *Hypercoagulable state* (HS):  -↑↑A10, MCF-EXT/INT/FIB  -↓↓CFT INTEM  -↓ML (<2%)-EXT/INT/FIB  (median in all) pts) | -All under thromboprophylaxis (enoxaparin 40mg/day). TE: 33%.  -HS: prothrombotic tendency evaluated by VET, but not by SCT. ↑fibr. + ↑ clot firmness + minimal fibrinolysis are key findings. - should be considered as a cause of clinical deterioration in ICU and perhaps beyond. |
| **Clinical**  **Trial 2020** | **n** | | **Age**  **(mean)** | **Sex**  **M/F** | **Study**  **Local** | **Clinical**  **Status** | **Standard**  **Laboratory** | **TEG**  **Profile** | **Study Conclusion,**  **AC Therapy** |
| ***Panigada***  ***et al* 1**  Single-center,  Prospective  Observational  Study | 24  6/24: 30  Observa-  tions in  2 days | | NA | NA | Hospital  Maggiore,  Milan,  Italy | ARDS, ICU  MV | -↑↑Fibrinogen  -↑↑DD  -↑ CRP  -↑FVIII, ↑vWF  -↑PC  -↓AT,↓PS,  -NV or↑ Platelet nº  PT, APTT | *Hypercoagulability state (HS)*:  -↓ R (50% patients)  -↓ K (83% patients)  -↓ LYS30 (100% patients)  -↑ K angle (72% patients)  -↑MA (83% patients) | -Hypercoagulability together with a  severe inflammatory state - may explain  TE (PE/DVT)observed in some and support  thromboprophylaxis.  -Escalating dose from prophylaxis to  treatment needs careful decision based  on risk/benefit ratio, at least until clinical  trials will inform about the best decision. |
| ***Wright***  ***et al* 41**  Single-center,  Prospective  Observational  Study | 44 | | 54  (42-59 | M:  63.6% | Univ.  Colorado  Denver  USA | ARDS, ICU  MV  AH:47%  Diab.:41% | -↑↑DD  -DD>2.6ng/ml was  Predictive for  dialysis need  (p=0.005)  -↑↑DD,Fibrinogen | *Hypercoagulability state (HS)*:  -↑MA; LYS30; ↓R ;↑K angle  - LY30 of 0% (57% pts) predicted  VTE (p=0.021)  - LY30= 0% + DD>2.6ng/ml: with  markedly high risk: Renal failure  (80%;p=0.004)), VTE and TE  (50%, P=0.008) | COVID-19-associated HS measured by TEG  + associated fibrinolysis shutdown  (defined by LY30<0.8%).  Fibrinolysis shutdown predicts TE and  need for dialysis in severe COVID-19.  Additional trials are required to ascertain  the need of early AC and fibrinolytic  therapy (t-PA). |
| ***Maatman***  ***et al* 40**  Multicentre,  retrospective,  observational  study | 12/109  With TEG | | 61±16  (18-95)  years | M:  62% | Indianopolis  (3 Hosp.)  USA | ARDS, ICU  MV(94%)  VS (64%)  KRT:15%  Comorbidities:  AH:68%;  Diab.39% | -↑↑DD,Fibrinogen  -↑↑CRP, Troponin  -DD>2.6ng/ml was  the best predictor  of VTE (p<0.0001) | *Hypercoagulability state*:  ≥2 and ≥1 hypercoagulable TEG  Parameters in 58% and 83% pts  Respectively.  -↓ R (67% pts); ↓ K ; ↓LYS30  -↑ α angle; ↑MA; ↑CI  - CI hypercoagulable in 50%pts | COVID-19 results in a HS.  HS and/or fibrinolysis shutdown were  found to have higher rate and shorter  time to VTE (40 vs 5% in pts without  shutdown, p=0.013). Routine VTE  prophylaxis may be inadequate in TE  prevention in severe COVID-19. |
| ***Mortus***  ***et al* 42**  Single-centre,  retrospective,  observational  study | 21 | | 68  (50-89)  Years | Male:  57% | Baylor  College of  Medicine  Houston  USA | ARDS, ICU  MV  ECMO:19%  KRT:86%  Comorbidities:  97% (3/pts) | -↑↑DD  -↑↑Fibrinogen  -NV: PT,APTT  Platelet | *Hypercoagulable TEG (90%):*  74%TEG defined by fibr.activity  (↑K/α) + MA criteria; 26% TEG  defined only by MA criteria.  -***Innate TEG MA***: sig. greater for  the high TE rate group than the  low TE group (75 vs 61mm;p=0.01);  providing 100% sensitivity and  100% Negative predictive value. | all under thromboprophylaxis  TE: 62%→therapeutic anticoagulation  -TEG may be critical in accurately  Identifying pts at ↑ thrombosis risk  (where full heparinization is needed),  avoiding unnecessary AC in low  thrombosis risk group. |
| ***Eugene Fan***  ***et al 10***  clinical case | 1 | | 39 | M  (Bangla  desh) | Singapore  Hospital  Tan Tock  Seng | Ward: no AC  ↓ D+13:  Acute limb  Ischaemia+ CAC,  Extensive Arterial  Thrombosis →  UFH + Vascular  Surg. → Successful  Endovascular  Stent Graft exclusion  of aortic thrombus  and right lower  limb embolectomy | On presentation of acute ischaemic limb → HS: | | UFH pre-operative →successful vascular surgery  → LMWH on post-operative day 1 (mean  anti-Xa 0.61IU/ml) + aspirin to prevent in stent  thrombosis →warfarin ≥12 weeks  **C*onclusions***: TEG appears to be a useful  tool in detecting HS even in the presence  of heparin or anti-phospholipid syndrome  in CAC. VET may be useful in the early  identification of a HS and management of  thrombosis in covid-19 infection. |
| ↑PT, APTT,↑CRP  Lupus AC (LA)  ↑Ab anti-cardiolipin  IgG/IgM  ↑DD, ↑Fibrinogen  ↑CF:↑FII,FV, FVIII,  ↑FIX, vWF:Ag  NV:PC,PS,AT,  Homocysteine | -↑CRT-MA  -↑CK-MA  -↑CFF-MA (↑↑ fibrinogen  on clot strength)  DIC: score 2 (low DIC risk) |
| **Clinical**  **Trial 2020** | **n** | | **Age**  **(mean)** | **Sex**  **M/F** | **Study**  **Local** | **Clinical**  **Status** | **Standard**  **Laboratory** | ***Quantra***  **Profile** | **Study Conclusion,**  **AC Therapy** |
| ***Ranucci***  ***et al* 44**  Single-center,  Prospective,  Observational  study | 16 | | 61  (55-65)  years | M-15  F-1 | San  Rafaello  Hospital  Italy | ARDS, ICU  MV | *At Baseline on ICU: Procoagulant profile* | | # Increased AC therapy:↑LMWH (4.000IU  b.i.d to 6.000IU b.i.d), AT if <70%,  Clopidogrel 300mg if Platelet >400x109/L.  ***Conclusion*:** Procoagulant pattern of  these pts may justify the clinical reports  of thromboembolic events (PE) during  the course of the disease.  CT and CTH: are useful to control  anticoagulant therapy |
| -↑↑DD  -↑↑Fibrinogen  Associated/correlated  with ↑IL-6 (p=0.003) | - NV of CT  - ↑CS  - ↑PCS  - ↑FCS |
| *After ↑ LMWH dose*# *and 2 weeks later, significant:* | |
| -↓↓ Fibr.(p=0.001)  -↓↓DD (p=0.017) | -↓CS (p=0.013)  -↓PCS (p=0.035);-↓FCS (p=0.038) |
| ***Masi P***  ***et al* 45**  Single-center,  Prospective,  Observational  cohort  study | 17  Versus  11 pts  non-covid  with  ARDS | | 34  (28-55)  48  (42-58)  years | M: 12  M: 7 | Hospital  Pitié-  Salpêtriére  Paris  France | ARDS, ICU  MV | Compared with non-covid-19, COVID-19 patients  exhibited *significantly ↑↑procoagulant factors*,mainly: | | Blood collection samples at hospital  admission. All patients received LMWH.  PE: in 17.6% Covid-19 patients.  No fibrinolysis shutdown seen, neither CC  ***Conclusion:***  Covid-19 ARDS was associated with a  Significantly ↑ in procoagulants,  suggesting that the systemic Inflammatory  response is a major contributor to CAC,  supporting the concept of  thromboinflammation. |
| -↑↑Fibr., FVIII  (p=0.03 each)  -↑↑FV (p<0.0001)  -↑↑CRP (p=0.05)  -↑↑α1-anti GP  (p=0.02)  All these parameters:  strongly correlated  each other (p<0.05-all)  -↑↑ t-PA, PAI-1  closely correlated  (p<0.001) | -↑↑ CS (p=0.0077)  -↑↑ PCS (p=0.014)  -↑↑ FCS (p<0.001)  -CS was strongly correlated  with:   * Fibrinogen (p=0.02), * FV (p=0.043), * FVIII (p<0,001),   but not with PAI-1 levels  (p=0.606) |

\*\* pneumonia with prolonged hemostatic initiation, shortened clot propagation and, notably, with a pronounced clot firmness indicating hypercoagulability27.

↑, increase; ↓, decrease; ++. mainly or more pronounced; AC, anticoagulant AH, arterial hypertension;; APTT, activated partial thrombin time; ARDS, Acute distress respiratory syndrome; AT, antithrombin; FIB,FIBTEM; C, correlation; CAC, COVID-19-associated coagulopathy; CC, consumptive coagulopathy; CF, coagulation factors; CFF, citrated functional fibrinogen; CFT, clot formation time; CI, coagulation index; CK, citrated kaolin; CRP, C reactive protein; CRT, catheter-related thrombosis; CRT-MA, citrated rapid TEG-MA; CS, clot strength/stiffness; CT, clot time; CTH, clot time heparinase; d, days; DD,D-Dimer; Diab, diabetes; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; ETP, endogenous thrombin potential; EXT,EXTEM;F, female; FCS, fibrinogen contribution to the CS; Fibr., fibrinogen; GP, glycoprotein; Hosp., hospital;HS, Hypercoagulable state; ICU, intensive care unit; IL-6, interleukin 6; INR, international normalized ratio; HE, hemorrhagic event; HS, hypercoagulability syndrome; IU, international unit; INT,INTEM; K, speed of clot formation; KRT, Kidney replacement therapy; LA, lupus anticoagulant; Lab, laboratory;LI30/LI60, lysis at 30/60 minutes; LMWH, low molecular weight heparin; LYS-30, % decrease of clot amplitude at 30 minutes post-MA; M, male; M, months; MA, maximal amplitude of the clot; MCF, maximum clot firmness; ML. maximum lysis; MV, mechanical ventilation; nº, number; NA, not available; NV, normal value; PAI-1, plasminogen activator inhibitor; PCS, platelet contribution to the CS; PE, pulmonary embolism; PE, pulmonary embolism; PC, protein C; PS, protein S; PT, prothrombin time; R, reaction time(=clotting time); SCT, standard coagulation tets (PT, APTT, Fibrinogen, Platelets); SIC, sepsis induced coagulopathy; sig, significantly; st, study; SOFA, sequential organ failure assessment; TAC, thrombin antithrombin complex; TAFIa, thrombin activable fibrinolysis inhibitor activated ; TAFIi, thrombin activable fibrinolysis inhibitor inactivated; TE, thrombotic event; t-PA, tissue plasminogen activator; VET, viscoelastic test; vs, versus; vWF:Ag, von Willebrand factor: antigen; UFH, unfractionated heparin; α, alpha; α2-AP, alpha 2 antiplasmin; Y, years; Wards, regular wards;