**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 | 63years | 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 | 53years | F | Japan | ARDS, ICUSevere 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 | 22Versus Healthy Control | 68 ± 8years | M: 20F: 2 | Padova Univ. HospitalItaly | 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% | MarylandUSA | ARDS, ICUMVAH: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%) | HospitalClinicBarcelonaSpain | ARDS, ICUMVAH:47%Diab:19%SOFA:4DIC/SIC:1/1.8 | SCT,DD plus ROTEM:24-48h after ICU admission: | -All pts under thromboprophylaxis ***Conclusion***: ROTEM showed hypercoagulabilitywith decreased fibrinolytic capacitydespite 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±14.4years | M:51F:27 | HospitalEdouardHerriotLyonFrance | ICU: ARDSMV-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 ±13years | M: 60%F: 40% | FlorenceItaly | ARDS, ICUSevere pneumonia15% DVT5% TE30% 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 51-74ICU: 62 y55-66  | MaleWard70%ICU: 60% | Stockholm , SwedenWards/ ICU | ARDSSevere pneumoniaWard/ICUAH: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.IsraelitaAlbertEinsteinSão PauloBrazil | ARDS, ICUMV/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, retrospectiveobservational study | 6 | 69(64-73) | M:5F:1 | RoyalAdelaideHospitalAdelaideAustralia | ARDS, ICUMV: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  |  246/24: 30 Observa-tions in 2 days |  NA | NA | Hospital Maggiore,Milan,Italy | ARDS, ICUMV | -↑↑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 asevere inflammatory state - may explainTE (PE/DVT)observed in some and supportthromboprophylaxis.-Escalating dose from prophylaxis totreatment needs careful decision basedon risk/benefit ratio, at least until clinicaltrials will inform about the best decision. |
| ***Wright*** ***et al* 41**Single-center, Prospective Observational Study  | 44 | 54(42-59 | M:63.6% | Univ.ColoradoDenverUSA | ARDS, ICUMVAH:47%Diab.:41% | -↑↑DD-DD>2.6ng/ml wasPredictive fordialysis 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: withmarkedly 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 andneed for dialysis in severe COVID-19.Additional trials are required to ascertainthe need of early AC and fibrinolytictherapy (t-PA). |
| ***Maatman*** ***et al* 40**Multicentre, retrospective, observational study | 12/109With TEG | 61±16(18-95)years | M:62% | Indianopolis(3 Hosp.)USA | ARDS, ICUMV(94%)VS (64%)KRT:15%Comorbidities:AH:68%;Diab.39% | -↑↑DD,Fibrinogen-↑↑CRP, Troponin-DD>2.6ng/ml wasthe best predictorof VTE (p<0.0001) | *Hypercoagulability state*:≥2 and ≥1 hypercoagulable TEG Parameters in 58% and 83% ptsRespectively.-↓ 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 werefound to have higher rate and shortertime to VTE (40 vs 5% in pts withoutshutdown, p=0.013). Routine VTEprophylaxis may be inadequate in TEprevention in severe COVID-19. |
| ***Mortus*** ***et al* 42**Single-centre, retrospective, observational study | 21 | 68(50-89)Years | Male:57% | BaylorCollege ofMedicineHoustonUSA | ARDS, ICUMVECMO: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 thelow 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 lowthrombosis risk group. |
| ***Eugene Fan*** ***et al 10***clinical case | 1 | 39 | M(Bangladesh) | SingaporeHospitalTan TockSeng | Ward: no AC↓ D+13:Acute limbIschaemia+ CAC,Extensive ArterialThrombosis →UFH + VascularSurg. → SuccessfulEndovascularStent Graft exclusionof aortic thrombusand right lowerlimb embolectomy | On presentation of acute ischaemic limb → HS:  | UFH pre-operative →successful vascular surgery→ LMWH on post-operative day 1 (meananti-Xa 0.61IU/ml) + aspirin to prevent in stent thrombosis →warfarin ≥12 weeks**C*onclusions***: TEG appears to be a usefultool in detecting HS even in the presenceof heparin or anti-phospholipid syndromein CAC. VET may be useful in the earlyidentification of a HS and management ofthrombosis in covid-19 infection. |
| ↑PT, APTT,↑CRPLupus AC (LA)↑Ab anti-cardiolipin IgG/IgM↑DD, ↑Fibrinogen↑CF:↑FII,FV, FVIII, ↑FIX, vWF:AgNV: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,Observationalstudy | 16 | 61(55-65)years | M-15F-1 | SanRafaelloHospitalItaly | ARDS, ICUMV | *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 ofthese pts may justify the clinical reportsof thromboembolic events (PE) duringthe course of the disease.CT and CTH: are useful to controlanticoagulant therapy |
| -↑↑DD-↑↑FibrinogenAssociated/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,Observationalcohortstudy | 17Versus11 ptsnon-covidwithARDS | 34(28-55)48(42-58)years | M: 12M: 7 | HospitalPitié-SalpêtriéreParisFrance | ARDS, ICUMV | Compared with non-covid-19, COVID-19 patientsexhibited *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 Inflammatoryresponse 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;