



Point-of-Care Coagulation Tests in COVID-19

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3.1 Point-of-Care Devices and Tests

A point-of-care device is a kind of diagnostic testing placed and performed at or in proximity of the site where the patient is receiving medical care. This kind of device is normally positioned outside the central laboratory, generally in intensive care units, clinical wards, or operating rooms. POC devices allow a rapid assessment of the overall activity of the coagulation factors and of the interaction between platelets and fibrinogen as clot production and stability. Among the most known devices used in COVID-19 setting there are the thromboelastograph TEG[®] and rotational thromboelastometer ROTEM[®], the sonorheometry-based Quantra[®], and the ClotPro[®] based on the elastic motion thromboelastography. All the abovementioned devices work on whole blood, innate or anticoagulated with citrate, allowing a comprehensive assessment of clot properties.

TEG[®] and ROTEM[®] both employ the cup (rotating in TEG[®], still in ROTEM[®]) and pin (still in TEG[®] and rotating in ROTEM[®]) methodology and use whole blood activated with kaolin (TEG[®]) or specific activators for intrinsic and extrinsic pathways (EXTEM and INTEM, respectively, ROTEM[®]). The growing viscoelasticity of the coagulating blood is continuously measured by electromechanical (TEG[®]) or optical (ROTEM[®]) sensors, translated into a graphical curve and visualized in real time on the monitor of a computer.

The overall activity of the coagulation factors (except fibrinogen) is defined by the R time (minutes) in TEG[®] and CT (clotting time, seconds) in ROTEM[®], i.e., the time until the gelification given by the first fibrin polymer assembling occurs. Additional parameters are K time (minutes, TEG[®]) and CFT (clot formation time,

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seconds, ROTEM®)—time required until a certain clot amplitude is reached. The alpha angle is a measure of speed of clot formation; on TEG® it is defined in one of the two ways, either as the angle between baseline and a line defined by the points R and K or as the angle between baseline and a line tangential to the curve at 2 mm amplitude. On ROTEM® the alpha angle is the angle of tangent between 0 mm and the curve when the clot firmness is 20 mm. R/CT parameter is prolonged in case of inherited or acquired coagulation factor deficiencies, often associated with bleeding; otherwise it has been speculated that a shortening of the R/CT could indicate a hypercoagulable prothrombotic state. Addition of the heparinase allows ruling out heparin presence in the blood sample.

The strength and stability of the forming clot are represented by the maximum amplitude (MA, mm) on TEG® and maximum clot firmness (MCF, mm) on ROTEM®. This parameter incorporates the contribution of both platelets and fibrinogen; thus a reduced value of MA/MCF is not able to rule out the single deficiencies. The functional fibrinogen on TEG® and the FIBTEM test on ROTEM® inhibit platelet aggregation within the blood sample providing information about fibrinogen contribution to the clot.

Fully automated cartridge-based version of the devices is available for both TEG® (TEG® 6S) and ROTEM® (ROTEM® sigma). Despite technical differences between the manual and cartridge-based analyzers, correlation of the results between the analyzers of the same family has been reported [4], at least partially [5].

The Quantra® is a fully automated POC VET device based on SEER sonorheometry technology. Briefly, a sample of citrated whole blood is drawn into a multi-well cartridge and mixed with lyophilized reagent. An ultrasound pulse is sent in order to generate a shear wave, and the following deformation is measured. The frequency and amplitude of the induced deformation are directly related to the viscoelastic properties of the sample [6].

The Quantra QPlus® cartridge includes four parallel channels, each pre-filled with specific lyophilized reagents and performing simultaneous measurements. Clot coagulation time (CT and CTH, seconds) is assessed after blood activation with kaolin both with and without heparinase. The overall clot stiffness (CS, hPa) is given together with fibrinogen contribution to the overall clot stiffness (FCS, hPa, measured) and platelet contribution (PCS, hPa, calculated).

ClotPro® uses elastic motion thromboelastography with the established cup (rotating) and pin (still) semiautomated methodology and records kinetic changes in a sample of citrated whole blood. The device has been described previously [7]. The device allows performing six tests simultaneously, including the TPA test where the tissue factor-triggered extrinsic pathway is coupled to the activation of fibrinolysis by high-dose recombinant tissue plasminogen activator (tPA), reflecting the resistance to fibrinolysis.

The indisputable advantage of VETs is their capability to report different components and stages of the overall coagulation process with a single test/cartridge. Closed systems of the cartridge-based devices are particularly advantageous in a COVID working ward because of minimizing the risks of manual blood manipulations.

3.2 Thromboelastography

As early as April 2020, Panigada and associates pointed out that critically ill patients admitted to ICU showed a peculiar hypercoagulable profile [8]. Using a previously established reference healthy population, they found that COVID-19 patients have a shorter R and K time, a greater alpha angle and MA, and, most importantly, shut-down of fibrinolysis (LY30 lower than the mean of the reference cohort in 100% of cases). Interestingly, the authors observed a concomitant endothelial dysfunction indicated by the elevation of the von Willebrand factor antigen. These findings were further confirmed by similar studies [9, 10].

A typical pattern of hypercoagulability at TEG is shown in Fig. 3.1.

Cordier and colleagues compared TEG findings of critically ill patients on ICU admission to those of healthy controls [10]. The statistical significance ($P < 0.001$) was reached for all the analyzed parameters—patients affected by COVID-19 were characterized by significantly decreased R, K, and LY30, and significantly increased values of alpha angle, MA, CI (coagulation index, a composite compilation of R, K, angle, and MA), and TTG (total thrombin generation, a parameter calculated from the first derivative of the TEG waveform). With respect to TEG parameters, no differences between patients with and without obesity (body mass index, BMI, $>30 \text{ kg/m}^2$) and between patients who survived versus who did not were found. The procoagulant profile persisted in patients who survived and had a good clinical course. There was no association between TEG values and severity of CT (computerized tomography) lesions. Anyway, a trend towards a stronger hypercoagulability in patients who developed thrombosis was noted.

On the other hand, Yuriditsky and associates reported no differences in thromboelastographic parameters between patients with venous thromboembolism (VTE) and patients without and no association between TEG and combined outcome measure (either death or confirmed VTE) [11]. Fifty percent of the analyzed population showed hypercoagulable state expressed as a CI >3 despite receiving prophylactic or therapeutic anticoagulation with heparin. Sixty percent had a maximum amplitude (MA) above the normal range, i.e., 70 mm. The median heparinase R time was below the lower limit of normal range in a significant proportion of patients (43.8%). Even if no direct association was found, the authors pointed out that the cohort was characterized by a high incidence of renal failure preceding VTE diagnosis. Wright and associates observed a complete shutdown of fibrinolysis (LY30 = 0%) in 57% of their population of 44 COVID-positive ICU patients that predicted venous thromboembolic events with an area under the receiver operating characteristic curve of 0.742 ($P = 0.021$) [12]. Patients with no fibrinolytic activity at 30 min on TEG and a D-dimer $>2600 \text{ ng/mL}$ had VTE with a rate of 50% compared to 0% of patients with neither risk factor ($P = 0.008$). Consistent with the findings of Yuriditsky [11], the hemodialysis rate in the high-risk group was 80% compared to 14% of the low-risk patients ($P = 0.004$).

Stattin and colleagues performed a prospective study following the evolution of the inflammatory and coagulation profile of the ICU patients over time (7 and more days) on the TEG 6S® platform [13]. The majority of patients maintained the

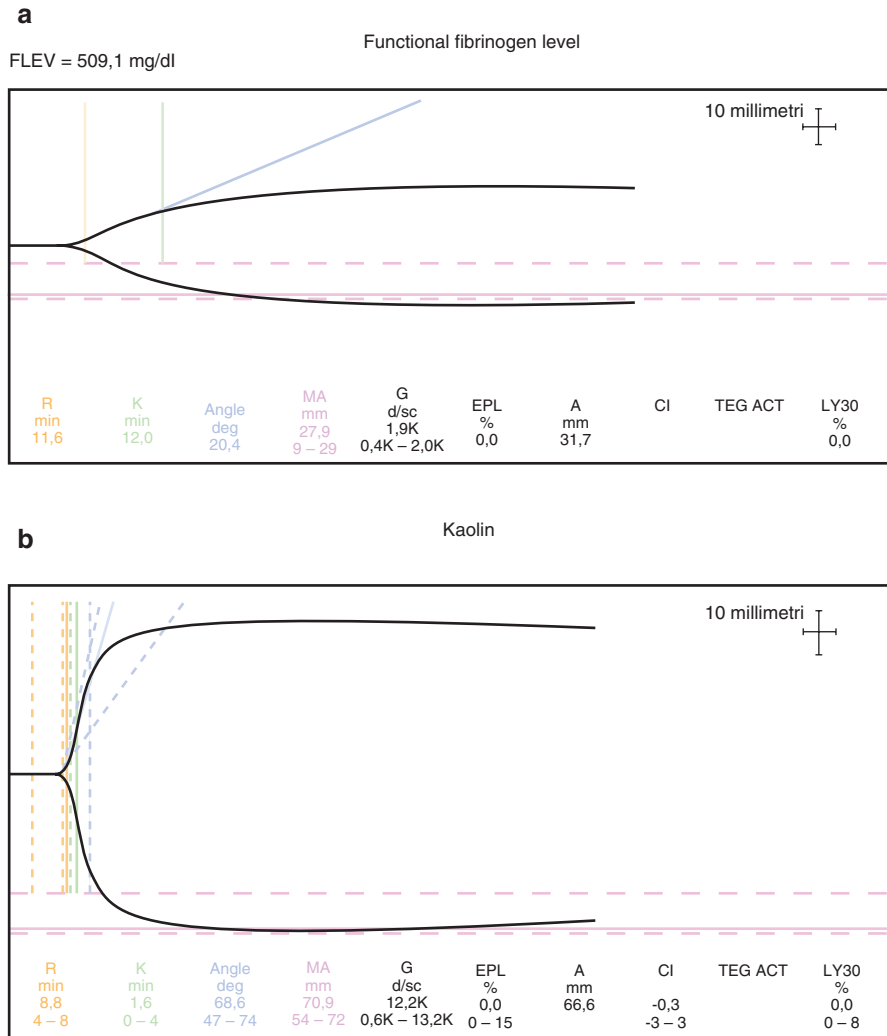


Fig. 3.1 Example of a typical TEG tracing presenting with a procoagulant pattern from a critically ill COVID-19-positive patient. A. Functional fibrinogen testing and fibrinogen level (FLEV) calculated by the software. B. Basal kaolin testing. High fibrinogen level and total absence of fibrinolysis are of note. Abbreviations: MA maximum amplitude, EPL estimated percent lysis, CI coagulation index, LY30 percent lysis after 30 min

hypercoagulable profile during the hospitalization, seen as an elevation of the MA and not as a decrease in R time. Moreover, the authors pointed out the insufficient capacity of TEG® to reliably detect the effect of LMWH administration.

Analogously, the group of Bocci did not observe significant differences in thromboelastographic parameters of TEG 6S® of COVID-positive ICU patients after a 7-day follow-up with a maintenance of a hypercoagulable state, expressed as a

distribution above the normal range of the CK-MA, rTEG-MA, and FF-MA despite systemic anticoagulation [14]. TEG-ACT, a parameter calculated by the TEG 6S[®], was reduced, whereas CKH-R and CKH-K stood in normal range. Seven-day-long anticoagulation therapy, either low-molecular-weight or unfractionated heparin, had no impact on TEG parameters. Shah and associates found analogous increase of alpha angle, MA, and FF-MA on TEG 6S[®] [15]. No difference in TEG parameters between patients with or without TE events was found in this study. Vlot and colleagues performed TEG 6S[®] in COVID-positive ICU-hospitalized patients on mechanical ventilation administered with high-dose LMWH in which peak Xa activity of 0.38 IU/ml was within the target range, still finding a strong procoagulant pattern despite anticoagulation with very high CFF-MA levels with overall fibrin contribution to the clot of 71% (56–85), instead of 20–25% in normal clots [16].

Chandel and associates evaluated patients on veno-venous (vv) ECMO and confirmed high values of MA (median 72.8 mm) on thromboelastography [17]. No statistically significant difference between patients with macrothrombosis versus patients without TE was found with respect to TEG-MA.

Low fibrinolytic activity, represented by the resistance to exogenously induced fibrinolysis, was specifically tested by Maier and colleagues adding tPA to platelet-poor plasma samples of 14 patients affected by acute COVID-19 disease (pooling together ICU and standard ward) and compared to 14 healthy controls [18]. Consistent with other reports, the COVID-positive patients and the controls significantly differed for the MA (43.6 ± 6.9 vs. 23.2 ± 5.5 mm, $P < 0.0001$). The induced fibrinolysis was 21% less in COVID patients as compared to controls at 30 min (LY30, 37.9 ± 16.5 vs. 58.9 ± 18.3 , $P = 0.0035$). Off-label use of tPA (alteplase) in four patients for clinical evidence or suspicion of microvascular or macrovascular thromboses and hypercoagulable values on thromboelastography has been reported with benefit [19].

Attempts to stratify patients based on the definition of a hypercoagulable state (HS) have been done. Mortus and colleagues arbitrarily defined hypercoagulability as elevated fibrinogen activity greater than 73° angle or MA greater than 65 mm on TEG with heparinase correction [20]. Salem and colleagues defined HS as MA > 69 mm (upper limit of normal, ULN), alpha angle >77° (ULN), R < 4.3 min (lower limit of normal, LLN), or K < 0.8 min (LLN) [20]. The incidence of HS varies between studies and populations from 30% [20] to up to 90% [8, 11, 20] and HS was mainly due to high MA and alpha angle. In Salem's study, HS was not associated with the occurrence of thromboembolic events; only LY30 was significantly lower in the TE group ($P = 0.041$) [21]. In the study of Mortus [20], stratifying the population based on the number of thromboembolic events (less than 2 versus 2+ TE events), elevated MA was observed in ten patients (100%) in the high-event group versus five patients (45%) in the low-event group, providing 100% sensitivity and 100% negative predictive value. On contrast, in a population of 40 ICU COVID-positive patients who developed VTE (DVT or PE) analyzed by Marvi and associates the venous thromboembolism rate was higher in patients who were not hypercoagulable for maximum amplitude ($P = 0.04$) and alpha angle ($P = 0.001$) [22].

In summary, all the studies agree on pathological increase of the clot strength (MA) attributing an important role to fibrinogen contribution, whereas contrasting findings are reported in relation to the coagulation initiation. In addition, the research for association between viscoelastic parameters, single or combined, with thromboembolic events showed different results. This could be explained by the fact that the available literature is mostly retrospective and that the protocols for TE assessment vary greatly between published reports (as variable is the reported incidence of TE in COVID-positive patients).

An overview of the published papers is given in Table 3.1.

3.3 Rotational Thromboelastometry

Similar to the TEG studies, most of the reports agree on the presence of high values of MCF in EXTEM/INTEM and especially in FIBTEM tests with higher values associated with severity of disease—from healthy controls to COVID-positive patients hospitalized in non-intensive wards to patients admitted to ICU department [23–26].

Variable observations are available on the values of CT in EXTEM and INTEM tests. Almskog found longer EXTEM CT but shorter CFT in COVID-positive patients as compared to healthy controls, and longer CT but shorter CFT values in intensive versus non-intensive patients, standing for a prolongation in clot activation but a strengthening of clot propagation and an increasing clot firmness (resistant to fibrinolysis) [23]. All the comparisons were statistically significant with a $P < 0.001$. These findings are consistent with other studies [27, 28].

A typical pattern of hypercoagulability at thromboelastometry is shown in Fig. 3.2.

Shorter CFT in EXTEM was also observed by Tsantes and colleagues in ICU-treated COVID-positive patients as compared to non-COVID-ICU patients, patients with mild COVID, and healthy controls (40.7 ± 13.0 vs. 63.7 ± 34.7 vs. 59.5 ± 24.9 vs. 89.2 ± 24.7 s, respectively, overall $P < 0.001$) [24]. Lower EXTEM ML was also peculiar to ICU patients with COVID (1.8 ± 2.3 vs. 3.2 ± 3.7 vs. $6.2 \pm 8.4 \pm 4.6\%$, respectively, overall $P < 0.001$), as well as higher MCF (75.7 ± 5.0 vs. 69.4 ± 8.5 vs. 72.4 ± 4.0 vs. 59.9 mm respectively, overall $P < 0.001$).

Boss and colleagues compared thromboelastometric findings in patients with COVID-associated severe sepsis versus patients with severe sepsis but without COVID-19 disease [25]. Higher values of MCF on EXTEM (70.4 ± 10.4 vs. 60.6 ± 14.8 mm, $P = 0.022$) and FIBTEM (38.4 ± 10.1 vs. 29.6 ± 10.8 mm, $P = 0.012$) and lower level of lysis (ML 60, 0.6 ± 1.2 vs. $3.3 \pm 3.7\%$, $P = 0.013$) characterized patients with COVID-19. No statistically significant differences in ROTEM® parameters between COVID-19 patients with or without thromboembolic events were found.

Spiezia and associates found similar differences between COVID ICU patients and a group of healthy age-, sex-, and body weight-matched subjects with the

Table 3.1 Overview of the papers on thromboelastography in COVID-19 setting

Author and year	Population	Study type Enrollment period	Device and tests performed
Bocci et al. (2020)	Critically ill patients admitted to ICU, $n = 40$; second assessment, $n = 26$	Observational study February–March 2020	TEG 6S [®]
Chandel et al. (2021)	Critically ill patients admitted to ICU and on vvECMO, $n = 24$	Retrospective study March–May 2020	TEG [®] 5000
Cordier et al. (2021)	Critically ill patients admitted to ICU, $n = 24$ on ICU admission, second sampling $n = 10$ Healthy control group, $n = 20$	Retrospective study March–April 2020	TEG [®] 5000 Citratated K, KH
Hightower et al. (2020)	Critically ill patients admitted to ICU, $n = 5$	Observational study April 2020	TEG [®] 5000 Citratated K, KH
Maatman et al. (2020)	Critically ill patients admitted to ICU, $n = 12$	Observational cohort study March 2020	TEG [®] 5000 Citratated K, KH
Marvi et al. (2021)	Critically ill patients admitted to ICU, $n = 40$	Prospective study April–July 2020	TEG [®] 5000 Citratated KH
Mortus et al. (2020)	Critically ill patients admitted to ICU, $n = 21$	Retrospective study March–April 2020	TEG [®] 5000 K, KH
Panigada et al. (2020)	Critically ill patients admitted to ICU, $n = 24$	Observational study March 2020	TEG [®] 5000 KH
Sadd et al. (2020)	Critically ill patients admitted to ICU, $n = 10$	Retrospective study Unknown period of enrollment	TEG 6S [®]
Salem et al. (2020)	Critically ill patients admitted to ICU, $n = 52$	Retrospective study April–May 2020	TEG 6S [®]
Shah et al. (2020)	Critically ill patients admitted to ICU, $n = 20$	Retrospective study March–May 2020	TEG 6S [®]
Stattin et al. (2020)	Critically ill patients admitted to ICU, $n = 31$	Prospective observational study March–April	TEG 6S [®]
Stillson et al. (2021)	Critically ill patients admitted to ICU, $n = 31$	Prospective study April–September 2020	TEG [®] 5000 Citratated K, KH
Vlot et al. (2020)	Critically ill patients admitted to ICU, $n = 16$	Observational study Unknown period of enrollment	TEG 6S [®]
Wright et al. (2020)	Critically ill patients admitted to ICU, $n = 44$	Observational cohort study March–April 2020	TEG [®] 5000 Citratated K, KH
Yuriditsky et al. (2020)	Critically ill patients admitted to ICU, $n = 64$	Retrospective cohort study April 2020	TEG [®] 5000 Citratated K, KH

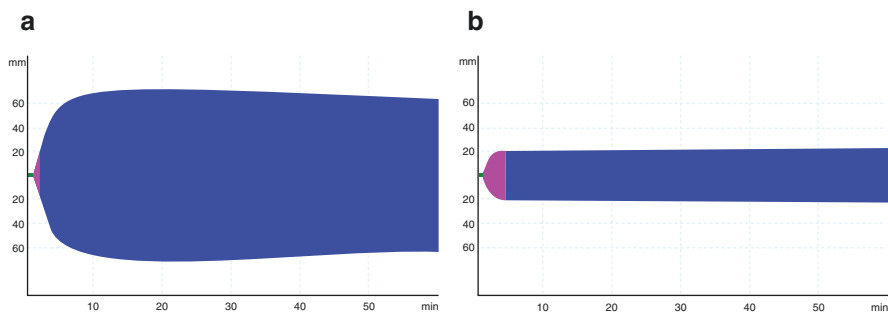


Fig. 3.2 Typical procoagulant ROTEM tracing from a representative critically ill COVID-19-positive patient. **(a)** EXTEM test. **(b)** FIBTEM test. MCF values of both the test are close to the upper limit of the normal reference range

former showing a more pronounced hypercoagulation (shorter CFT in INTEM and EXTEM and higher MCF in INTEM, EXTEM, and FIBTEM tests) [29]. In contrast to most reports, lysis parameters showed no difference between the two groups.

In a series of 40 consecutive patients admitted to ICU, Pavoni and colleagues analyzed ROTEM parameters at three time points, at ICU admission and at days 5 and 10 [30]. They observed a hypercoagulable state analogous to the other studies (significantly higher MCF in FIBTEM, tendency to a shorter CFT and a higher MCF in INTEM and EXTEM) but also highlighted that some parameters tend to improve over time—FIBTEM MCF decreasing from 35.9 ± 5.9 mm at day 0– 23 ± 3.3 mm at day 10 ($P = 0.017$), among others.

Ibanez and associates substantially confirmed what was previously found on increased clot strength and furtherly pointed out the decreased clot lysis parameters as compared to reported levels in healthy population [26]. Others [31] tried to define fibrinolysis shutdown in COVID-19 patients in a way similar to the trauma setting, as EXTEM maximum lysis of $<3.5\%$ [32]. According to this definition, 11 out of 25 (44%) of the patients in the cohort analyzed by Creel-Bulos and colleagues experienced a fibrinolysis shutdown and 8 out of 9 patients who underwent thromboembolic complications met the shutdown criterion [31].

Thromboelastometry could be modified in order to evaluate the resistance of the clot to be lysed. Nougier and colleagues added $0.625 \mu\text{g}\cdot\text{mL}^{-1}$ tPA and analyzed the lysis index LY30 (residual clot firmness after 30 min after coagulation time in % to MCF) in 23 patients with and without thrombotic events, and compared them to healthy controls [33]. They showed that in healthy controls the clot is almost completely lysed under stimulation with tPA, and that LY30 of ICU patients with thrombosis was significantly higher than that of other COVID-positive ICU patients with similar disease severity (63 ± 39 vs. $18 \pm 35\%$, $P = 0.022$). The impaired fibrinolysis was supported by higher levels of t-PA, PAI-1, and TAFI in patients with a more severe disease.

Hoechter and colleagues compared COVID-positive intubated ICU patients with ARDS versus ICU patients with ARDS due to other bacterial/viral pneumonia [34]. They found no difference between group concerning MCF nor ML on EXTEM but a significantly higher FIBTEM MCF in COVID group (29 vs. 22 mm; $P = 0.005$) with 9 out of 11 COVID-positive patients showing MCF values above the upper limit of the normal range (9–25 mm).

Similar to thromboelastography, small patient population and inhomogeneity of TE assessing protocols do not allow solid results on association between particular hypercoagulable conditions on ROTEM and risk of developing thromboembolic complications during COVID-19 disease. More rigorous studies are required to establish such a relationship.

An overview of the published papers is given in Table 3.2.

Table 3.2 Overview of the papers on rotational thromboelastometry in COVID-19 setting

Author and year	Population	Study type Enrollment period	Device and tests performed
Almskog et al. (2021)	ICU-positive intensive and non-intensive patients, $n = 60$, vs. healthy controls, $n = 86$	Prospective study May 2020	ROTEM® sigma EXTEM, INTEM, FIBTEM, HEPTEM
Boss et al. (2021)	Patients with severe COVID-related sepsis, $n = 20$, vs. patients with severe sepsis without COVID, $n = 20$	Retrospective study March–June 2020	ROTEM® delta EXTEM, INTEM, FIBTEM, APTEM
Collett et al. (2021)	Critically ill patients admitted to ICU, $n = 6$	Retrospective study Unknown enrollment period	ROTEM® sigma EXTEM, INTEM, FIBTEM
Creel-Bulos et al. (2021)	Critically ill patients admitted to ICU, $n = 25$	Retrospective study April 2020	ROTEM® delta EXTEM, FIBTEM
Hoechter et al. (2020)	Intubated patients with ARDS: $n = 22$ COVID vs. $n = 14$ non-COVID	Retrospective study March–April 2020 (COVID group)	ROTEM® delta EXTEM, FIBTEM
Ibanez et al. (2021)	Critically ill patients admitted to ICU, $n = 19$	Prospective study April 2020	ROTEM® sigma EXTEM, INTEM, FIBTEM
Nougier et al. (2021)	COVID-positive patients admitted to ICU, $n = 48$, and internal medicine department, $n = 30$	Prospective study Unknown period of enrollment	ROTEM® delta tPA-modified EXTEM

(continued)

Table 3.2 (continued)

Author and year	Population	Study type Enrollment period	Device and tests performed
Pavoni et al. (2020)	Critically ill patients admitted to ICU, $n = 40$	Retrospective study February–April 2020	ROTEM® gamma EXTEM, INTEM, FIBTEM
Spiezia et al. (2020)	Critically ill patients admitted to ICU, $n = 22$ vs. matched healthy controls, $n = 44$	Prospective study March 2020	ROTEM® delta EXTEM, INTEM, FIBTEM
Tsantes et al. (2020)	COVID-positive patients with severe (ICU, $n = 11$) vs. mild ($n = 21$) disease, non-COVID ICU patients $n = 9$, healthy controls $n = 20$	Prospective study Unknown period of enrollment	Unknown ROTEM® EXTEM
Van Veenendaal et al. (2020)	Critically ill patients admitted to ICU, $n = 47$	Retrospective study April 2020	ROTEM® sigma EXTEM, INTEM, FIBTEM

3.4 ClotPro

Three studies have been carried out on critically ill COVID-19 patients.

Bachler and associates retrospectively analyzed 20 critically ill COVID-19 patients and 60 healthy controls for coagulation and fibrinolysis markers [35]. As compared to controls, COVID patients showed hypercoagulable EX test MCF (68 vs. 61 mm, $P < 0.01$) and FIB test MCF (34 vs. 17 mm, $P < 0.01$). Consistent with the findings by other viscoelastic analyzers, the disproportion between platelet and fibrinogen contribution to clot strength, normally with 75–80% of the overall stiffness ascribable to platelets and 20–25% to fibrinogen and here strongly shifted towards a fibrinogen predominance, is clear. Clotting time of EX test showed no statistical difference between groups, and IN test CT was longer for COVID patients (188 vs. 159 s, $P < 0.01$) but still within the reference range.

The most peculiar finding was that the fibrinolytic response as expressed by the lysis time (LT) of TPA test (fibrinolysis induced by the recombinant tissue plasminogen activator) in COVID patients was significantly longer than in controls (508 vs. 210 s, $P < 0.01$), as well as by maximum lysis (ML) on EX test (3 vs. 6%, $P < 0.01$). Overall, 70% of the patients suffered from an impairment in fibrinolysis, but no differences in thrombotic event occurrence were registered between patients with hypofibrinolysis and patients without such a condition.

Hammer and colleagues [36] also focused on fibrinolysis shutdown in a cohort of 29 patients hospitalized for COVID-19 with a diagnosis of both moderate (ward, $n = 9$) and severe (ICU, $n = 20$, 8 out of 20 were on vv-ECMO support) disease.

Blood samples from 10 healthy donors were used as reference. Severe COVID-19 patients showed a significant reduction of the spontaneous clot lysis after activation of the extrinsic coagulation pathway when compared to healthy donors (3.25% vs. 6.2%, $P = 0.013$), very similar to the findings of Bachler [35]. No significant difference was observed between non-ICU COVID-positive patients and healthy controls. Resistance to the fibrinolytic effect of tPA was significant in all the patients, both severe and moderate, when compared to controls (ICU COVID patients vs. controls, 365.7 s vs. 193.2 s, $P = 0.0014$; non-ICU COVID patients vs. controls, 354.3 s vs. 193.2 s, $P = 0.0005$). These data were supported by the increased concentration of plasma tPA (profibrinolytic), no increase in plasminogen (fibrinolytic), and increased PAI-1 (antifibrinolytic) in ICU COVID-19 patients indicating that, despite the profibrinolytic signaling, PAI-1 overcomes the competence of the fibrinolytic system with the final fibrinolysis slowdown effect. No association with thrombotic events or mortality was found in this cohort.

Findings of Heinz and associates [37] in a cohort of 29 COVID-positive ICU patients with ARDS (compared to 12 healthy controls) agree with those of the two previously discussed studies. In particular, the lysis time significantly differed between two groups (530 s vs. 211 s, $P < 0.001$), as well as EX test MCF (68 mm vs. 57 mm, $P < 0.001$) and FIB test MCF (37 mm vs. 15 mm, $P < 0.001$). Association of viscoelastic parameters with outcome and thrombotic incidence has not been investigated in this cohort.

3.5 SEER: QUANTRA

In COVID-19 setting QUANTRA analyzer was used in one study only.

Ranucci and colleagues [38] investigated a cohort of 16 COVID-positive critically ill ICU patients with a baseline coagulation assessment after 2–5 days of ICU admission, followed by a second assessment after 14 days for 9 patients. Clotting time (CT) was within the normal range and did not differ between the two assessments. The overall clot strength at baseline was higher than normal: 55 (35–63) hPa with reference range (RR) being 13–33.2 hPa. Both platelet (PCS) and fibrinogen (FCS) were above the upper limit of the reference range—43 (24–45) hPa (RR 11.9–29.8 hPa) and 12 (6–13.5) hPa (RR 1–3.7), respectively. After 2-week follow-up, a significant decrease of CS ($P = 0.013$), PCS ($P = 0.035$), and FCS ($P = 0.038$) was found. Thromboembolic prophylaxis included LMWH 6000 twice a day (8000 if BMI >35), antithrombin III correction of values <70%, clopidogrel 300 mg loading dose, and 75 mg daily maintenance if platelet count >400,000 cells/ μ L. No major thromboembolic events were observed in this cohort.

A Quantra screenshot of a hypercoagulable COVID-19 patient is shown in Fig. 3.3.

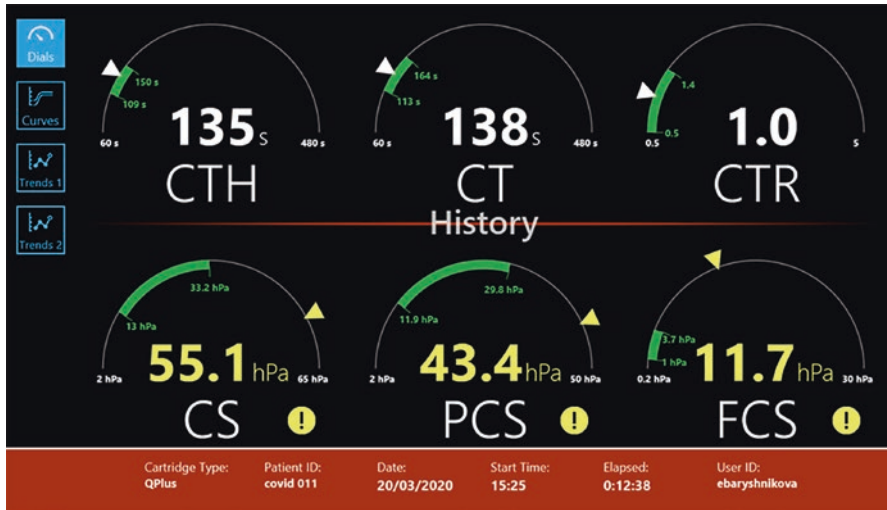


Fig. 3.3 Typical Quantra tracing from a representative critically ill COVID-19-positive patient with a procoagulant pattern. Very high level of fibrinogen contribution to clot stiffness (FCS) is of note. On the dial view of the results, the green space represents the normal range and the yellow arrow indicates the position of the patient's value. The exclamation point stands for a value out of normal range and worth of the operator's attention. Abbreviations: CT, coagulation time; CTH, coagulation time with heparinase; CTR, coagulation time ratio; CS, clot stiffness; PCS, platelet contribution to clot stiffness; FCS, fibrinogen contribution to clot stiffness

3.6 Viscoelastic Tests to Monitor Hypocoagulability and Bleeding in COVID-19 Patients

Hemorrhagic complications have been reported in a small but significant proportion of COVID-19 patients (8–21%), the most common being gastrointestinal bleeding [15, 39–41]. The extensive use of anticoagulation with some authors prompting more aggressive therapies in higher risk patients requires specific monitoring and established protocols for shifting therapies at varying conditions. Use of viscoelastic tests coupled to standard coagulation tests was suggested to be beneficial in monitoring coagulation by the recent ISTH guidance [42]. The American Society of Hematology (ASH) and American College of Surgeons (ACS) included viscoelastic tests (TEG and ROTEM) in their online COVID-19 resources for the management of coagulopathy and monitoring anticoagulation [43, 44].

Stillson and associates [45] investigated the use of TEG coupled to standard coagulation tests to predict bleeding as defined by the World Health Organization (WHO) bleeding scale score ≥ 2 [46] for COVID-19 intensive care unit patients who received intermediate or therapeutic anticoagulation. They were able to include in the analysis 10 patients who met the criteria of the WHO bleeding score of 2 or more (bleeding group) and 21 patients in the non-bleeding group. The following parameters were associated with bleeding: R ($P = 0.0001$), K ($P = 0.0002$), alpha angle ($P = 0.0001$) for the TEG, and aPTT ($P = 0.0006$) and fibrinogen ($P = 0.0019$)

for the standard coagulation tests. The findings of this investigation prompted the authors to modify their current anticoagulation protocol and adopt a TEG-guided protocol for anticoagulation management in COVID-19 critically ill patients that allowed them to significantly reduce bleeding events in their patient population.

3.7 Conclusions

All the available data agree that critically ill COVID-19 patients are affected by a complex hypercoagulable state where platelets and fibrinogen (expressed as clot strength/stiffness) seem to play a central role. In addition, the hypofibrinolytic condition contributes to the severity of the disease. Standard coagulation tests, though outlining the single alterations, lack the capacity to report the overall hemostatic competency of the patient. Point-of-care tests make up for this necessity.

At full value, inclusion of POC tests in international guidelines for monitoring and therapeutic decision-making in the setting of COVID-19 disease requires more rigorous studies and time but some indications have already been provided in interim recommendations and online resources of the major societies.

The main limitation of the above-presented studies is that most of them look at one moment in time (mainly ICU admission), present variable protocols for prophylactic and therapeutic anticoagulation, and differ in strategies for scanning for TE events.

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