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2. **Author information:**

   Klaus Görlinger, MD, Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany, and Medical Department, Tem Innovations GmbH, Munich, Germany.

   Hawra Almutawah, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Fatimah Almutawaa, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Maryam Alwabari, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Zahra Alsultan, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Jumanah Almajed, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Mahmoud Alwabari, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Maryam Alsultan, Doctor Internship, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Dur I Shahwar, Assistant Professor, MD, Anaesthesia Division/Surgery Department, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.

   Khaled A Yassen, Associate Professor, MD, FFARCSI, Anaesthesia Division/Surgery Department, College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Saudi Arabia.
3. **Running title:** Thromboelastometry in COVID-19 Pandemic

4. **Corresponding author:** Klaus Görlinger, MD, Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany, and Medical Department, Tem Innovations GmbH, Munich, Germany, email: kgoerlinger@ilww.com, phone: +49 172 6596 069.

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The Role of Rotational Thromboelastometry during the COVID-19 Pandemic: a narrative review

Running title: Thromboelastometry in COVID-19 Pandemic
Abstract
Corona virus 2 (SARS-CoV-2) pandemic is currently a global health crisis. This viral infection is frequently associated with hypercoagulability with a high incidence of thromboembolic complications that can be fatal. In many situations, the standard coagulation tests (SCT) fail to detect this state of hypercoagulability in COVID-19 since clotting times are not or only mildly affected. The role of viscoelastic tests such as rotational thromboelastometry (ROTEM®) during this pandemic has been explored in this review. COVID-19-associated coagulopathy as evident from thromboelastometry parameters can vary from hypercoagulability due to increased fibrin polymerization and decreased fibrinolysis to bleeding from hypocoagulability. A multi-modal diagnostic and monitoring approach including both thromboelastometry and SCT such as plasma fibrinogen and D-dimer concentrations is recommended. Thromboelastometry provides comprehensive information about the full coagulation status of each patient and detects individual variations. Since COVID-19-associated coagulopathy is a very dynamic process, the phenotype can change during the course of infection and in response to anticoagulation therapy. Data from published literature provide evidence that combined thromboelastometry and SCT analysis will be helpful in detecting hemostasis issues, guiding anticoagulant therapy and improving outcome in COVID-19 patients. However, more research is needed to develop guidelines and protocols.

Keywords: Anticoagulation; coagulopathy; COVID-19; fibrinolysis shutdown; hypercoagulability; thromboelastometry; SARS-CoV-2; thromboelastometry; thrombosis.
Corona virus 2 (SARS-CoV-2) disease known as COVID-19 was firstly reported in Wuhan city located in China towards the end of 2019 before it became a global pandemic. It is highly contagious and the clinical picture varies from asymptomatic courses to acute respiratory failure [1]. COVID-19-associated hypercoagulability and subsequent pulmonary thrombosis is one of the leading causes of death during this pandemic. This hypercoagulability can be resistant to standard doses of low molecular weight heparin (LMWH), reflected by low anti-Xa levels (< 0.4 IU ml) in patients with subtherapeutic or therapeutic anticoagulation. Furthermore, hypercoagulability in COVID-19 is characterized by high plasma fibrinogen concentrations and elevated D-dimer levels > 2500 μg/l. Published data suggest that both, hypercoagulability and the significant increase in proinflammatory cytokines (cytokine storm) are leading causes for multiple organ failure in critically ill COVID-19 patients (immunothrombosis) [2-5]. Here, hypercoagulability is initiated by activating pro-inflammatory cytokines such as IL-6 and TNF-α [6]. This is followed by an elevation in plasma fibrinogen concentration and D-dimer levels which correlate well with the severity of the disease and can predict mortality on hospital and ICU admission [7]. Other co-existing diseases such as cardiovascular or cerebral diseases also increase the risk for morbidity and mortality [8]. Standard coagulation tests (SCT) such as platelet count, PT, PTT and INR may show normal results in patients with COVID-19 despite hypercoagulability presented in thromboelastometry and microvascular thrombosis [9-11].

In contrast, viscoelastic tests (VETs) can evaluate the mechanical properties of clot formation and lyses. The most frequent used VETs are thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®). Published literature during this pandemic explored the ability of TEG® and ROTEM® in detecting COVID-19-associated coagulopathy [12,13]. The increase in thrombin generation and clot formation plays an important role in COVID-19 and identifies the level of severity as well as the risk of complications [14,15].

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Aim and Method of the Narrative Review

The aim of this narrative review is to identify and discuss the peer reviewed literature dealing with the role of thromboelastometry for COVID-19 patients suffering from coagulopathy. This review provides important information to clinicians and healthcare authorities regarding the possible role of thromboelastometry as a diagnostic and monitoring tool during this current COVID-19 pandemic.

A literature review was performed following approval of the local research and ethics committee on October 18th, 2020 (No. 2020–10–50) of the College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Kingdom of Saudi Arabia. This review explored and identified related published research focusing on the role of thromboelastometry in critically ill patients with COVID-19. The literature search used online available databases such as Medline, Scopus, PubMed and Google Scholar published manuscripts between January and December 2020. This included current peer-reviewed and accepted online ahead of print publications. The PubMed search (COVID-19>Title/Abstract) OR SARS-CoV-2>Title/Abstract) AND (ROTEM>Title/Abstract) OR thromboelastometry>Title/Abstract) achieved 24 results.

Rotational Thromboelastometry (ROTEM®) Basics

Thromboelastometry is a point-of-care device which has the capability to evaluate the viscoelastic properties and kinetics of the whole coagulation process including clot formation and lysis, in vitro. Thromboelastometry can assess both, extrinsic and intrinsic coagulation pathways depending on the reagents used [16]. These tests include EXTEM, INTEM, FIBTEM and HEPTEM which represent the extrinsic, intrinsic coagulation pathways, fibrin contribution to clot firmness, and heparin-like effects, respectively. Thromboelastometry parameters include CT, CFT, A5, A10, and MCF. CT is the time needed to initiate clot development (clot firmness = 2 mm). CFT characterizes clot
kinetics by the time needed to increase clot firmness from 2 to 20 mm. MCF is the maximum clot firmness in mm achieved during the thromboelastometric measurement. Finally fibrinolysis is characterized by maximum lysis (ML in %) which is defined as the decrease in clot firmness in percentage of MCF during run time. In order to detect hypofibrinolysis/fibrinolysis shutdown, run time should be at least 60 minutes. Lysis onset time (LOT in seconds) is defined as the time from CT until a decrease of clot firmness amplitude by 15% as compared to MCF has been achieved. LOT is not achieved during a 60 minutes run time in hypofibrinolysis/fibrinolysis shutdown or prolonged in TPATEM/TPA-test with r-tPA-challenge in patients with COVID-19. Lysis time (LT in seconds), defined as the time from CT until clot firmness is decreased to 50% (in ClotPro®) or 10% (in ROTEM®) as compared to MCF, can be used to characterize fibrinolysis resistance, too. Here, r-TPA-doses (Alteplase, Boehringer-Ingelheim, Ingelheim, Germany) between 0.125 and 0.625 µg/ml have been used for r-tPA-challenge by different investigators. Lysis index 30 and 60 are defined as the residual clot firmness in percentage of MCF at 30 or 60 minutes after CT, respectively. Fibrinolysis resistance is characterized by a prolonged LOT, prolonged LT and increased LI30 in TPATEM/TPA-test. Figure 1 displays the thromboelastometry parameters and indices mentioned above [16].

Several studies prior to the COVID-19 pandemic demonstrated that EXTEM or INTEM MCF > 68 mm (A10 > 61.5 mm) is a strong indicator for the presence of hypercoagulability and predictor of thrombosis [17,18]. FIBTEM MCF results > 25 mm have been shown to be associated with a 5-fold increased risk of thrombosis in cirrhotic patients with hepatocellular carcinoma [19,20]. Hypercoagulability in COVID-19 patients were assessed by thromboelastometry used as a diagnosis tool [21,22]. Criterion for hypofibrinolysis/fibrinolysis shutdown in thromboelastometry is an EXTEM ML < 3.5% following 60 min runtime, corresponding to an EXTEM LI60 > 96.5%.
Accordingly, thromboelastometry analysis should run for 65-70 minutes in COVID-19 patients in order to confirming or exclude hypofibrinolysis/fibrinolysis shutdown [22-24].

**COVID-19-associated Hypercoagulability in Thromboelastometry**

Between April and August 2020, several independent research groups (Pavoni et al. [5], Spiezia et al. [25], Collet et al. [26], and Hoechter et al. [27]) reported and confirmed the presence of hypercoagulability in thromboelastometric analyses in COVID-19 patients and that it is associated with an increased risk of thrombosis. Kong et al. [21] described this hypercoagulability as an increase in MCF in both EXTEM and FIBTEM (Figure 2). Moreover, Ibañez et al. [28] attributed this hypercoagulability to hypofibrinolysis/fibrinolysis shutdown. Chaudhary et al. [29] suggested that thromboelastometry can act as a monitor for hypercoagulability/hypofibrinolysis and a predictor for thromboembolic complications. In October 2020, Almskog et al. [30] demonstrated that EXTEM and FIBTEM MCF, assessed at hospital admission, could discriminate between hospitalized COVID-19 patients which can be treated at the regular ward and patients which will require treatment at specialized intensive care units (ICUs) with the option of mechanical ventilation. They also suggested that this could be used in future triage protocols. Three further studies by Spiezia et al. [31], van Veenendaal et al. [32], and Blasi et al. [33] confirmed that these thromboelastometry findings provides supportive evidences to indicate that hypercoagulability in EXTEM, INTEM, and FIBTEM were associated with more severe COVID-19. Roh et al. [34] also suggested that the significant increase in fibrinogen plasma concentrations and FIBTEM MCF indicates the severity of COVID-19 and can be used for risk stratification for thrombosis, respiratory failure and mortality. Actually, a multinational (11 countries), multicenter (16 hospitals) observational trial is running to assess the value of thromboelastometry and SCTs in predicting the
need for hospital resources, patients’ course and outcomes in 500 hospitalized patients with COVID-19 (ROHOCO study; DRKS00023934) [22].

COVID-19-associated Hypofibrinolysis/Fibrinolysis Shutdown in Thromboelastometry
The failure of LMWH or UFH to reduce the incidence of thrombosis was reported by Creel-Bulos et al. [24] and was attributed to the presence of hypofibrinolysis/fibrinolysis shutdown, characterized by an EXTEM ML < 3.5% corresponding to an EXTEM LI60 > 96.5%. Here, 8 out of 9 (89%) patients with venous thrombosis met the criteria for hypofibrinolysis/fibrinolysis shutdown, or the other way round, 8 out of 11 (73%) patients with hypofibrinolysis/fibrinolysis shutdown developed thrombosis whereas only 1 out of 14 (7%) patient without hypofibrinolysis/fibrinolysis shutdown developed thrombosis. The cut-off value for hypofibrinolysis/fibrinolysis shutdown reported by Creel-Bulos et al. [24] is in-line with the cut-off values for hypofibrinolysis/fibrinolysis shutdown published by Adamzik et al. [35] and Schmitt et al. [36] for bacterial sepsis and Gomez-Builes et al. [23] and Stettler et al. [37] for trauma patients.

COVID-19-associated Fibrinolysis Resistance in Thromboelastometry
Weiss et al. [38] and Nougier et al. [39] demonstrated that clots from some critically ill COVID-19 were even resistant to a fibrinolysis challenge with r-tPA in thromboelastometry (TPATEM = EXTEM with 0.125-0.625 µg/ml r-tPA (Alteplase, Boehringer-Ingelheim, Ingelheim, Germany)) despite high D-dimer plasma concentrations. Fibrinolysis resistance was defined as a delay in lysis onset time (LOS in seconds), or as an increased lysis index 30 (LI30 in % of MCF) after in vitro r-tPA challenge (Figure 3). Here, healthy controls showed a LI30 of 1.8 ± 3.2%, non-ICU COVID-19 patients 18 ± 35%, ICU COVID-19 patients 63 ± 39%, and ICU COVID-19 patients with thrombosis 82 ± 26% (P = 0.0029). A TPATEM assay with 0.125 µg/ml r-tPA has been validated.
on ROTEM® delta [40], but actually, a CE-marked TPA-test is only available on the ClotPro® device, a modification of rotational thromboelastometry [41]. Lysis time (LT in seconds), defined as the time from CT until clot firmness is decreased to 50% (on ClotPro®) or 10% (on ROTEM®) as compared to MCF, can be used to characterize fibrinolysis resistance, too [41]. In COVID-19 patients with thrombosis, LT is significantly prolonged in TPATEM/TPA-test. Whether detection of fibrinolysis resistance provides additional clinically relevant information compared to the detection of hypofibrinolysis/fibrinolysis shutdown is actually unknown and requires further investigation.

High D-dimer Levels combined with Hypofibrinolysis/Fibrinolysis Shutdown as a strong Predictor for Thrombosis in COVID-19

Several authors demonstrated that the combination of high D-dimer levels and hypofibrinolysis/fibrinolysis shutdown in viscoelastic testing provided the best predictive value for venous thromboembolism (VTE), thrombotic stroke and renal failure with the need for dialysis in COVID-19 [42,43]. Here, Wright et al. [42] demonstrated that the receiver operating characteristics area under the curve (ROC AUC) to predict VTE was 0.742 (95% CI, 0.581-0.903; P = 0.022) for TEG® lysis 30 (TEG® LY30 in % = decrease of clot firmness amplitude in percentage of maximum amplitude (MA) at 30 minutes after MA) and 0.582 (95% CI, 0.372-0.792; P = 0.440) for D-dimer. The ROC AUC to predict renal failure with the need for dialysis was 0.799 (95% CI, 0.610-0.949; P = 0.005) for D-dimer and 0.606 (95% CI, 0.414-0.797; P = 0.292) for TEG® LY30. Combined analysis resulted in an incidence of VTE, thrombotic stroke and renal failure with the need for dialysis was 5%, 7% and 14%, respectively, in COVID-19 patients with D-dimer ≤ 2600 FEU and TEG® LY30 > 0%. If either D-dimer were higher than 2600 FEU or TEG® LY30 was 0%, the incidence of VTE, thrombotic stroke and renal failure with the need for dialysis increased to 30%,
10% and 30%, respectively. If D-dimer were higher than 2600 FEU and LY30 was 0%, the incidence of VTE, thrombotic stroke and renal failure with the need for dialysis increased to 50% (P = 0.008), 30% (P = 0.274) and 80% (P = 0.004), respectively. These results are in-line with the data published recently by Kruse et al. [43]. Here, EXTEM ML was inversely (ROC AUC, 0.8 (95% CI, 0.7-0.9); P = 0.002) and D-dimers directly (ROC AUC, 0.78 (95% CI, 0.6-0.9); P < 0.001) associated with an enhanced risk of VTE complications. Combining values for EXTEM ML with D-dimer concentrations revealed high sensitivity and specificity of VTE risk prediction (D-dimer (µg/l) – EXTEM ML (%) cut-off, 3.7; ROC AUC, 0.92 (95% CI, 0.8-1.0); P < 0.001; sensitivity, 94%, specificity > 90%). Accordingly, the combination of hypofibrinolysis/fibrinolysis shutdown and increased D-dimers is actually the best predictor for VTE, thrombotic stroke and renal failure with the need for dialysis in critically ill COVID-19 patients. Primarily, this combination resulted in some confusion since increased D-dimer levels have been misinterpreted as a biomarker of increased fibrinolysis [28]. However, both Almskog et al. [30] and Madathil et al. [44] showed that only 0.02-0.2% of the fibrinogen mass is cleaved to D-dimers in COVID-19. Accordingly, increased D-dimer levels in COVID-19 reflect an increased fibrin deposition but not an increased breakdown of fibrin (fibrinolysis). Finally, the combination of increase fibrin deposition in the microcirculation combine with hypofibrinolysis results in multiple organ failure (lungs, kidney and brain).

Potential Implications of Hypofibrinolysis/Fibrinolysis Shutdown for the Therapy of COVID-19-associated Coagulopathy

These data suggest that COVID-19 patients with respiratory failure (hypoxia (PaO₂/FiO₂ < 150 mmHg for more than 4 hours) despite optimum mechanical ventilation and prone position), hypercoagulability and hypofibrinolysis/ fibrinolysis shutdown might benefit from
subtherapeutic/therapeutic anticoagulation and/or additional thrombolytic therapy with r-tPA (Alteplase, Boehringer-Ingelheim, Ingelheim, Germany) [34,45-49]. Recent case series showed that r-tPA therapy can improve oxygenation and may improve survival in this specific patient population [50-53].

The required r-tPA-dose can vary from patient to patient and therefore monitoring of the effect of the thrombolytic therapy in COVID-19 patients by thromboelastometry is recommended [50,53]. Here, thromboelastometry can not only be helpful to select the COVID-19 patient population who might benefit from thrombolytic therapy, but can also detect the patient population with a high risk of bleeding complications under thrombolytic therapy. Symptomatic intracerebral hemorrhage usually occurs within 24-36 h after thrombolytic infusion and remains one of the most feared complications of thrombolytic therapy. Campello et al. [54] demonstrated that a baseline level of FIBTEM MCF below 13.5 mm is a quickly and easily available marker to predict which patients have a high risk of developing a hemorrhagic event after r-tPA therapy (sensitivity 94% and specificity 80%). Furthermore, bleeders showed higher EXTEM ML after r-tPA infusion, borderline for hyperfibrinolysis (median [IQR], 14% [10-18%] versus 6% [5-8.5%]; P = 0.007). Accordingly, thrombolytic therapy might be harmful at advanced stage of COVID-19 where the hemostatic status changed from hyper- to hypocoagulability and from hypo- to hyperfibrinolysis in case of disseminated intravascular coagulation (DIC) [55]. A phase IIa randomized controlled trial on the efficacy and safety of different doses of alteplase (50-100 mg IV) for respiratory failure in COVID-19 is actually running (STARS trial) [56]. Thrombolytic therapy will be followed by heparin infusion for therapeutic anticoagulation.

Inhalation Therapy with Thrombolytic Agents in severe COVID-19
Furthermore, nebulizer r-tPA may provide a targeted approach in COVID-19 patients to degrade fibrin and improving oxygenation with limited bleeding risk in critically ill patients [57]. Administration of thrombolytic drugs by inhalation might improve alveolar ventilation by resolving fibrin-containing exudates in the pulmonary alveolar space and dissolving fibrin thrombi at the level of the microcirculation near the alveoli. Inhalation therapy with tPA has gradually been reported to be efficacious for various situations of ARDS or plastic bronchitis. Actually, a phase II clinical trial of r-tPA inhalation is underway (PLATyPuS; alteplase, NCT02315898). Other authors reported promising results for plasminogen inhalation in COVID-19 patients [58]. If r-tPA is not available, nebulization of streptokinase might be an alternative. Abdelaal et al. [59] performed a randomized controlled trial comparing nebulized streptokinase versus nebulized heparin and standard of care in patients with severe acute respiratory distress syndrome (ARDS) (PaO₂/FiO₂ < 100 mmHg) nonresponsive to recruitment maneuver and prone position. Here, streptokinase (250,000 IU/4h by nebulizer, with a total daily dose of nebulized streptokinase of 1,500,000 IU) or heparin (dose of 10,000 IU/4h by nebulizer, with a total daily dose of 60,000 IU UFH) prepared in 3 ml volume of distilled water and nebulized for a period of 15 minutes every 4 hours was administered. Nebulized streptokinase resulted in an improvement of oxygenation (increased PaO₂/FiO₂), decreased PaCO₂ (P < 0.0001), improved lung compliance, reduced plateau pressure, and decreased ICU mortality compared to nebulized heparin and standard of care therapy.

COVID-19, Heparin Resistance and Anticoagulation Monitoring with Thromboelastometry

Heparin resistance can be defined as a decrease in the heparin dose-response-curve. Furthermore, heparin resistance can be defined as the need for more than 35000 IU unfractionated heparin (UFH) per 24 hours to prolong the activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to the therapeutic range [60,61]. Predictors of heparin resistance are an antithrombin activity
of less than 60%, age above 65 years, increased factor VIII and fibrinogen levels and platelets greater than 300,000/µl [62]. Whereas antithrombin activity rarely drops below 60% in COVID-19 patients, increased age, factor VIII and fibrinogen levels and high platelet counts are common in severe COVID-19 [25,27,63,64].

Low molecular weight heparin (LMWH, e.g., enoxaparin, 20-30 mg SC once a day) is used as thromboprophylaxis in COVID-19 patients with low thrombotic risk and fibrinogen plasma concentrations < 500 mg/dl provided that an anti-Xa activity target of 0.1-0.4 IU/ml is achieved 2-4 hours after SC injection. For subtherapeutic or therapeutic anticoagulation in COVID-19 patients with moderate to high risk of venous thromboembolism (VTE), 0.5 to 1 mg/kg enoxaparin SC twice per day can be used if the anti-Xa activity target of 0.4-0.6 or 0.6-1.0 IU/ml is achieved 2-4 hours after SC injection. In critically ill COVID-19 patients with the need for vasopressor therapy, SC injection of LMWH might be inappropriate due to peripheral vasoconstriction and reduced resorption of the drug. Here, IV infusion of UFH or LMWH might be an alternative but the effect might be limited by heparin resistance, again (anti-Xa activity targets for subtherapeutic (200 IU/kg/24h) and therapeutic anticoagulation (400 IU/kg/24h) with UFH are 0.15-0.30 and 0.3-0.7 IU/ml, respectively).

To monitor the effect of heparin anticoagulation or to diagnose heparin resistance with thromboelastometry, it is important to consider that INTEM is not very sensitive to detect the effect of LMWH. The INTEM/HEPTEM CT-ratio correlates well with anti-Xa activity for UFH (r = 0.72 compared to 0.36 for aPTT) [65]. The native thromboelastometry test NATEM is more sensitive to LMWH and the NATEM/NaHEPTEM CT-ratio correlates well with the anti-Xa activity calibrated for LMWH [unpublished data].

The direct factor Xa inhibitor apixaban can used for thromboprophylaxis or alternative anticoagulation in COVID-19 in case of heparin resistance and if oral administration is preferred.
Notably, very high direct oral anticoagulant (DOAC) plasma concentrations can occur if DOACs are combined with antiviral drugs in COVID-19 patients [70]. Therefore, these combinations should be avoided or DOAC concentrations should be monitored. In order to monitor the effect of apixaban with thromboelastometry, modified assays with lower tissue factor concentrations are needed [71,72].

In critically ill patients with high VTE risk and fibrinogen plasma concentrations > 500 mg/dl, argatroban can be used off-label for alternative anticoagulation, particularly in patients with heparin resistance [60]. Argatroban is a direct thrombin inhibitor approved for thromboprophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). Argatroban plasma concentrations needed for therapeutic anticoagulation are between 0.2 and 0.5 IU/ml anti-IIa activity. Here, EXTEM CT correlates better to argatroban plasma concentrations compared to aPTT (r = 0.71; P < 0.001 and r = 0.214; P = 0.117, respectively) [73,74]. Furthermore, the importance of viscoelastic testing in patients anticoagulated with direct thrombin inhibitors was highlighted by Rànucci et al. [75] and Maier et al. [76]. They pointed out that fibrinogen plasma concentration assessed by the Clauss method are no reliable in the presence of direct thrombin inhibitors and result in falsely low values. Therefore, they recommend using FIBTEM and TEG® functional fibrinogen measurements to assess fibrinogen plasma concentration in these patients and to guide argatroban or bivalirudin dosage [75,76].

**Bleeding in COVID-19**

In hospitalized COVID-19 patients receiving standard-dose thromboprophylaxis, Al-Samkari et al. [77] reported an overall and major bleeding rate of 4.8% (95% CI, 2.9-7.3) and 2.3% (95% CI, 1.0-4.2), respectively. Similar results were reported by Jimenez et al. [78]. In this systematic review, the pooled incidence for VTE was 17.0% (95% CI, 13.4-20.9), 12.1% (95%CI, 8.4-16.4) for DVT,
7.1% (95% CI, 5.3-9.1) for pulmonary embolism, 7.8% (95% CI, 2.6-15.3) for bleeding, and 3.9% (95% CI, 1.2-7.9) for major bleeding. The highest pooled incidence estimate of bleeding was reported for patients receiving intermediate- or full-dose anticoagulation (21.4%).

On the one hand, patients with COVID-19 have an increased risk of thrombosis, and mortality can be reduced by thromboprophylaxis in hospitalized patients [48,68,79,80]. On the other hand, patients with therapeutic anticoagulation have an increased incidence of major bleeding (11% versus 4%; P = 0.04) and significantly higher mortality (41.6% versus 15.3%; P < 0.0001) compared to patients with pharmacologic thromboprophylaxis [81]. After multivariate logistic regression, therapeutic anticoagulation was still associated with increased mortality with an odds ratio of 6.16 (95% CI, 2.96-12.83; P < 0.0001). Major bleeding and CNS bleeding was associated with increased mortality (40% versus 21.5%; P = 0.054 and 100% versus 21.9%; P = 0.001, respectively) whereas gastrointestinal bleeding was not (16.7% versus 22.7%; P = 1.000). Dogra et al. [82] reported about 33 COVID-19 positive patients with intracerebral hemorrhage (ICH). Almost all patients with ICH received either therapeutic dose anticoagulation (66.7%) or prophylactic dose (9.1%) prior to ICH discovery. Accordingly, the risk of ICH should be taken into account when developing an anticoagulation regime in COVID-19. Usman et al. [83] reported about a case series of COVID-19 patients treated with veno-venous extracorporeal membrane oxygenation. Four of 10 patients had hemorrhagic strokes, 3 of which resulted in death. Schmidt et al. [84] confirmed an incidence of major bleeding of 42%, an incidence of hemorrhagic stroke of 5% and a mortality of 36% in COVID-19 patients treated with ECMO. Accordingly, close monitoring of all hematologic parameters including viscoelastic testing and personalized antithrombotic therapy is recommended in severe COVID-19, particularly during ECMO support [29]. The degree of anticoagulation can be assessed by anti-Xa activity or INTEM/HEPTEM CT-ratio for UFH, by anti-Xa activity or NATEM/NaHEPTEM CT-ratio for LMWH, and by anti-IIa activity, EXTEM CT or
ECATEM/ECA-test CT for IV direct thrombin inhibitors such as argatroban and bivalirudin [65,73,74,85-90]. Furthermore, the hemostatic phenotype of COVID-19 patients may change in advanced stages from hyper- to hypocoagulability and from hypo- to hyperfibrinolysis in case of DIC [21,55]. The combination of thromboelastometry and SCT enables the monitoring of these dynamic changes in COVID-19-associated coagulopathy and its corresponding therapy.

Conclusions

A Multi-modal diagnostic approach that includes SCT, such as fibrinogen plasma concentration and D-dimers, as well as thromboelastometry is required for the detection, monitoring and management of COVID-19-associated coagulopathy. Fibrinogen plasma concentrations, D-dimer levels and FIBTEM clot firmness play an important role in risk stratification, prediction of the level of care needed during hospitalization and patients’ outcome in hospitalized COVID-19 patients. SCTs such as aPTT and PT/INR may fail to detect hypercoagulability. In contrast, the combination of increased D-dimer levels and hypofibrinolysis/fibrinolysis shutdown detect by thromboelastometry is actually the best predictor for thromboembolic complications in COVID-19. The ability of thromboelastometry to guide personalized management and monitor individual responses to treatment should be utilized. There is an urgent need to develop thromboelastometry-guided protocols and algorithms for the management of COVID-19-associated coagulopathy.
References


**Figure 1**

**ROTEM® Parameters and Indices.** FDPs = fibrin(ogen) degrading products; F XIII = coagulation factor XIII. Courtesy of Klaus Görlinger, Munich, Germany.
**Figure 2**

**COVID-19-associated Coagulopathy.** Diagnostic value of D-dimer, fibrinogen, anti-Xa activity and thromboelastometry parameters. Courtesy of Klaus Görlinger, Munich, Germany.
**Figure 3**

TPATEM/TPA-test Findings in COVID-19 Patients. Representative TPATEM curves from a healthy donor (green curve), a COVID-19 patient without thrombosis (black curve), and from a COVID-19 patient with thrombosis (red curve). In COVID-19 patients, LOT and LT are prolonged, and MCF and LI30 are increased compared to healthy controls after r-tPA challenge (TPATEM = EXTEM + 0.625 µg/mL r-tPA). EXTEM = thromboelastometry assay with extrinsic activation; LI30 = lysis index 30 min after CT [% MCF]; LOT = lysis onset time [s]; Lysis time [s]; MCF = maximum clot firmness [mm]; r-tPA = recombinant tissue plasminogen activator. Courtesy of Klaus Görlinger, Munich, Germany.