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Whole blood viscoelastic testing profile and mortality in patients hospitalized with acute COVID-19 pneumonia: A systematic review and meta-analysis

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ABSTRACT

Background: Several studies have evaluated the possible association between whole blood viscoelastic testing (VET) parameters in patients hospitalized for acute Coronavirus disease 2019 (COVID-19) pneumonia and mortality. A few studies found no significant differences between survivors and non-survivors, though other studies identified potential predictors of COVID-19-related mortality. We conducted a systematic review and meta-analysis of the literature to evaluate the possible association between standard thromboelastometry/graphy parameters and mortality in patients hospitalized for acute COVID-19 pneumonia.

Methods: Relevant studies were searched through MEDLINE, EMBASE, and Google Scholar from their inception until 15th June 2023. We aimed to identify any study including: i) adults admitted to intensive care units (ICU) or medicine wards (MW) for acute COVID-19 pneumonia; ii) viscoelastic testing; iii) mortality.

Results: We included 13 studies: nine prospective and four retrospective, 231 (30.4 %) non-survivors and 528 (69.6 %) survivors. Mortality rates ranged from 12.8 % to 67.5 %. The studies using the TEG apparatus found a significant difference in K time in the Kaolin test among survivors vs. non-survivors (mean difference [MD] 0.20, 95 % confidence interval [CI] 0.12, 0.28, I^2 0%). The studies using the rotational thromboelastometry apparatus found a significant difference in CT-INTEM (MD −17.14, 95 % CI −29.23, −5.06, I^2 0%) and LI60-EXTEM (MD −1.00, 95 % CI −1.00, −1.00, I^2 0%) assays among survivors vs. non-survivors.

Conclusion: We identified no specific hypercoagulable or hypocoagulable profile associated with mortality in patients with COVID-19-related pneumonia. Large prospective studies are needed to explore the possible prognostic role of VET in this subset of patients.

1. Introduction

Patients hospitalized with acute Coronavirus disease 2019 (COVID-19) pneumonia between 2019 and 2022 were particularly prone to develop thrombotic events [1–3]. This incidence rate remained high, both in intensive care units (ICU) and medical wards (MW), despite the systematic implementation of thromboprophylaxis [4,5]. Several pathogenetic mechanisms have been proposed to explain the correlation between the prothrombotic state associated with acute COVID-19 and the increased risk of developing thrombotic events. In particular, the cytokine storm observed in patients with acute COVID-19 promotes a hypercoagulable state mainly via four mechanisms endothelial damage, activation of coagulation and platelets, and suppression of fibrinolysis [6–9]. Moreover, the activation of neutrophils results in the release of neutrophil extracellular traps (NETs) that occlude blood vessels, leading to thrombotic complications [10]. Traditional coagulation tests are limited in their ability to characterize COVID-19-associated hypercoagulability. Several studies have reported that whole blood viscoelastic testing (VET) provides a more comprehensive evaluation of coagulation processes — increased cloth strength and hypofibrinolysis — involved in COVID-19-associated hypercoagulability [11–14]. Nevertheless, the ability of VET parameters to accurately predict poor outcomes (e.g., development of thrombosis, ICU admission, intubation and mechanical ventilation, extracorporeal membrane oxygenation [ECMO], or death) is still a matter of debate. Although some studies reported no significant differences in thromboelastography parameters between survivors and

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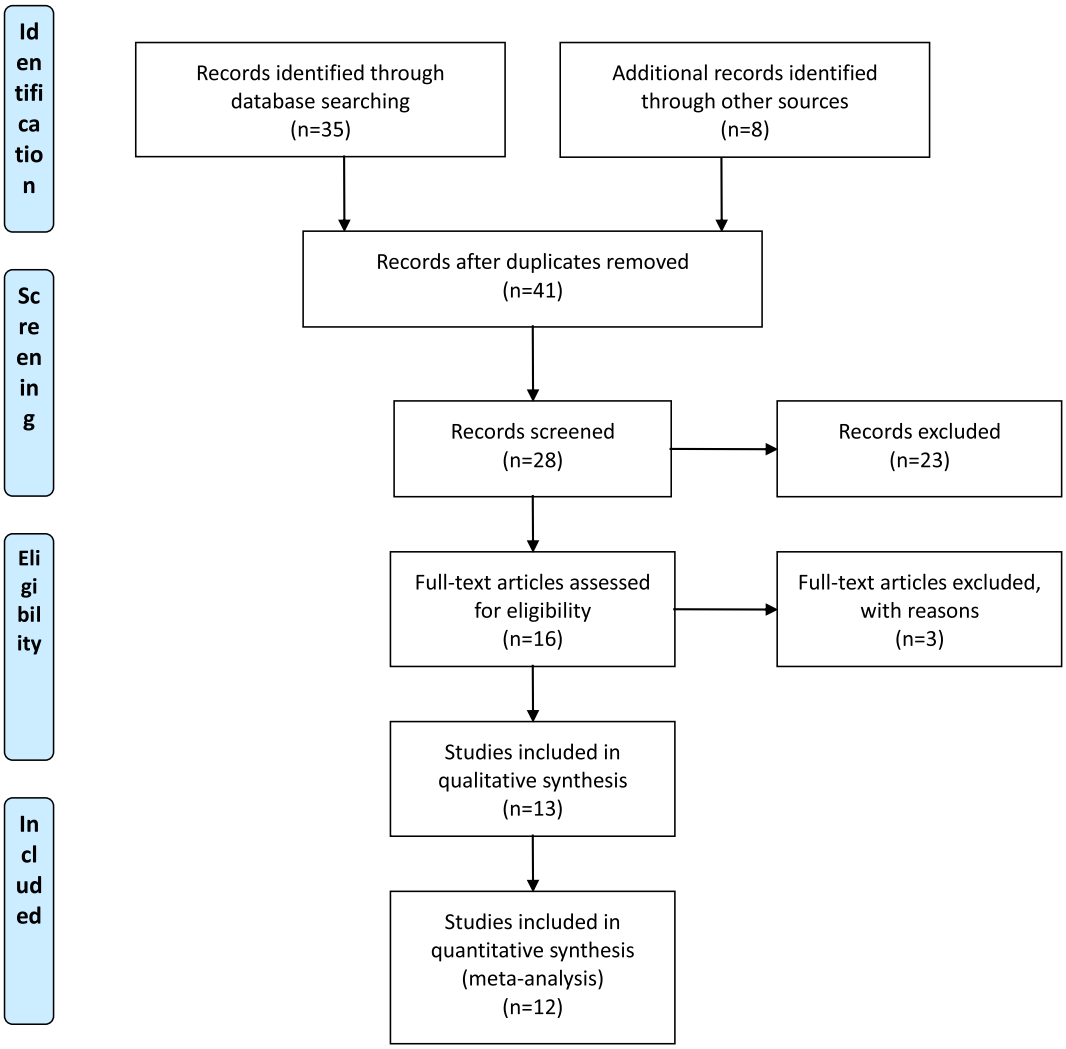

Fig. 1. PRISMA 2009 flow diagram.

non-survivors as it relates to mortality rates [15,16], Almskog LM et al. found that VET parameters were associated with hypercoagulability, with a positive correlation with disease severity [17]. Furthermore, we previously found a significant prolongation of clotting time (CT) in EXTEM assay – that evaluates extrinsic coagulation pathway – in non-survivors than survivors [18]. Therefore, we conducted a systematic review and meta-analysis of the literature to assess the possible association between VET parameters and mortality in patients hospitalized with acute COVID-19 pneumonia.

2. Materials and methods

2.1. Data sources and search strategy

This study was registered on PROSPERO (registration ID: CRD42023408160) and conducted in compliance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplemental Table 1) [19]. We searched for eligible articles in MEDLINE, EMBASE, and Google Scholar. Reference lists of selected papers were used to search for other potential studies. The search was performed from May 2023 through July 2023. There were no language restrictions.

2.2. Study population

Patients hospitalized with acute COVID-19 pneumonia reported in observational studies and clinical trials.

2.3. Data extraction

Two independent reviewers (LS and EC) screened articles and determined eligibility based on the criteria mentioned above. Studies were only included if both reviewers agreed and conflicts were resolved by a knowledgeable third reviewer (PS). We compiled a flow diagram covering the entire article selection process, from the initial identification (database search and other sources) to the final inclusion of the qualitative and quantitative synthesis. The same independent reviewers (LS and EC) extracted data from selected articles by consensus, and conflicts were resolved by a knowledgeable third reviewer (PS). Data extraction tables were compiled, including the main characteristics of the study and patients. The authors of the selected studies were contacted in case of missing, incomplete, or unpublished data.

2.4. Data synthesis and analysis

The effect size of continuous outcomes with similar measurement methods across studies was reported as mean difference (MD) with 95 % confidence interval (CI); otherwise, they were reported as standardized

mean difference (SMD). When needed, medians and corresponding interquartile ranges were transformed into means and standard deviations using the method proposed by Wan et al. [20]. Respective weights of the selected studies and pooled effect size were provided using a random-effects model and presented as forest plots. Moreover, the corresponding prediction intervals were calculated using the method proposed by Higgins et al. [21]. The Hartung and Knapp method was used to adjust statistics and CIs. Heterogeneity between studies was assessed using the I^2 statistic and Cochran's Q test. The between-study variance τ^2 was calculated using restricted maximum-likelihood (REML) estimation. There was no correction for multiple testing. All statistical analyses were performed using the 'meta' package in R statistical software version 4.3.1 (R Project for Statistical Computing) and RStudio version 2023.06.0 (R Foundation for Statistical Computing©).

2.5. Risk of bias

For clinical trials, two independent reviewers (LS and EC) assessed the risk of bias in the included studies using the Cochrane Collaboration's tool for assessing the risk of bias in the following six key domains: (*i*) random sequence generation; (*ii*) allocation concealment; (*iii*) blinding of participants and personnel, (*iv*) blinding of outcome assessment; (*v*) selective reporting; (*vi*) other biases. The risk of bias was formulated as follows: "low risk" (bias, if present, will be considered unlikely to have altered results), "high risk" (risk of bias will elicit reservations about obtained results), and "unclear" (bias may significantly alter results). A bias for a trial was deemed "low risk" if found in all six key domains and "high risk" if present in at least one domain. When a study presented an unclear risk of bias in at least one domain, without any domain showing a high risk of bias, it could be defined as having an "unclear risk" of bias. In non-randomized studies of interventions, the risk of bias was assessed using the ROBINS-I tool. Cohort and case-control studies were appraised using the Newcastle-Ottawa Scale (NOS) [22].

3. Results

3.1. Study characteristics

Database searches, snowballing, and contacts with experts yielded a total of 43 articles. After removing duplicate studies, we retrieved 41 articles for further examination: 16 full-text articles were assessed for eligibility, and three were excluded. The study selection process is outlined in Fig. 1. Ultimately, 13 studies met the inclusion criteria and were included in this systematic review and meta-analysis [15–18,23–31]. The Newcastle-Ottawa Scale for the included studies is reported in Supplemental Table 2. The baseline characteristics of the included studies are summarized in Table 1. The studies were conducted in Europe [15,17,18,26–29], India [24,25,30], South Africa [16,31], and the United States [23]. Overall, nine studies comprised patients admitted to ICU [15,16,23–29], one study comprised patients admitted to MW [30], and three studies comprised both patients admitted to ICU and MW [17,18,31]. There were three retrospective studies [18,23,27] and 10 prospective studies [15–17,24–26,28–31]. The baseline characteristics of the included participants are summarized in Table 2. Mortality was assessed at different time points: at 30 days in four studies [16,17,24,30], 28 days in two studies [15,29], 10 days in one study [31], and the remaining six studies recorded in-hospital mortality [17,23,25–28]. The mortality rate across studies ranged between 12.8 % [17] and 67.5 % [16]. Overall, this systematic literature review included 759 patients, of whom 231 (30,4 %) died during the study period. Apparatus, tests, and parameters are summarized in Table 3. Thromboelastography (TEG) apparatus was used in five studies: four used the TEG6s [15,16,30,31] and one the TEG 5000 [25]. Rotational thromboelastometry (ROTEM) apparatus was used in seven studies: four used the ROTEM Delta [18,23,24,29], and three used the ROTEM Sigma [17,27,29]. Finally, ClotPro apparatus was used only in one study [28].

Table 1
Baseline characteristics of the included studies.

First author, year[ref]	Country	Study period	Setting	Study design
Bocci MG, 2020 [15]	Italy	February–March 2020	ICU	Prospective
Neethling C, 2021 [16]	South Africa	July–August 2020	ICU	Prospective
Almskog LM, 2021 [17]	Sweden	May–August 2020	MW and ICU	Prospective
Capone F, 2022 [18]	Italy	March–May 2020	MW and ICU	Retrospective
Corey KM, 2022 [23]	US	April–October 2020	ICU	Prospective
Kamal M, 2022 [24]	India	July–August 2020	ICU	Retrospective
Mohan G, 2022 [25]	India	May 2021	ICU	Prospective
Calvet L, 2022 [26]	France	April 2020–March 2021	ICU	Prospective
Heubner L, 2022 [27]	Germany	January–March 2021	ICU	Retrospective
Hulshof AM, 2021 [28]	Netherlands	April–June 2020	ICU	Prospective
Boscolo A, 2020 [29]	Italy	February–April 2020	ICU	Prospective
Sehgal T, 2022 [30]	India	May–June 2021	MW	Prospective
van Blydenstein SA, 2021 [31]	South Africa	Nov. 2020-March 2021	MW and ICU	Prospective

ICU: intensive care unit; MW: medical ward.

Table 2
Baseline characteristics of the included participants.

First author, year[ref]	Tested patients	Sex (M/F)	Age	Mortality	
				Definition	N. (Rate, %)
Bocci MG, 2020 [15]	40	29/11	67.5 (55–77)	28-day	17 (42.5)
Neethling C, 2021 [16]	40	26/14	55 ± 8	30-day	27 (67.5)
Almskog LM, 2021 [17]	141	87/54	63 (51–75)	30-day	18 (12.8)
Capone F, 2022 [18]	104	70/34	67 (58–77)	In-hospital	15 (14.4)
Corey KM, 2022 [23]	46	34/12	57 ± 6	In-hospital	11 (23.9)
Kamal M, 2022 [24]	23	16/7	61.6 ± 15.8	30-day	12 (52.2)
Mohan G, 2022 [25]	43	31/12	58.34 ± 15.35	In-hospital	14 (32.6)
Calvet L, 2022 [26]	133	95/38	71.2 (63.4–76.4)	In-hospital	46 (34.6)
Heubner L, 2022 [27]	55	43/12	65 (58–69)	In-hospital	30 (54.5)
Hulshof AM, 2021 [28]	36	29/7	61 (55–70)	In-hospital	7 (19.4)
Boscolo A, 2020 [29]	32	26/6	68 (62–65)	28-day	8 (25.0)
Sehgal T, 2022 [30]	25	12/13	50 (40–60)	30-day	8 (32.0)
van Blydenstein SA, 2021 [31]	41	15/26	61 (50–67)	10-day	18 (43.9)

3.2. Comparison of TEG parameters between survivors and non-survivors

3.2.1. Meta-analysis

The values of TEG parameters in survivors and non-survivors are summarized in Table 4. Studies that performed Kaolin tests and Kaolin

Table 3
Apparatus, tests, and parameters.

First author, year[ref]	Apparatus	Test	Standard parameters
Bocci MG, 2020 [15]	TEG6s	Kaolin	R time, K time, alpha angle, LY30
		Kaolin with heparinase	R time, K time, alpha angle, MA
		Rapid TEG	R time, K time, alpha angle, MA
		Functional Fibrinogen	MA
Neethling C, 2021 [16]	TEG6s	Kaolin with heparinase	R time, K time, alpha angle, MA, LY30
		Functional Fibrinogen	MA
Almskog LM, 2021 [17]	ROTEM sigma	EXTEM	CT, CFT, MCF, LI30, LI60
		INTEM	CT, CFT, MCF, LI30, LI60
		FIBTEM	MCF
		HEPTEM	CT
Capone F, 2022 [18]	ROTEM delta	EXTEM	CT, CFT, MCF, LI30, ML
		INTEM	CT, CFT, MCF, LI30, ML
		FIBTEM	MCF
Corey KM, 2022 [23]	ROTEM delta	EXTEM	CFT, alpha angle, MCF, LI30
		INTEM	CFT, alpha angle, MCF, LI30
		FIBTEM	MCF
Kamal M, 2022 [24]	ROTEM delta	INTEM	CT, CFT, A5, A10, MCF, LI30, LI60, AUC
		FIBTEM	CT, CFT, MCF, A5, A10, LI60, AUC
Mohan G, 2022 [25]	TEG 5000	Kaolin	R time, K time, alpha angle, MA, LY30
Calvet L, 2022 [26]	ROTEM sigma	EXTEM	CFT, A5, MCF, LI60
Heubner L, 2022 [27]	ClotPro	EX-test	CT, MCF, ML
		IN-test	CT, MCF
		FIB-test	MCF
		TPA-test	MCF, LT, ML
Hulshof AM, 2021 [28]	ROTEM sigma	EXTEM	CT, CFT, MCF
		FIBTEM	CT, MCF
Boscolo A, 2020 [29]	ROTEM delta	EXTEM	CT, CFT, MCF
		INTEM	CT, CFT, MCF
		FIBTEM	MCF
Sehgal T, 2022 [30]	TEG6s	Kaolin with heparinase	R time, K time, alpha angle, MA, LY30
van Blydenstein SA, 2021 [31]	TEG6s	Kaolin	LY30
		Kaolin with heparinase	R time, K time, alpha angle, MA

MA: maximum amplitude; CT: clotting time; CFT: clot formation time; MCF: maximum clot firmness; A5 and A10: clot firmness at 5 and 10 min, respectively; AUC, area under the curve; LT, lysis time; LY/LI 30 and LY/LI 60: lysis index at 30 and 60 min, respectively; ML: maximum lysis.

with heparinase tests considered the following four parameters: R time, K time, alpha angle, and maximum amplitude (MA) values [15,16,25,30,31]. Functional fibrinogen was assessed in two studies [15,16]. Overall, the studies that used the TEG apparatus found a significantly prolonged K time on Kaolin tests among survivors vs. non-survivors (mean difference [MD] 0.20, 95 % confidence interval [CI] 0.12, 0.28, I^2 0%) (Figs. 2–10).

3.2.2. Descriptive analysis

The parameters that could not be included in the meta-analysis are listed in Table 5. The values of lysis index at 30 min (LY30) on Kaolin tests were reported in three studies [15,24,31], whereas two studies reported LY30 values on Kaolin with heparinase tests [16,30]. Bocci et al. [15] also reported the results of the rapid TEG. They found no significant differences between survivors and non-survivors regarding R time, K time, alpha angle, and MA.

Table 4
Summary and findings of TEG parameters between survivors and non-survivors.

Test and parameters	Survivors	Non-Survivors	MD	95 % CI	I [2] (%)
Kaolin					
R Time	52	31	−0.98	−2.11; 0.15	0
K Time	52	31	0.20	0.12; 0.28	0
Alpha angle	52	31	0.03	−17.68; 17.73	24
MA	46	22	−0.50	−95.23; 94.24	75
Kaolin with heparinase					
R Time	76	70	0.47	−0.71; 1.64	31
K Time	76	70	−0.02	−0.22; 0.17	0
Alpha angle	76	70	0.13	−1.65; 1.90	0
MA	76	70	−0.04	−2.75; 2.66	24
Functional Fibrinogen					
MA	36	44	−0.09	−50.50; 50.32	63

MD: Mean difference; CI: Confidence interval. MA: Maximum amplitude.

3.3. Comparison of ROTEM parameters between survivors and non-survivors

3.3.1. Meta-analysis

The values of ROTEM parameters in survivors and non-survivors are summarized in Table 6. As regards INTEM assays, four studies reported clotting time (CT) values [17,18,24,28], and five studies reported clot formation time (CFT) and maximum clot firmness (MCF) values [17,18,23,24,28]. As for EXTEM assays, four studies reported CT values [17,24,28,29], six studies reported CFT and MCF values [17,23,24,28,29], and two studies reported lysis index at 60 min (LI60) [13,18]. Finally, two studies reported CT values [24,28], and six reported MCF values in FIBTEM assays [17,18,23,24,28,29]. Overall, the studies that used the ROTEM apparatus found a significantly prolonged CT-INTEM (MD −17.14, 95 % CI −29.23, −5.06, I^2 0%) and LI60-EXTEM (MD −1.00, 95 % CI −1.00, −1.00, I^2 0%) in survivors vs. non-survivors (Figs. 11–19).

3.3.2. Descriptive analysis

The parameters that could not be included in the meta-analysis are listed in Table 7. INTEM assays: one study reported alpha angle values [23], and one study reported clot firmness at 5 and 10 min (A5 and A10, respectively) values [24]; four studies reported LY30 values [17,18,23,24], and two studies reported LI60 values [17,24]; one study reported maximum lysis (ML) values [23]. EXTEM assays: one study reported alpha angle values [23], and one study reported A5 values [26]; LI30 values were reported in three studies [17,18,23]; ML values were reported in one study [18].

3.4. Comparison of ClotPro parameters between survivors and non-survivors

Heubner et al. [27] reported the results of ClotPro testing, and according to the assays (i.e., EX-test, IN-test, FIB-test, and TPA-test) and the parameters (i.e., CT, MCF, ML, and LT) considered, they found no significant differences between survivors and non-survivors.

4. Discussion

Our systematic review and meta-analysis revealed that the studies that used the TEG apparatus found a significant association between mortality and reduced K time on the Kaolin test. In contrast, the studies conducted with the ROTEM apparatus found a significant association between mortality and prolonged CT in INTEM and decreased LY60 in EXTEM. Several studies by different groups have highlighted the

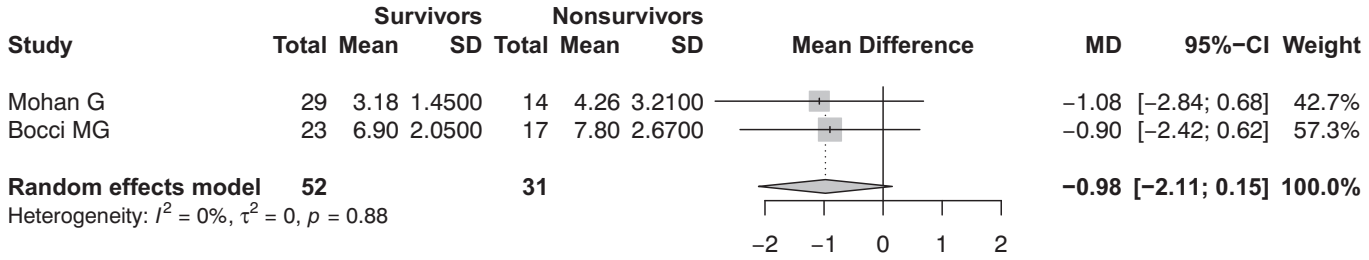

Fig. 2. TEG R time Kaolin.

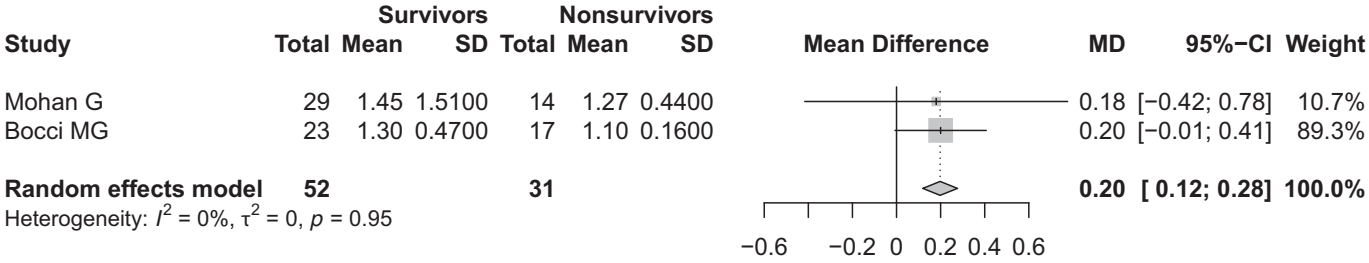

Fig. 3. TEG K time Kaolin.

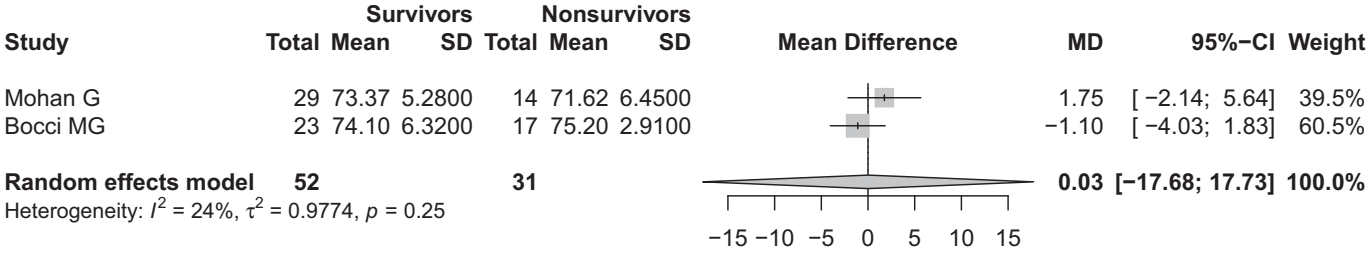

Fig. 4. TEG Alpha angle Kaolin.

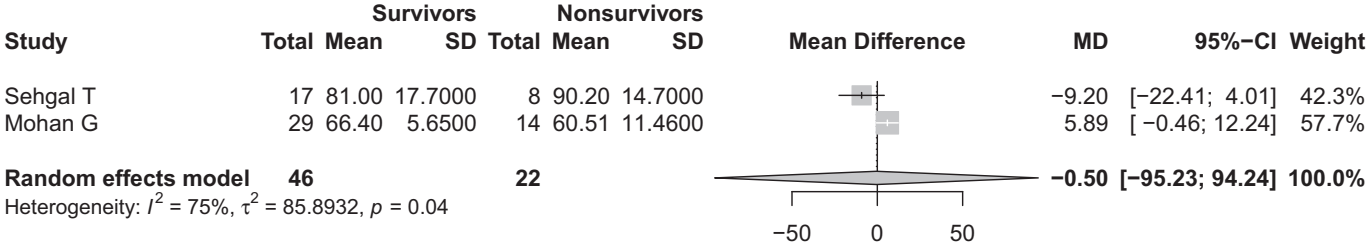

Fig. 5. TEG MA Kaolin.

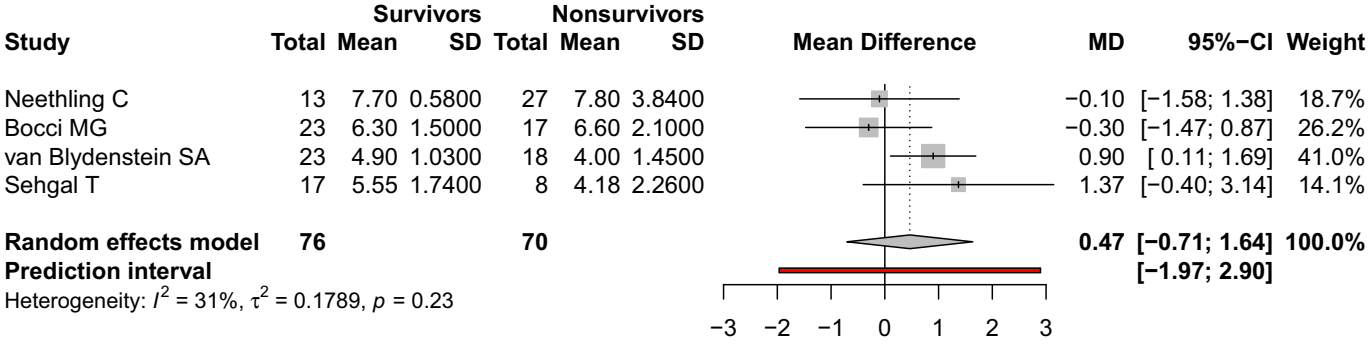

Fig. 6. TEG R time Heparinase.

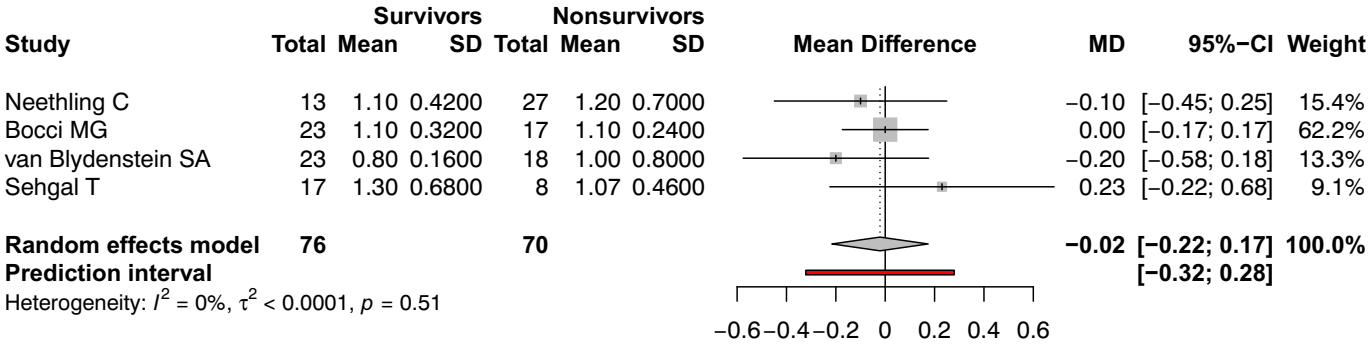

Fig. 7. TEG K time Heparinase.

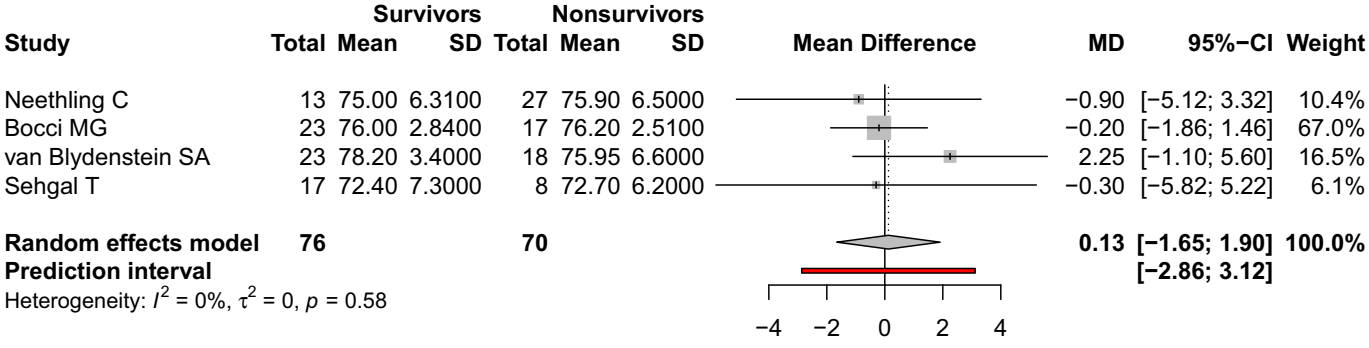

Fig. 8. TEG Alpha angle Heparinase.

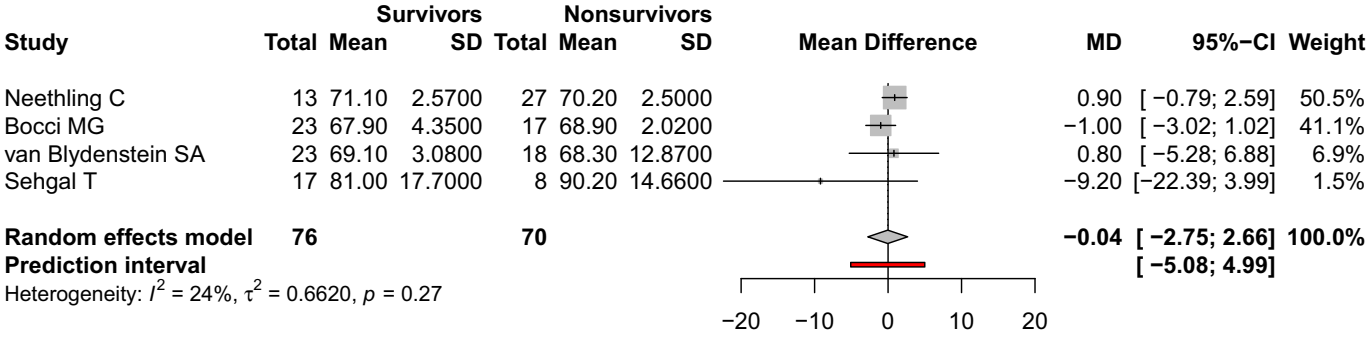

Fig. 9. TEG MA Heparinase.

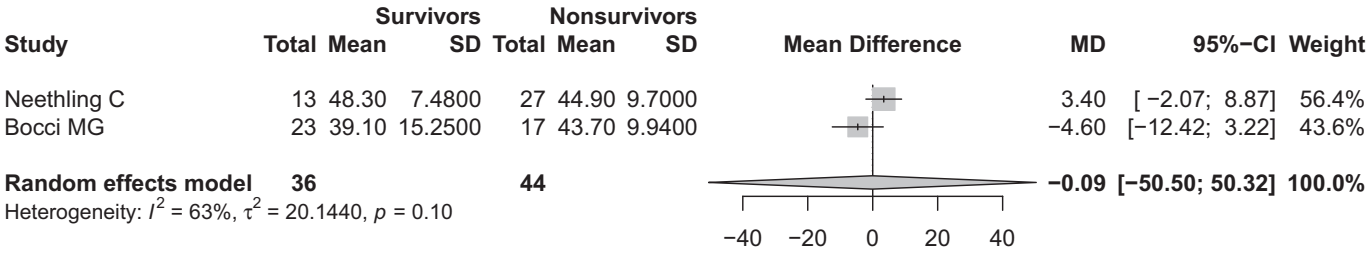

Fig. 10. TEG Fibrinogen.

importance of viscoelastic testing in detecting and characterizing the hypercoagulable state in patients with COVID-19 pneumonia [12,29,32,33]. It bears noting that this hypercoagulability has been explicitly linked to COVID-19-related pneumonia rather than pneumonia from other etiologies [34,35]. Hypercoagulability is also linked to increased thrombotic risk [36,37], which remains high even after initiating an adequate regimen of antithrombotic prophylaxis [4,5,38,39]. Furthermore, alterations of traditional coagulation parameters have been found to correlate with mortality [40]. Therefore, several studies have attempted to ascertain whether VET parameters could accurately predict poor outcomes — particularly mortality — with conflicting results. Bocci et al. [15], evaluated a cohort of 40 consecutive

Table 5
Main findings of TEG parameters included in the descriptive analysis.

Test and parameters	Included studies,[ref]	Survivors[a]	Non-survivors[a]	P-value
Kaolin				
LY30	Bocci MG, 2020 [15]	0 ± 0	0 ± 0	0.18
	Mohan G, 2022 [25]	8.5 ± 11.2	22.5 ± 28.1	0.02
	van Blydenstein SA, 2021 [31]	0.7 ± 1.6	0 ± 0	0.006
Kaolin with heparinase				
LY30	Neethling C, 2021 [12]	0.03 ± 0.1	0.2 ± 0.5	0.70
	Sehgal T, 2022 [30]	1.7 ± 4.5	0	–

[a] Mean ± standard deviation. LY30: lysis at 30 min.

Table 6
Summary and findings of ROTEM parameters between survivors and non-survivors.

Test and parameters	Survivors	Non-survivors	MD	95 % CI	I^2 (%)
INTEM					
CT	247	53	−17.14	−29.23; −5.06	0
CFT	282	64	−2.26	−6.12; 1.59	0
MCF	282	64	−0.53	−6.30; 5.24	80
EXTEM					
CT	265	48	−9.14	−27.14; 8.85	51
CFT	387	105	−1.18	−4.19; 1.83	0
MCF	387	105	0.34	−3.08; 3.76	74
LI60	185	39	−1.00	−1.00; −1.00	0
FIBTEM					
CT	40	19	−2.45	−174.24; 169.35	0
MCF	311	71	−0,69	−5.24; 3.86	40

MD: mean difference; CI: confidence interval. CT: clotting time; CFT: clot formation time; MCF: maximum clot firmness; LI60: lysis index at 60 min.

COVID-19 patients admitted to ICU and found no significant differences in TEG parameters between survivors and non-survivors. Neethling et al. [16] and Sehgal et al. [30] also used a TEG apparatus and found similar results. As regards the ROTEM apparatus, Almskog et al. [17] found that CT in EXTEM, INTEM, and HEPTEM was significantly prolonged in non-survivors than survivors, and MCF in EXTEM and INTEM was considerably higher in non-survivors than survivors. Capone et al. [18] also found a significant prolongation of CT in EXTEM in non-survivors than survivors but could not confirm the other findings. On the contrary, Kamal et al. [24] found no significant differences in ROTEM parameters between survivors and non-survivors. The studies above failed to identify a single parameter or a specific coagulation profile that can predict mortality in patients with COVID-19-related pneumonia. Therefore, we decided to conduct a meta-analysis to ascertain whether considering the results of these studies may yield more conclusive results. Nevertheless, our study could not identify any specific VET profile (i.e., hypercoagulability or hypocoagulability) significantly associated with early mortality in patients with COVID-19 pneumonia. However, we observed a significant association between mortality and prolonging CT-INTEM. We previously reported similar results in patients with sepsis [41]. The explanation for this association is unclear. The prolonged CT-INTEM may be either linked to the use of heparin or constitute the initial expression of a consumptive coagulopathy likely due to an exaggerated systemic inflammatory response.

One plausible explanation for the lack of a significant association between a specific VET profile (i.e., hypercoagulability or hypocoagulability) and mortality may be that VET profiles in patients with COVID-19-related pneumonia can be affected by several factors not uniquely associated with mortality. For example, some papers have associated specific VET profiles with the presence of thrombosis [12,13,42,43]. The anticoagulant treatment administered during hospitalization can also influence VET profiles [16,17,30,31]. In that regard, our results may partially explain why some studies found no greater likelihood of survival after hospital discharge in patients treated with therapeutic anticoagulation vs. usual care thromboprophylaxis [44,45]. Moreover, although mortality in COVID-19 patients has a multifactorial etiology underpinned by massive inflammation and thrombotic changes in the microcirculation stemming from coagulation disorders, several conditions not directly linked to coagulation abnormalities (e.g., age and previous health conditions) may also significantly affect the mortality rate in this population. Hence the absence of a significant correlation between abnormal coagulation parameters and mortality. Likewise, we previously demonstrated that cardiac injury (i.e., elevated high-sensitivity cardiac troponin I) rather than a hypercoagulable VET profile can predict mortality during hospitalization [18]. Furthermore, the significant heterogeneity of the studies considered (e.g., patients' characteristics, apparatus used, test performed, parameters assessed, the test timing, lack of longitudinal evaluation, disease severity, and treatment received) may also explain our findings. Studies considered patients admitted to the ICU, in MW, or both in ICU and MW. Some authors (i.e., Neethling et al. [16] and Heubner et al. [27]) reported a very high mortality rate (68 % and 55 %, respectively). In contrast, other authors (i.e., Almskog et al. [17] and Capone et al. [18]) reported a much lower mortality rate (13 % and 14 %, respectively). The sample size also varied considerably across the studies. Almskog et al. [17] and Calvet et al. [26] enrolled 141 and 133 patients, respectively, vs. 23 and 25 patients for Kamal et al. [24] and Sehgal et al. [30]. Some studies evaluated patients at hospital admission (i.e., Capone et al. [18] and Boscolo et al. [29]). In contrast, other studies evaluated patients at a more advanced stage of the disease (Neethling et al. [16]). There was also a wide heterogeneity across studies regarding the apparatus used and the tests performed/parameters assessed. In particular, only one study used the ClotPro machine (Heubner et al. [27]), thus preventing us from using the results of this study in the quantitative meta-analysis. Similarly, only one study performed the Rapid TEG (Bocci et al. [15]) and was thus excluded from the quantitative meta-analysis. Finally, several parameters measured

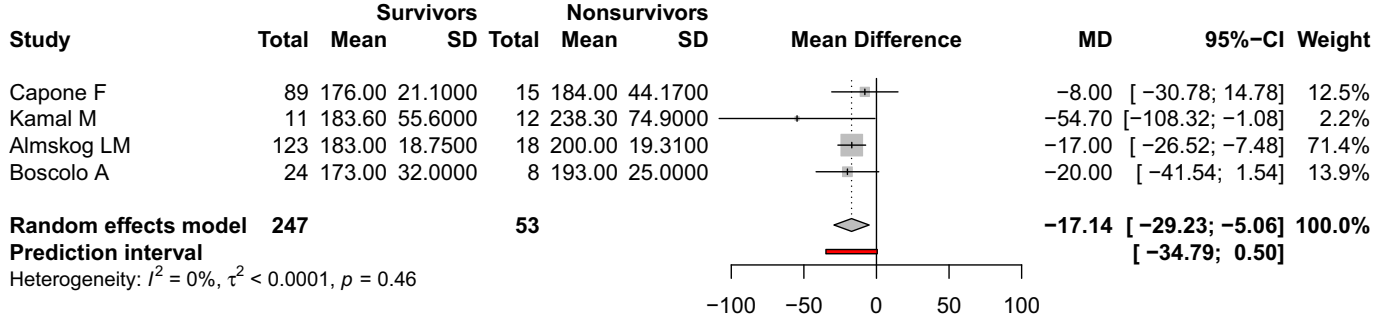

Fig. 11. ROTEM CT INTEM.

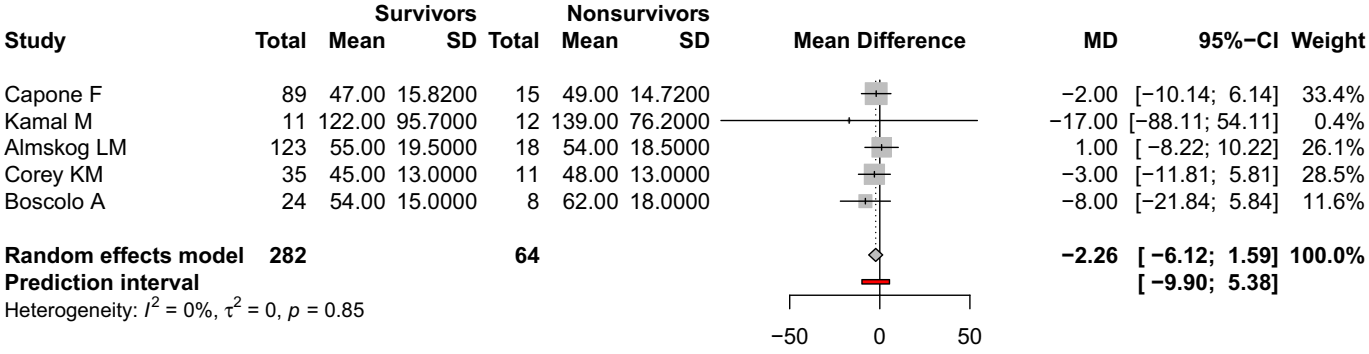

Fig. 12. ROTEM CFT INTEM.

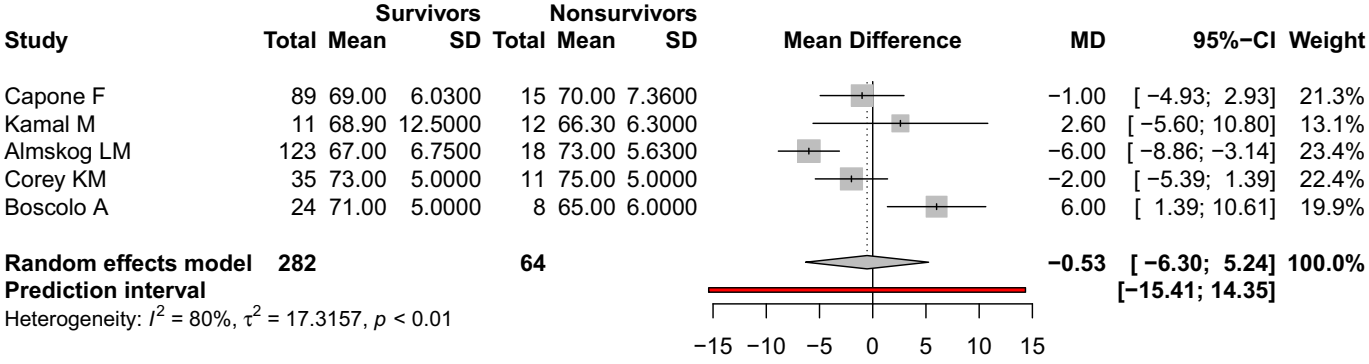

Fig. 13. ROTEM MCF INTEM.

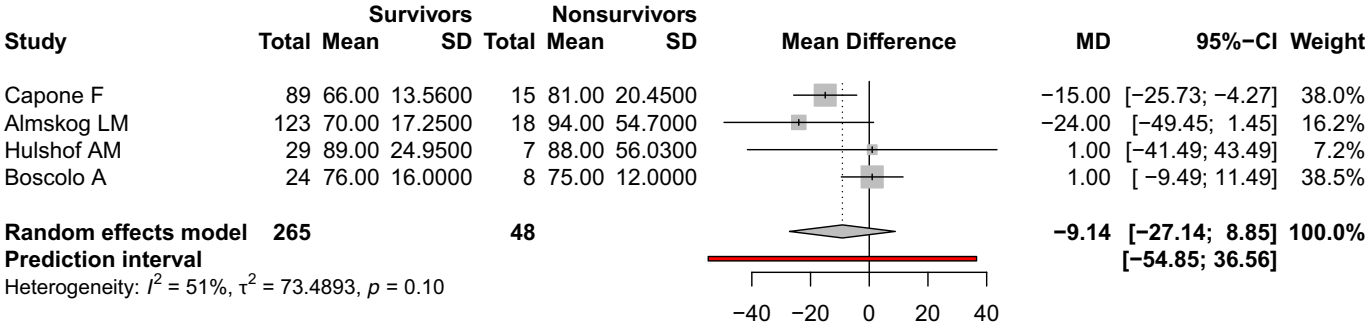

Fig. 14. ROTEM CT EXTEM.

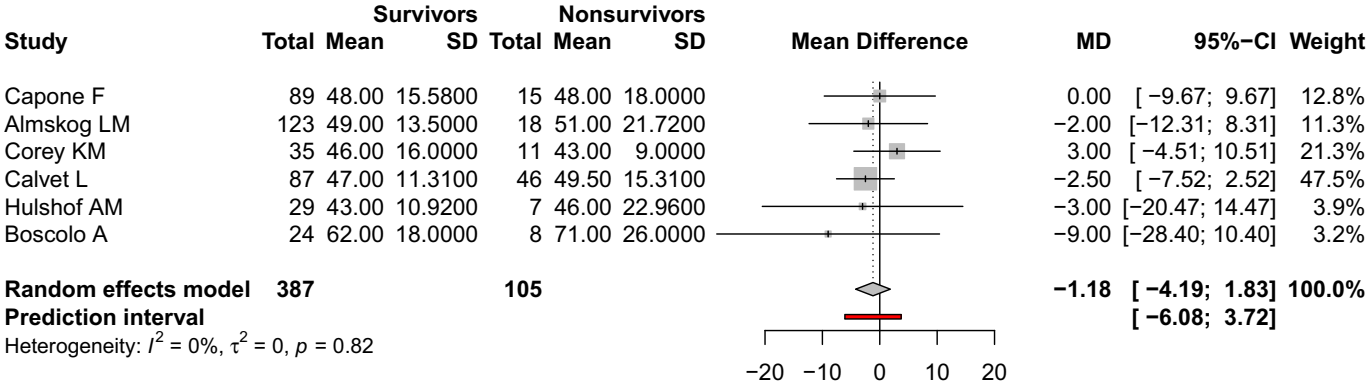

Fig. 15. ROTEM CFT EXTEM.

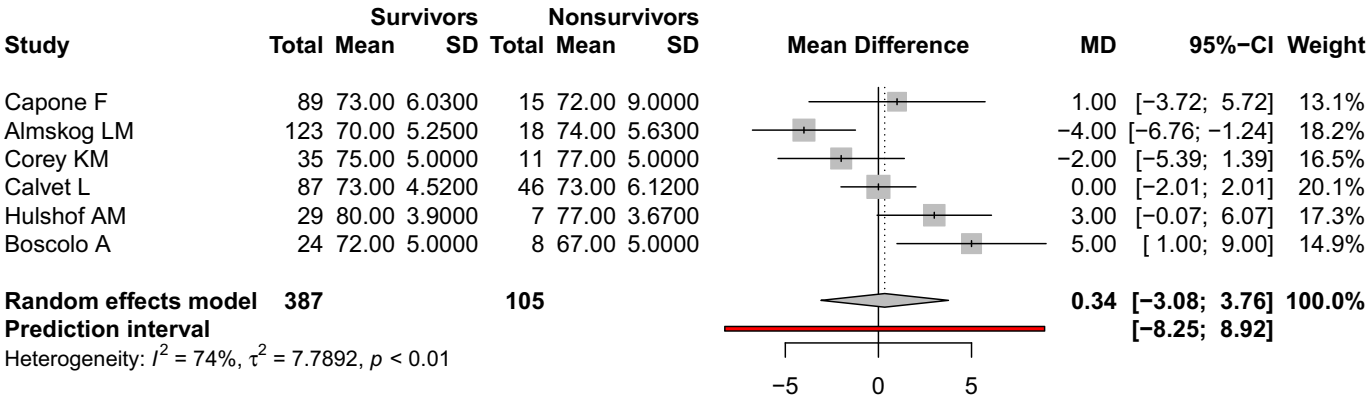

Fig. 16. ROTEM MCF EXTEM.

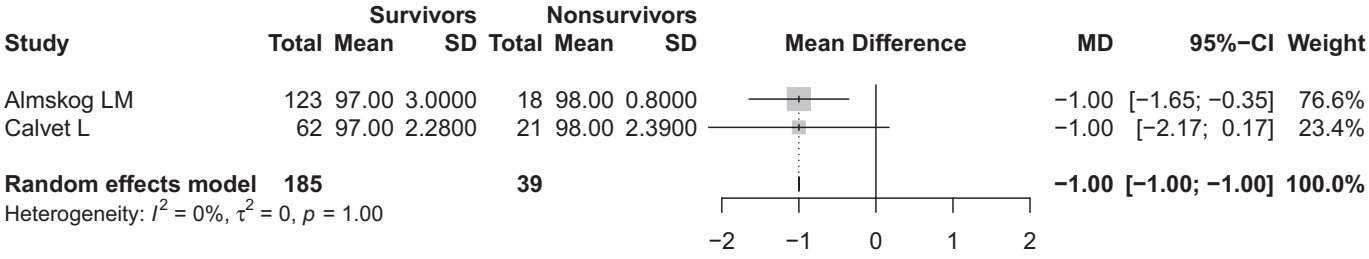

Fig. 17. ROTEM LI60 EXTEM.

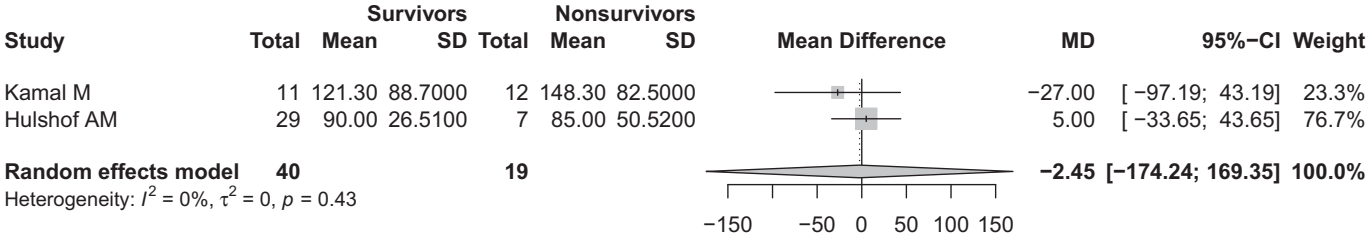

Fig. 18. ROTEM CT FIBTEM.

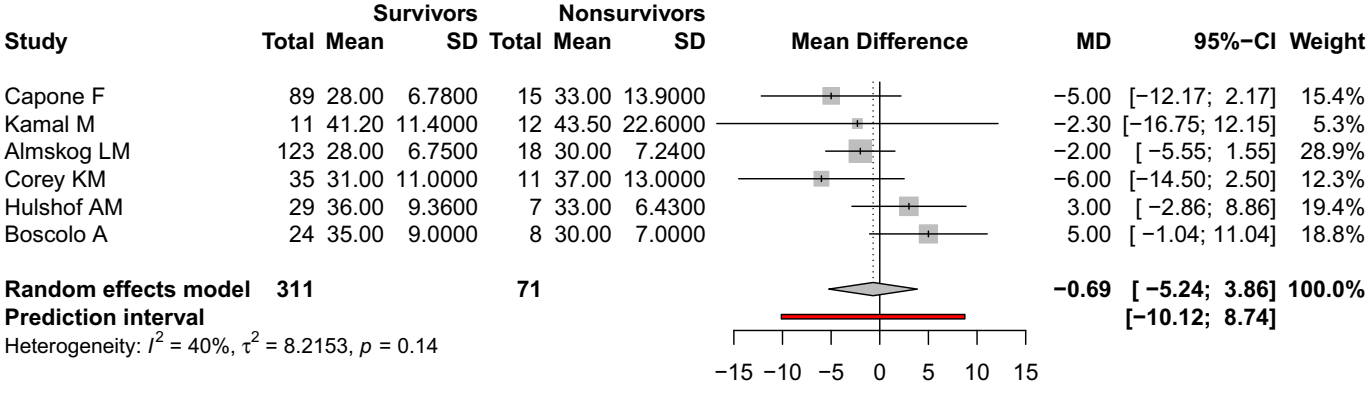

Fig. 19. ROTEM MCF FIBTEM.

with the TEG and ROTEM apparatus (see Tables 5 and 7) could not be analyzed quantitatively because they were reported in individual studies.

Although several literature reviews have previously evaluated the role of VET in patients with COVID-19 infection, the present study introduces some novel elements. Notably, we selected mortality as our endpoint, whereas most reviews published in the literature chose either the hypercoagulable state or the thrombotic disease as the primary outcome. Furthermore, we used a meta-analytic approach in contrast with the descriptive approach favored by other studies published to date. However, we acknowledge the limitations of our study. First, the heterogeneity of the studied sample varies widely according to the

Table 7
Main findings of ROTEM parameters included in the descriptive analysis.

Test and parameters	Included studies,[ref]	Survivors	Non-survivors[a]	P-value
INTEM				
Alpha angle	Corey KM, 2022 [23]	81 ± 3	80 ± 1	–
A5	Kamal M, 2022 [24]	41 ± 20	36 ± 14	0.49
A10	Kamal M, 2022 [24]	57 ± 14	48 ± 18	0.20
LI30	Almskog LM, 2021 [17]	100 ± 0	100 ± 0	–
	Capone F, 2022 [18]	100 ± 0	100 ± 0	–
	Corey KM, 2022 [23]	99 ± 1	100 ± 0.3	–
	Kamal M, 2022 [24]	97 ± 9	100 ± 0	0.30
LI60	Almskog LM, 2021 [17]	97 ± 3	99 ± 0	0.05
	Kamal M, 2022 [24]	100 ± 0.4	99 ± 2	0.37
ML	Capone F, 2022 [18]	0.3 ± 0.8	0.3 ± 0.8	–
EXTEM				
Alpha angle	Corey KM, 2022 [23]	81 ± 3	82 ± 2	–
A5	Calvet L, 2022 [26]	55 ± 5	55 ± 9	0.92
LI30	Almskog LM, 2021 [17]	100 ± 0	100 ± 0	–
	Capone F, 2022 [18]	100 ± 0	100 ± 0	–
	Corey KM, 2022 [23]	100 ± 0.8	100 ± 0.4	–
ML	Capone F, 2022 [18]	0.3 ± 0.8	0.3 ± 0.8	–
HEPTEM				
CT	Almskog LM, 2021 [17]	182 ± 16.5	204 ± 24.23	0.01

[a] Mean ± standard deviation. A5 and A10: clot firmness at 5 and 10 min, respectively; LI30 and LI60: lysis index at 30 and 60 min, respectively; ML: maximum lysis; CT, clotting time.

specific characteristics of each study. The heterogeneity was further highlighted as we included patients hospitalized in intensive care and in medical wards, thus affecting characteristics such as disease severity, treatments received (e.g., prophylactic or therapeutic anticoagulant treatment), etc. We attempted to mitigate the issue by performing sub-analyses, but unfortunately, the overall sample size thwarted our efforts. Finally, considering that COVID-19-associated coagulopathy evolves, a VET profile performed at admission cannot capture changes occurring during hospitalization, which may account for the patient's survival.

In conclusion, our findings did not identify a single parameter or a specific hypercoagulable or hypocoagulable profile that could predict mortality in patients hospitalized with COVID-19 pneumonia.

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CRediT authorship contribution statement

Luca Spiezia: Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization. **Elena Campello:** Writing – review & editing, Validation, Methodology, Data curation. **Paolo Simioni:** Writing – review & editing, Validation, Data curation, Conceptualization. **Mario I. Lumbreras-Marquez:** Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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