Heart & Lung 61 (2023) 72–83

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Comparison of anticoagulation monitoring strategies for adults supported on extracorporeal membrane oxygenation: A systematic review

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ARTICLE INFO

Article History:
Received 1 March 2023
Revised 19 April 2023
Accepted 6 May 2023
Available online 9 May 2023

Keywords:
Extracorporeal membrane oxygenation
Anticoagulation
Monitoring
Antithrombin

ABSTRACT

Background: Anticoagulation is critical in patients supported on extracorporeal membrane oxygenation (ECMO). The appropriate monitoring strategies for heparin remain unclear.
Objectives: This systematic review aimed to compare the accuracy and safety of various monitoring strategies for patients supported on ECMO.
Methods: The PubMed and Web of Science databases were searched for articles in March 2023 without restrictions on publication date. Anticoagulation monitoring strategies for adults supported on ECMO were compared across all included studies. The incidence of bleeding, thrombosis, mortality, blood transfusion, correlation between tests and heparin dose, and the discordance between different tests were discussed in the included studies. The risk of bias was assessed using the Newcastle–Ottawa Scale and Cochrane Collaboration's tool.
Results: Twenty-six studies, including a total of 1,684 patients, met the inclusion criteria. The monitoring of anticoagulation by activated partial thromboplastin time (aPTT) resulted in less blood product transfusion than that by activated clotting time (ACT). Moreover, the monitoring of anticoagulation by anti-factor Xa (Anti-Xa) resulted in a more stable anticoagulation than that by aPTT. Anti-Xa and aPTT correlated with heparin dose better than ACT, and the discordance between different monitoring tests was common. Finally, combined monitoring showed some advantages in reducing mortality and blood product transfusion.
Conclusion: Anti-Xa and aPTT are more suitable for anticoagulation monitoring for patients supported on ECMO than ACT. Thromboelastography and combination strategies are less applied. Most of the studies were retrospective, and their sample sizes were relatively small; thus, more appropriate monitoring strategies and higher quality research are needed.

Introduction

As an advanced life support device to temporarily assist patients' cardiopulmonary function, extracorporeal membrane oxygenation (ECMO) has been widely used and is effective in treating severe cardiopulmonary diseases.[1,2] However, when in contact with an artificial surface, platelets are activated and inflammatory cytokines are simultaneously released, which together lead to a coagulation cascade.[3,4] To avoid the occurrence of thrombotic events, systemic anticoagulation is recommended as one of the necessary preparations for ECMO.[5] However, unreasonable anticoagulation therapy can lead to hemorrhagic complications and increased mortality.[6,7] Therefore, selecting an appropriate anticoagulation strategy to balance coagulation and anticoagulation has become essential for reducing the complications of ECMO.[8,9]

The choice of anticoagulants and monitoring strategies are the two core components of an anticoagulation protocol. Although several studies have reported on the applications of new anticoagulants such as direct thrombin inhibitors (DTIs) to replace heparin, most of

Abbreviations: ACT, activated clotting time; Anti-Xa, anti-factor Xa; AT, antithrombin; aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; CT, clotting time; DTIs, direct thrombin inhibitors; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasm; MA, maximum amplitude; NOS, Newcastle–Ottawa scale; PTT, partial thromboplastin time; RCT, randomized controlled trial; ROTEM, rotational thromboelastometry; R-time, reaction time; r, Pearson's correlation coefficient; rho, Spearman's correlation coefficient; TEG, thromboelastography

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https://doi.org/10.1016/j.hrtlng.2023.05.003
0147-9563/

them are limited by issues such as small sample size and retrospective observational study design.[10–12] Therefore, the efficacy of DTIs needs to be investigated further using a multi-center randomized controlled trial (RCT) with a large sample size. Activated clotting time (ACT), activated partial thromboplastin time (aPTT), and anti-factor Xa (Anti-Xa) are the most commonly used monitoring tests of heparin anticoagulation; however, they often show obvious differences in the demonstration of anticoagulation.[13,14] Compared with the commonly used monitoring tests, thromboelastography (TEG) can provide comprehensive coagulation information such as the clotting time, platelet count and function, and fibrinogen and fibrinolysis state, which can better guide anticoagulation monitoring in theory.[15,16] Moreover, the application of heparinase in TEG can directly measure the efficacy of heparin when the values of ACT, aPTT, and Anti-Xa are discordant.[17,18] The combination of two or more tests has shown some advantages over the use of a single test for monitoring.[19–21]

At present, the optimal monitoring strategy remains controversial. Although there have been systematic reviews and meta-analyses on anticoagulation monitoring,[22,23] they only selected partial tests for research. The present systematic review summarizes all the comparative studies of anticoagulation monitoring strategies. Because of the difference in coagulation function between infants and adults,[24,25] the study aimed to review only the studies conducted on adults. The objective of this study was to discuss the appropriate monitoring strategies of anticoagulation in adults supported on ECMO, to improve their prognosis.

Methods

Search strategy

This systematic review has been completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[26] Articles were searched from the PubMed and Web of Science databases in March 2023. There was no restriction on the year of publication; however, only articles written in English were included. The full search strategy is presented in Additional file 1: Table S1.

Study selection

The titles, abstracts, and full-texts were independently screened by two investigators (JS and YM). Anticoagulation monitoring strategies for adults supported on ECMO were compared in all included studies. RCTs and prospective and retrospective studies were included. Articles were excluded: (1) if they included reviews, case reports, letters, surveys, editorial materials, books, or conference abstracts; (2) if full-texts were not available; (3) if they included animal experiments, pediatric and neonatal patients, non-heparin anticoagulants, or non-ECMO patients; (4) if they compared low and high anticoagulation target or different monitoring equipment; and (5) if they only focused on the first 24 h of ECMO.

Data extraction

The relevant data were independently extracted by two investigators (JS and YM), and any disagreements were resolved following discussion. The extracted information included the name of the first author; year of publication; study design; sample size; age of participants; ECMO mode, indication, and duration; measures and targets of anticoagulation monitoring; and main outcomes of the included studies.

Quality assessment

The Cochrane Collaboration tool was used to assess the quality of the included RCTs, and the Newcastle–Ottawa scale (NOS) was used for non-RCTs. Selection, comparability, and outcome are the three parts of the NOS. The full score of the NOS is 9 points. Studies with scores of 7–9 are classified as high quality; those with scores of 5–6, as medium quality; and those with scores of 0–4, as low quality.

Results

General description

The flow diagram of the study selection process is represented in Fig. 1. Of the 1,202 related articles identified from the databases, 33 were screened for full text, and 26 of these studies with a total of 1,684 patients were finally included in the systematic review.[13,14,17,19–21,27–46] The reasons for exclusion of studies after full text screening are presented in Additional file 1: Table S2. The included studies were one RCT,[17] six prospective cohort studies,[14,19,38,41,43,44] and 19 retrospective cohort studies.[13,20,21,27–37,39,40,42,45,46] Adults were the target population in the included studies, and heparin was used as the anticoagulant. The publication year ranged from 2014 to 2022. The main characteristics and outcomes of the included studies are outlined in Tables 1 and 2, respectively. Among the 26 studies, seven compared the incidence of bleeding, thrombosis, mortality, blood product transfusion, or other outcomes under different single monitoring tests[17,19,20,27–30]; two showed whether there was a difference in the value of tests between the bleeding and non-bleeding groups, or the thrombosis and non-thrombosis groups[44,46]; eight compared the correlation between the monitoring tests and heparin dose[14,28,31–33,36,37,45]; 16 evaluated the discordance between different monitoring tests[13,14,19,28,32,33,36–43,45,46]; and three compared the incidence of bleeding, thrombosis, mortality, blood product transfusion, or other outcomes of single tests with a combination of monitoring tests.[21,34,35] The definitions of bleeding and thrombosis for the included studies are presented in Additional file 1: Table S3.

Quality assessment

The NOS assessment results for the included non-RCT studies are shown in Additional file 1: Table S4. The NOS score ranged from 6 to 8, and no study had low quality. The RCT showed only a low risk of bias.

Comparison of single monitoring tests

ACT Versus aPTT (or PTT)

The comparison of ACT vs. aPTT was conducted in four studies; most of the results showed that aPTT was safer than ACT. Fitousis et al.[27] showed that patients in an aPTT group required less platelet transfusion, and their in-hospital mortality was lower, than that of an ACT group. Mazzeffi et al.[29] also found that patients managed with ACT received approximately 30% more blood product transfusion than that of an aPTT group after adjusting for age and total ECMO days. Liu et al.[28] showed that the times of heparin dose changes per day was significantly fewer in an aPTT group than that of an ACT group. Shah et al.[30] conducted a comparison of ACT, high-partial thromboplastin time (H-PTT, 60–80s) and low-partial thromboplastin time (L-PTT, 45–55s). The results showed that the ACT group required more fresh frozen plasma (FFP) transfusion and the L-PTT group required less red blood cell transfusion.[30]

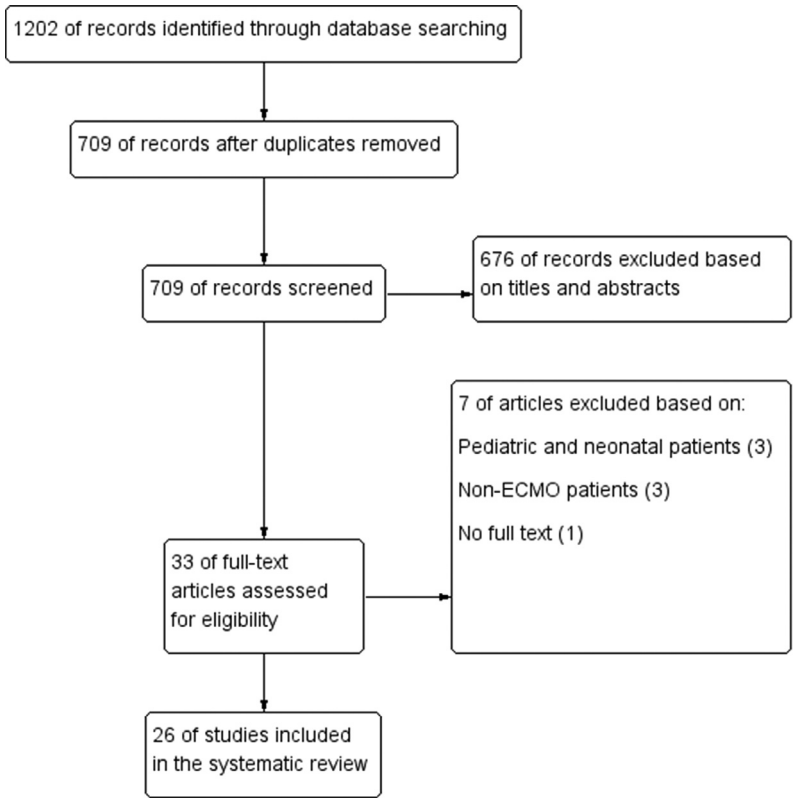

Fig. 1. Flow diagram of the identification process for eligible studies

ACT versus Anti-Xa

The results of the comparison between ACT and Anti-Xa were not significant. A retrospective study showed that anticoagulation based on Anti-Xa was associated with a decreased hazard of major bleeding in patients on temporary mechanical circulatory support; however, the result was not significant in a subgroup of patients on ECMO support.[34]

Anti-Xa versus aPTT

There was a discordance as to which test, Anti-Xa or aPTT, was better. A retrospective study showed that the frequency of the value of aPTT above reference range was significantly higher than that of Anti-Xa.[35] Vo et al.[46] found that half of the hemorrhagic events were associated with high aPTT but not with anti-Xa.

TEG (or ROTEM) versus aPTT

There were few comparative studies related to TEG. A pilot trial of RCT showed that bleeding events at the surgical site were fewer in the TEG group than the aPTT group; however, it requires more frequent adjustments of the heparin dose to maintain the reaction time (R-time) within the target range.[17] Hellmann et al.[44] showed that both rotational thromboelastometry (ROTEM) clotting time (CT) and aPTT were significantly different in groups with different severity of bleeding, and ROTEM could not provide additional information to predict bleeding compared to that by aPTT.

Correlation between monitoring test and heparin dose

Most of studies showed a poor correlation between ACT and heparin dose. The correlation of other tests, such as Anti-Xa and aPTT, with heparin dose varied across studies and conditions. However, none of the tests had a high correlation with heparin dose.

Two studies conducted a significance test. One of the studies showed that the correlation of Anti-Xa with heparin dose was better than that of aPTT.[31] The other study showed that both Anti-Xa and aPTT correlated higher with heparin dose than ACT; the correlation of Anti-Xa with heparin dose was higher in the veno-arterial subgroup and that of aPTT was higher in the veno-venous subgroup.[36]

Significance test was not conducted in other studies and the correlation was often classified as weak, moderate, or strong. Nguyen et al.[33] showed that Anti-Xa and aPTT were moderately correlated with heparin dose in the group without antithrombin (AT) deficiency, and that ACT was poorly correlated with heparin dose. Al-Jazairi et al.[19] showed that both Anti-Xa and aPTT were correlated better with heparin dose than ACT. Atallah et al.[32] showed that there was little to no correlation between ACT and heparin dose, whereas there was a moderate correlation between aPTT and heparin dose. Other studies also showed that aPTT, ACT and ROTEM CT correlated weakly with heparin dose.[28,37] There was no correlation between ACT and heparin dose, whereas there was a weak correlation between Anti-Xa and heparin dose.[14] By calculating the determination coefficient, Scott et al.[45] showed that the proportion of variation in Anti-Xa that could be attributed to the heparin dose was larger than that in aPTT.

Discordance between different monitoring tests

Concordance refers to the values of two tests measured at the same time being simultaneously within, above or below the recommended range. Discordance between different tests was common in the included studies.

Four studies calculated the percentage of concordance to the total sample. The percentage of Anti-Xa and aPTT ranged from 23% to 50.8%,[19,42,45,46] and was 23% for Anti-Xa and ACT.[19] Scott et al.[45] found that the degree of discordance was related to ECMO duration, heparin dose, and the international normalized ratio. Moussa et al.[42] also found that the values of Anti-Xa and aPTT were not associated with the occurrence of serious bleeding and thrombosis.

Table 1
Characteristics of included studies

Study	Comparison	Design	Number of patients	Age (years)	ECMO mode	ECMO indication	ECMO duration	Measures and targets
Fitousis 2017 [27]	aPTT and ACT	Retrospective study	122 61 aPTT, 61 ACT	aPTT: 51±14 ACT: 54±16	VV: 83 (aPTT 46, ACT 37) VA: 39 (aPTT 15, ACT 24)	NA	aPTT: 292±316.3 h ACT: 244±326.1h	aPTT gruop: NA ACT group: 140-180s
Liu 2022 [28]	aPTT and ACT	Retrospective study	36 19 aPTT, 17 ACT	aPTT: 60.42±14.65 ACT: 50.82±17.21	VV: 10 (aPTT 4, ACT 6) VA: 26 (aPTT 15, ACT 11)	NA	aPTT: 7 (3,14) days ACT: 10 (8,15) days	aPTT gruop: 2-3×baseline ACT group: VV 160-180s, VA 180-200s
Mazzeffi 2019 [29]	aPTT and ACT	Retrospective study	121 71 aPTT, 50 ACT	aPTT: 54 (37,64) ACT: 57 (45,64) years	VA	Postcardiotomy shock: 76 (aPTT 47, ACT 29) Other cardiotomy shock: 37 (aPTT 19, ACT 18) Respiratory failure with cardiac dysfunction: 8 (aPTT 5, ACT 3)	aPTT: 6 (4,11) days ACT: 5 (2,8) days	aPTT gruop: 60-80s ACT group: 180-200s
Shah 2022 [30]	aPTT and ACT	Retrospective study	123 70 aPTT (high: 25, low: 45), 53 ACT	aPTT (high): 44 (36,57) aPTT (low): 46 (29,59) ACT: 48 (31,56)	VV	ARDS: 118 Bridge-to-lung transplant: 5	aPTT (high): 8 (5,14) days aPTT (low): 9 (4,20) days ACT: 10 (5,17) days	aPTT gruop: 45-55s (low) or 60-80s (high) ACT group: 160-180s
Kulig 2021 [35]	aPTT and Anti-Xa	Retrospective study	41 29 aPTT, 12 Anti-Xa	aPTT: 57.28±18.43 Anti-Xa: 56.67±14.32	VA: 35 (aPTT 25, Anti-Xa 10) VAV: 6 (aPTT 4, Anti-Xa 2)	NA	aPTT: 95.42±87.07 h Anti-Xa: 74.91±49.38 h	aPTT group: NA Anti-Xa group: NA
Panigada 2018 [17]	aPTT and TEG	RCT	42 21 TEG, 21 aPTT	TEG: 43 (36,53) aPTT: 48 (40,58)	VV	ARDS: 30 (TEG 14, aPTT 16) Bridge to lung transplant: 11 (TEG 6, aPTT 5) Status asthmaticus: 1 (TEG 1, aPTT 0)	TEG: 9 (7,16) days aPTT: 11 (4,17) days	TEG: R-time 16–24 min (normal values: 4–8 min) aPTT: 1.5–2×baseline
Feih 2022 [34]	ACT and Anti-Xa	Retrospective study	74 45 ACT, 29 Anti-Xa	ACT: 56 (42,65) Anti-Xa: 52 (35,60)	NA	Respiratory failure: 38 (ACT 23, Anti-Xa 15) Acute cardiogenic shock: 24 (ACT 15, Anti-Xa 9) Failure to wean from CPB: 13 (ACT 6, Anti-Xa 7)	ACT: 99.0 (51.0,169.3) h Anti-Xa: 133.0 (87.0,260.2) h	ACT: 160-220s Anti-Xa: low-intensity (0.21-0.35IU/mL) or moderate (0.3-0.7IU/mL)
Arnouk 2020 [31]	aPTT and Anti-Xa	Retrospective study	34	56 (38,65)	VV: 13, VA: 18, VAV:3	ARDS: 10 Hypoxemic respiratory failure: 3 Cardiogenic shock: 21	3.9 (2.0,8.5) days	anti-Xa of 0.3–0.7IU/mL
Atallah 2014 [32]	aPTT and ACT	Retrospective study	46	56±15	NA	Cardiac: 21 Respiratory: 21 Both: 4	11±14.6 days	ACT of 140-180s
Delmas 2020 [14]	ACT and Anti-Xa	Prospective study	109	54 (41.8-60)	VV: 32, VA: 77	Cardiac arrests: 32 Cardiac shock: 40 ARDS: 28 Drug intoxications: 5 Lung transplantations: 2 Refractory bronchospasm: 2	5 (3-11) days	ACT of 180–220s
Hohlfelder 2022 [36]	aPTT, ACT and Anti-Xa	Retrospective study	48	48 (24-68)	VV: 22, VA: 26	Cardiac shock: 23 Respiratory failure: 20	7 (2-84) days	Initial: aPTT of 60-90s, ACT of 180–220s or Anti-Xa of 0.3–0.8IU/

(*continued on next page*)

Table 1 (*Continued*)

Study	Comparison	Design	Number of patients	Age (years)	ECMO mode	ECMO indication	ECMO duration	Measures and targets
						Post-solid organ transplant: 5		mL Later: aPTT of 60-80s, ACT of 180−220s or Anti-Xa of 0.3−0.7IU/mL
Nguyen 2021 [33]	aPTT, ACT and Anti-Xa	Retrospective study	37	40 (32,50)	VV: 13, VA: 23, VAV: 1	Acute myocarditis: 20 ARDS: 13 Myocardial infarction: 3 Severe anaphylaxis: 1	NA	aPTT of 45-80s (reference range 25.1−36.5s), ACT of 180−220s or Anti-Xa of 0.3−0.7IU/mL
Prakash 2016 [37]	aPTT, ACT and ROTEM	Retrospective study	20	44(27,62)	VV: 6, VA: 14	Cardiac shock: 4 ARDS: 5 perioperative valvular heart surgery: 4 Other: 7	5.1 (2.9, 13) days	aPTT: 40-60s, 50-80s or 60-90s
Al-Jazairi 2021 [19]	ACT and combining test (ACT +Anti-Xa)	Prospective study	40 20 ACT, 20 combining	combining: 42.9±12.9 ACT: 45.6±16.5	VV: 11 (combining 7, ACT 4) VA: 29 (combining 13, ACT 16)	Cardiac arrest refractory to CPR: 8 (combining 2, ACT 6) Failure to wean from CPB: 12 (combining 6, ACT 6) Bridging for transplant: 4 (combining 3, ACT 1) Acute respiratory failure: 5 (combining 3, ACT 2) Others: 11 (combining 6, ACT 5)	combining: 7 (4,19) days ACT: 15 (7,28) days	high-intensity: Anti-Xa of 0.3-0.7 IU/mL, ACT of 180-220s low-intensity: Anti-Xa of 0.2-0.4 IU/mL, ACT of 160-180s
Colman 2019 [20]	aPTT and combining test (aPTT +TEG)	Retrospective study	123 72 aPTT, 51 combining	aPTT: 56±15 combining: 60±12	VV: 21 (combining 8, aPTT 13) VA: 102 (combining 43, aPTT 59)	NA	aPTT: 6±6 days combining: 6±6 days	aPTT: 60-80s (1.5-2×baseline) combining: TEG R-time of 2-4×baseline, aPTT of 60-80s (1.5-2×baseline) and anti-Xa of 0.3−0.7IU/mL
Northam 2021 [21]	ACT and combining test (aPTT +Anti-Xa)	Retrospective study	100 26 ACT, 74 combining	ACT: 40.0 (30.0,50.8) combining: 45.0 (31.5,55.8)	VV: 99 (combining 73, ACT 26) VA: 1 (combining 1, ACT 0)	ARDS (bacteria): 31 (combining 21, ACT 10) ARDS (virus): 14 (combining 11, ACT 3) ARDS (other): 43 (combining 33, ACT 10) Inhalation injury: 12 (combining 9, ACT 3)	ACT: 5.0 (3.0,9.5) days combining: 5.0 (3.0,7.0) days	ACT: 180-200s combining: heparin correlation (aPTT) of 0.3-0.5 or Anti-Xa of 0.3-0.5IU/mL
Cunningham 2016 [13]	ACT and aPTT	Retrospective study	15	48.5±14.1	NA	NA	NA	NA
Giani 2021 [38]	ACT, aPTT, TEG and ROTEM	Prospective study	25	60 (50,65)	VV: 11 VA: 14	ARDS: 11 ECPR: 10 Cardiogenic shock: 3 Pulmonary embolism: 1	NA	aPTT: 1.5×baseline
Panigada 2016 [39]	ACT, aPTT, Anti-Xa and TEG	Retrospective study	12	69 (31,84)	VV	COPD: 8 ARDS: 4	8 (4,20) days	aPTT: 1.5-2×baseline
Nair 2015 [41]	aPTT and ROTEM	Prospective study	10	41 (38,52)	VV: 3 VA: 7	graft dysfunction: 5 (lung 2, heart 3)	10 (5,14) days	aPTT: 1.5-2×baseline

(*continued on next page*)

Table 1 (*Continued*)

Study	Comparison	Design	Number of patients	Age (years)	ECMO mode	ECMO indication	ECMO duration	Measures and targets
Moussa 2021 [42]	aPTT and Anti-Xa	Retrospective study	265	55±14	VA	ARDS: 1 Cardiogenic shock 2 Postcardiotomy: 2 Postoperative low cardiac output syndrome: 90 Primary graft dysfunction: 15 Myocardial infarction: 76 Acute on chronic heart disease: 40 Pulmonary embolism: 9 Myocarditis: 16 Poisoning: 7 Others: 12	7 (3,11) days	Anti-Xa of 0.2-0.4 IU/mL or 0.4-0.7 IU/mL
Panigada 2016 [40]	ACT, aPTT and TEG	Retrospective study	32	NA	VV	ARDS: 16 Bridging for transplant: 8 COPD: 8	8 (6,9) days	aPTT: 1.5-2×baseline
Yie 2016 [43]	ACT and aPTT	Prospective study	60	69.5±9.6	VA	Ischemic heart disease: 30 Massive pulmonary embolism: 6 Malignant arrhythmia: 8 Myocarditis: 6 Unknown: 10	83.4±25.9 hours	ACT: 170-210s
Hellmann 2018 [44]	aPTT and ROTEM	Prospective study	57	56 (19.5)	VV	NA	9 (7.25) days	aPTT:≤40s
Scott 2022 [45]	aPTT and Anti-Xa	Retrospective study	65	49.6±14.4	VV: 17 VA: 48	Postcardiotomy/cardiogenic shock: 28 ARDS: 24 ECPR: 13	82.9 (53.8, 130.2) hours	Anti-Xa of 0.3-0.5 IU/mL or 0.5-0.7 IU/mL
Vo 2022 [46]	aPTT and Anti-Xa	Retrospective study	27	53 (23-79)	VV: 20 VA: 7	COVID-19−related pneumonia: 20 Cardiovascular conditions: 7	10.5 (3-50) days	Anti-Xa of 0.3-0.7 IU/mL

*NA, not available; ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; aPTT, activated partial thromboplastin time; TEG, thromboelastography; ROTEM, rotational thromboelastometry; VA, veno-arterial; VV, veno-venous; VAV, from VA (VV) to VV (VA); RCT: randomized controlled trial; ARDS, acute respiratory distress syndrome; ECPR, extracorporeal cardiopulmonary resuscitation; COPD, chronic obstructive pulmonary disease; Continuous data was shown in mean±SD, median (min-max) or median (interquartile range); SD, standard deviation.

Table 2
Main outcomes of included studies

Study	Correlation/Concordance	Bleeding	Thrombosis	Mortality	Blood product transfusion
Fitousis 2017 [27]	NA	All: aPTT VS ACT = 80% VS 69%, p=0.145 Major: aPTT VS ACT = 15% VS 21%, p=0.346 Minor: aPTT VS ACT = 79% VS 59%, p=0.019	aPTT VS ACT = 39% VS 41%, p=0.853	In-hospital: aPTT VS ACT = 48% VS 82%, p<0.001	RBC: aPTT VS ACT =14.7±15.7 ml/hour VS 18.6± 31.8 ml/hour, p=0.39 PLT: aPTT VS ACT =2.3±3.5 ml/hour VS 5.7± 8.4 ml/hour, p=0.004 FFP: aPTT VS ACT =1.84±4.9 ml/hour VS 10.1± 34.5 ml/hour, p=0.066
Liu 2022 [28]	aPTT and heparin dose: rho=0.407 ACT and heparin dose: rho=0.165 aPTT and ACT: rho=0.518	aPTT VS ACT = 26.3% VS 52.9%, p=0.196	aPTT VS ACT = 15.8% VS 17.6%, p=1.0	In-hospital: aPTT VS ACT = 26.3% VS 23.5%, p=0.577	RBC: aPTT VS ACT =4.0 (1.5,16) U VS 10 (4.0,18.5) U, p=0.297 FFP: aPTT VS ACT =1000 (0,2560) ml VS 2040 (1140,4890) ml, p=0.113
Mazzeffi 2019 [29]	NA	aPTT VS ACT = 67.6% VS 78.0%, p=0.21	aPTT VS ACT = 19.7% VS 16.0%, p=0.60	In-hospital: aPTT VS ACT = 50.7% VS 64.0%, p=0.15	RBC: aPTT VS ACT =13 (16,28) U VS 23 (9,33) U, p=0.14 PLT: aPTT VS ACT =3 (0,7) U VS 5 (1,9) U, p=0.20 FFP: aPTT VS ACT =5 (0,12) U VS 8 (1,16) U, p=0.22
Shah 2022 [30]	NA	aPTT (high) VS aPTT (low) VS ACT = 88% VS 87% VS 91%, p=0.83	aPTT (high) VS aPTT (low) VS ACT = 12% VS 11% VS 11%, p=1	ECMO: aPTT (high) VS aPTT (low) VS ACT = 28% VS 22% VS 43%, p=0.08 In-hospital: aPTT (high) VS aPTT (low) VS ACT = 28% VS 24% VS 49%, p=0.06	RBC: aPTT (high) VS aPTT (low) VS ACT = 1.3 (0.6,1.9) U/day VS 0.9 (0.5,1.7) U/day VS 2.1 (1.2,2.9) U/day, p<0.001 PLT: aPTT (high) VS aPTT (low) VS ACT = 0.1 (0,0.4) U/day VS 0 (0,0.4) U/day VS 0.1 (0,0.3) U/day, p=0.99 FFP: aPTT (high) VS aPTT (low) VS ACT = 0 (0,0.2) U/day VS 0 (0,0.4) U/day VS 0.3 (0,0.9) U/day, p=0.006
Kulig 2021 [35]	NA	NA	aPTT VS Anti-Xa = 20.6% VS 0%, p is NA	In-hospital: aPTT VS Anti-Xa = 75.66% VS 66.67%, p=0.7	RBC: aPTT VS Anti-Xa = 0.45 U/hour VS 0.11 U/hour, p is NA PLT: aPTT VS Anti-Xa = 0.12 U/hour VS 0.07 U/ hour, p is NA Cryoprecipitate: aPTT VS Anti-Xa = 0.03 U/hour VS 0.001 U/hour, p is NA
Panigada 2018 [17]	NA	TEG VS aPTT = 47.6% VS 71.4%, p=0.21	TEG VS aPTT = 19.0% VS 19.0%, p=1.0	ICU: TEG VS aPTT = 19% VS 29%, p=0.72 In-hospital: TEG VS aPTT = 19% VS 29%, p=0.72	RBC: TEG VS aPTT = 198 (37,330) ml/day/patient VS 203 (155,247) ml/day/patient, p=0.74 PLT: TEG VS aPTT = 0 (0,61) ml/day/patient VS 0 (0,0) ml/day/patient, p=0.28 FFP: TEG VS aPTT =0 (0,79) ml/day/patient VS 0 (0,0) ml/day/patient, p=0.54
Feih 2022 [34]	NA	Major: ACT VS Anti-Xa = 55.6% VS 37.9%, p is NA Minor: ACT VS Anti-Xa = 44.4% VS 62.1%, p is NA	NA	ICU: ACT VS Anti-Xa = 62.2% VS 62.1%, p >0.99 In-hospital: ACT VS Anti-Xa = 64.4% VS 62.1%, p>0.99	NA
Arnouk 2020 [31]	aPTT and heparin dose: r=0.106 Anti-Xa and heparin dose: r=0.414	26.5%	14.7%	ECMO: 20.6% In-hospital: 52.9%	NA
Atallah 2014 [32]	aPTT and heparin dose: r=0.55 ACT and heparin dose: r=0.14 aPTT and ACT: r=0.41	NA	NA	In-hospital: 87%	NA
Delmas 2020 [14]	ACT and heparin dose: no Anti-Xa and heparin dose: weak ACT and Anti-Xa: rho<0.4, κ<0.2	NA	NA	NA	NA
Hohlfelder 2022 [36]	aPTT and heparin dose: r=0.405 ACT and heparin dose: r=0.171 Anti-Xa and heparin dose: r=0.353 aPTT and Anti-Xa: r=0.633 ACT and Anti-Xa: r=0.244 aPTT and ACT: r=0.491	38%	29%	In-hospital: 54%	NA
Nguyen 2021 [33]	aPTT and heparin dose: rho=0.14 ACT and heparin dose: rho=-0.03 Anti-Xa and heparin dose: rho=0.39	NA	NA	NA	NA

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Table 2 (*Continued*)

Study	Correlation/Concordance	Bleeding	Thrombosis	Mortality	Blood product transfusion
	aPTT and Anti-Xa: rho=0.72 ACT and Anti-Xa: rho=0.33				
Prakash 2016 [37]	aPTT and heparin dose: rho=0.322 ACT and heparin dose: rho=0.228 ROTEM CT and heparin dose: rho=0.364 aPTT and INTEM CT: rho=0.310 ACT and INTEM CT: rho=0.395 aPTT and ACT: rho=0.40	NA	NA	35%	NA
Al-Jazairi 2021 [19]	Strong correlation with heparin dose: aPTT 50%, ACT 10%, Anti-Xa 55% Concordance of Anti-Xa and ACT: 26% Concordance of Anti-Xa and aPTT: 23%	All: ACT VS combining = 85% VS 50%, p is NA Mild: ACT VS combining = 20% VS 30%, p is NA Moderate: ACT VS combining = 60% VS 0%, p is NA Severe: ACT VS combining = 5% VS 20%, p is NA	ACT VS combining = 20% VS 50%, p is NA	NA	NA
Colman 2019 [20]	NA	Major: aPTT VS combining = 69.4% VS 66.7%, p=0.85 Minor: aPTT VS combining = 8.3% VS 9.8%, p=0.78	aPTT VS combining = 20.8% VS 27.5%, p=0.39	ECMO: aPTT VS combining = 56.9% VS 33.3%, p=0.01 In-hospital: aPTT VS combining = 72.2% VS 56.9%, p=0.07	NA
Northam 2021 [21]	NA	Major: ACT VS combining = 69.2% VS 62.2%, p=0.345 Minor: ACT VS combining = 57.7% VS 60.8%, p=0.819	Major: ACT VS combining = 23% VS 14.9%, p=0.369 Minor: ACT VS combining = 80.8% VS 66.2%, p=0.216	In-hospital: ACT VS combining = 50.0% VS 43.2%, p=0.551	RBC: ACT VS combining = 100% VS 95.9%, p=0.566 PLT: ACT VS combining = 61.5% VS 55.4%, p=0.650 FFP: ACT VS combining = 23.1% VS 31.1%, p=0.616 Cryoprecipitate: ACT VS combining = 7.7% VS 8.1%, p=1.000 AT III: ACT VS combining = 61.5% VS 35.1%, p=0.023
Cunningham 2016 [13]	ACT and aPTT: r=0.55	NA	NA	NA	NA
Giani 2021 [38]	ROTEM CT and aPTT: rho^2=0.34 ROTEM CT and ACT: rho^2=0.296 TEG R-time and aPTT: rho^2=0.08 TEG R-time and ACT: rho^2=0.002 ROTEM CT and TEG R-time: rho^2=0.01	NA	NA	NA	NA
Panigada 2016 [39]	aPTT and Anti-Xa: rho=0.55 ACT and Anti-Xa: rho=-0.128 TEG R-time and Anti-Xa: rho=0.59 TEF R-time and aPTT: rho=0.45	Major: 25%	0%	ECMO: 33.3% ICU: 58.3%	RBC: 100% PLT and/or FFP: 41.7% AT: 50%
Nair 2015 [41]	ROTEM CT and aPTT: r=0.73	50%	NA	ICU: 40% In-hospital: 40%	50%
Moussa 2021 [42]	Concordance of aPTT and Anti-Xa: 50.7%	Serious: 56.6%	32.8%	28-day: 43% ICU: 47.5% In-hospital: 51.3%	RBC: 10 (5,18) U PLT: 3 (2,6) U FFP: 7 (3,11) U

(*continued on next page*)

Table 2 (*Continued*)

Study	Correlation/Concordance	Bleeding	Thrombosis	Mortality	Blood product transfusion
Panigada 2016 [40]	TEG R-time and aPTT: rho=0.36, κ=0.1 TEG R-time and ACT: rho=0.31, κ=0.03 ACT and aPTT: rho=0.30, κ=0.01 TEG R-time and heparin dose: rho=0.22 aPTT and heparin dose: rho=0.165 ACT and heparin dose: rho=0.12	Major: 22%	3.1%	ICU: 38%	RBC: 0.63 (0.33,1.1) U/day PLT: 34% FFP: 44%
Yie 2016 [43]	ACT and aPTT: r=0.450	33.3%	10%	In-hospital: 80%	NA
Hellmann 2018 [44]	NA	Minor: 39% Evident: 36%	NA	ECMO: 30% ICU: 56%	NA
Scott 2022 [45]	aPTT and heparin dose: r^2=0.025 Anti-Xa and heparin dose: r^2=0.298 aPTT and Anti-Xa: r^2=0.315 Concordance of aPTT and Anti-Xa: 50.8%	NA	NA	NA	NA
Vo 2022 [46]	aPTT and Anti-Xa: rho = 0.40 Concordance of aPTT and Anti-Xa: 48%	44.4%	7.4%	22%	NA

*NA, not available; r, Pearson's correlation coefficient; rho, Spearman's correlation coefficient; r^2 and rho^2, determination coefficient; κ, Cohen's coefficient (Kappa statistic); ACT, activated clotting time; aPTT, activated partial thromboplastin time; TEG, thromboelastography; ROTEM CT, rotational thromboelastometry clotting time; RBC, red blood cell; PLT, platelet; FFP, frozen fresh plasm; AT III, antithrombin III; Concordance, two tests measured at the same time were within, above or below the recommended range simultaneously; Continuous data was shown in mean±SD or median (interquartile range); SD, standard deviation.

Two studies used the Cohen's κ coefficient (Kappa statistic) to analyze concordance. Delmas et al.[14] found that the coefficient of ACT and Anti-Xa was less than 0.2. Panigada et al.[40] found that the coefficients of ACT, aPTT and TEG R-time were no more than 0.1.

Most of studies used Pearson's correlation coefficient (r), Spearman's correlation coefficient (rho), or determination coefficient (r^2 or rho^2) to discuss discordance. The correlation coefficients of ACT, aPTT, Anti-Xa, TEG R-time, and ROTEM CT were analyzed in 12 studies and the results varied widely between the studies.[13,14,28,32,33,36,37,39–41,43,46] However, most of the coefficients were less than 0.6, indicating a weak or moderate correlation between the different monitoring tests. Cunningham et al.[13] found that platelet count and urea were associated with the correlation between ACT and aPTT. Giani et al.[38] and Scott et al.[45] used the determination coefficient to elucidate that only a small proportion of variation in one monitoring test could be attributed to the other monitoring test.

Combined monitoring

Three studies showed some advantages of combined monitoring by comparing it with single monitoring. Ai-Jazairi et al.[19] adapted a multifaceted anticoagulation protocol using Anti-Xa and ACT, which might provide a better prediction of heparin dose by Anti-Xa compared to that by ACT because Anti-Xa had a better correlation with heparin dose. One of the studies demonstrated that mortality during ECMO and retroperitoneal bleeding were significantly reduced in a combination monitoring (TEG + aPTT) group compared with an aPTT group.[20] Northam et al.[21] reported that a multimodal monitoring protocol (Anti-Xa + aPTT) reduced AT administration compared with ACT.

Discussion

The results of the systematic review showed that monitoring of anticoagulation by aPTT resulted in less blood product transfusion than that by ACT. Monitoring of anticoagulation by Anti-Xa resulted in a more stable anticoagulation than that by aPTT. Anti-Xa and aPTT correlated with heparin dose better than ACT, and Anti-Xa was a better test for adjusting heparin dose. The discordance between different monitoring tests was common. Combined monitoring showed some advantages in reducing mortality and blood product transfusion over single monitoring.

ACT measures the time of fibrin clotting in whole blood; it is fast and can be measured at the bedside, whereas aPTT is a plasma-based test that is used to measure the time from factor XII activation to fibrin formation.[5,14] Both ACT and aPTT are commonly used for anticoagulation monitoring in ECMO, and the choice between ACT or aPTT is controversial.[27–29] The origin of anticoagulation monitoring based on ACT was from cardiopulmonary bypass (CPB).[47] The dose of heparin in CPB is large and the recommended range of ACT should be within 400–480 s, which is much higher than the recommended range of ECMO.[48] However, ACT is less sensitive to the low dose of heparin.[49] The values of ACT in patients supported on ECMO were not significantly different when the values of aPTT were within the therapeutic and supratherapeutic ranges.[32] Therefore, it can be inferred that ACT is not appropriate for anticoagulation monitoring for patients supported on ECMO.

Different from ACT, aPTT, or other monitoring tests that reflect the time of clotting, Anti-Xa indirectly reflects the heparin-antithrombin concentration in blood samples by the addition of excessive Xa to reflect the effective concentration of heparin.[50,51] Therefore, in theory, Anti-Xa has a good correlation with heparin dose; however, this correlation was not high in most of the relevant studies. The activity of AT may be one of the factors influencing the correlation.[52] Even if the dose of heparin is large enough, the anticoagulant effect is still

poor when the AT is insufficient, and the formation of thrombus is unavoidable. This is referred to as a type of heparin resistance (persistently subtherapeutic levels of heparin activity, despite high doses of heparin).[53] Arnouk et al.[31] demonstrated that the correlation coefficient between Anti-Xa and heparin dose significantly increased after excluding patients with heparin resistance; thus, the correlation increased from moderate to strong. However, the correlation coefficient of aPTT increased to a lesser extent; hence, the correlation remained very weak.[31] Therefore, if the real effect of heparin on anticoagulation alone is assessed, Anti-Xa may be a better method when AT is maintained within the normal range.

Nevertheless, the complex mechanism of coagulation in the body cannot be completely reflected simply by monitoring the effective concentration of heparin. Moreover, Anti-Xa can also be affected by various factors like hyperbilirubinemia and hypertriglyceridemia.[51] In addition, Anti-Xa monitoring focuses exclusively on the Anti-Xa mechanism of heparin, and ignores other effects of heparin such as thrombin and other coagulation factor inhibitions.[54] Therefore, the coagulation state in the body cannot be reflected completely. Other monitoring methods that provide additional information or can achieve complementary effects with Anti-Xa, are still needed.

TEG is one of the methods that reflects the whole clotting system including coagulation and fibrinolysis through R-time, kinetics time, α-angle, maximum amplitude (MA), and lysis index 30 min after MA.[5] The flat-line of TEG refers to a phenomenon indicating no formation of fibrin clotting for a prolonged time due to the high heparin concentration; and the frequency of the flat-line is very high when aPTT is maintained at 1.5–2×baseline.[18,40] Therefore, it can be inferred that if aPTT is used as the single target for anticoagulation, heparin overdose will frequently occur. Panigada et al.[17] concluded that there was no difference in the incidence of complications between the TEG R-time and aPTT groups; however, the heparin dose in the TEG group was lower and the bleeding events at the surgical site were lesser. In addition, Giani et al.[38] found no significant correlation between the CT of ROTEM and the R-time of TEG. Therefore, the viscoelastic hemostatic assay of which of the two methods is more appropriate for ECMO anticoagulation is still unclear.

It is noteworthy that although TEG can provide more coagulation information, the current comparative studies of anticoagulation monitoring in ECMO using TEG are limited to the use of R-time as the reference target,[17,20] and this cannot reflect the platelet, fibrinogen, and fibrinolysis states. Moreover, studies on TEG with heparinase in ECMO are also rare. TEG with and without heparinase can be used to detect the residual heparin activity after protamine neutralization in CPB, whereas ACT and Anti-X are less sensitive to low concentrations of heparin.[55,56] A study on pediatric patients supported on ECMO showed that the exclusion of heparin by heparinase could further help in the diagnosis of patients with covert coagulopathy.[57] However, further research is needed to confirm whether the adults supported on ECMO with heparin anticoagulation can benefit from TEG with heparinase.

Discordance and poor correlation among different tests are the reasons why it is difficult to choose an appropriate anticoagulation strategy.[13,14] In addition to the discordance between different tests, anticoagulation monitoring using a single test was confirmed not to be accurate or safe enough in many studies; however, a combination of monitoring tests was not widely applied.

Due to the discordance among several tests, it is difficult to simultaneously control the values of two or more tests within the normal range. Most of studies chose one of different tests as the anticoagulation target under different circumstances, and the strategies had shown some advantages.[20,21] Although Northam et al.[21] found the need for AT supplement was also reduced, it is related to the change in the indication of AT infusion from “AT less than 60%” to “AT less than 60% and heparin resistance.”[21] In general, the combination strategies differ, and the detailed reason for each combination strategy is also unclear. However, anticoagulation guidelines for ECMO indicate combination monitoring for adjusting the heparin dose according to the value of Anti-Xa and adjusting FFP infusion according to the value of aPTT when the two tests are discordant.[5] Anti-Xa is a test that reflects the effective concentration of heparin,[50,51] whereas aPTT is a test that reflects intrinsic and common pathways that can show the deficiency of coagulation factors.[58] Therefore, a combination of these two tests produces a complementary effect; however, the actual effect needs to be confirmed by further research.

The anticoagulation effect of heparin is achieved by enhancing the activity of AT; therefore, it is also important to monitor the activity of AT during the anticoagulation management of heparin. However, there is no consensus about AT infusion in patients supported on ECMO. Although AT supplementation showed no benefit when AT activity was not low, it reduced the dose of heparin when the activity was less than 60%–70%.[59,60] The results of one study indicated an association between AT supplementation and thrombosis; however, it should be considered in relation to the baseline AT level of the patients, because the risk of thrombosis is higher in patients with a lower level of AT.[20] As for when to initiate AT infusion, Iapichino et al.[60] demonstrated that the reduction of AT does not necessarily alter the anticoagulation effect; however, to determine whether to initiate AT supplementation or not should be based on the signs of inflammation and hypercoagulability such as the levels of C-reactive protein and fibrinogen. Furthermore, the presence of heparin resistance when AT activity is not low may be associated with elevated heparinase activity, which is increased during inflammation.[54,61] Therefore, routine AT supplementation is not recommended, and the influence of inflammation should also be considered.

From the existing studies, it can be inferred that both aPTT and Anti-Xa are superior to ACT. The combination of aPTT to guide the supplementation of FFP and Anti-Xa to adjust the dose of heparin still needs to be further studied in practice. In TEG, the influence of heparin can be excluded through heparinase, so as to further understand the coagulation conditions of patients, and whether TEG with heparinase can guide more standardized anticoagulation needs to be confirmed by further studies.

Due to the designs of the available studies and the nature of the data, quantitative synthesis (meta-analysis) was not conducted. This study could not draw the most accurate conclusion on anticoagulation monitoring based on the existing studies. The targeted ranges of the same monitoring test in different centers were sometimes different, and the methods of combining the monitoring tests also differed. Although the type and severity of the primary diseases were not considered, a more appropriate strategy must be chosen to decrease the risks of complications. Despite the limitations, our study not only discussed the difference between different monitoring strategies in adults, but also evaluated the feasibility of combining the monitoring strategies. We thus tried to determine the advantages of existing monitoring strategies through this systematic review.

Anti-Xa and aPTT are more suitable for anticoagulation monitoring and for patients supported on ECMO than ACT. Monitoring anticoagulation using combination strategies and TEG requires further research. More feasible anticoagulation strategies and strict indications for AT transfusion are needed to prevent complications and improve the prognosis of patients on ECMO.

Supplementary information

Additional file 1: Table S1. Search strategy, Table S2. Reasons for exclusion, Table S3. Definitions of bleeding and thrombosis for the included studies, Table S4. Newcastle–Ottawa Scale for the included studies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the submission of the manuscript.

Authors' contributions

JS, YM, SC and RD contributed to the conception and design of this research. JS and YM performed study selection and wrote the manuscript. WS, HM, ZG, QC and YZ extracted data. XM, SC and RD critically revised the manuscript. RD obtained funding. All authors read and approved the final manuscript.

Data availability

: The datasets used during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Funding

The study was supported by grants from the National Natural Science Foundation of China (82172174), LiaoNing Revitalization Talents Program (XLYC2007001) and Changjiang Scholars Program of Ministry of Education of China (TG2019081). The funders had no role in the study design, collection, analysis, or interpretation of data or manuscript writing.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2023.05.003.

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