Continuous renal replacement therapy without anticoagulation in critically ill patients at high risk of bleeding: a systematic review and meta-analysis

Wei Zhang
the Nephrology Department of Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China
Ming Bai (mingbai1983@126.com)
The Nephrology Department of Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China https://orcid.org/0000-0003-1852-2336
Yan Yu
the Nephrology Department of Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China
Xiaolan Chen
the Nephrology Department of Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China
Lijuan Zhao
the Nephrology Department of Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China
Xiangmei Chen
State Key Laboratory of Kidney Disease, Department of Nephrology, Chinese People's Liberation Army General Hospital and Military Medical Postgraduate College, Beijing, China

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Abstract

Abstract

Background: Continuous renal replacement therapy (CRRT) has been widely used in the critical care setting and anticoagulation is usually necessitated. However, critically ill patients are commonly at incremental risk of bleeding, which contributed to the hesitation of anticoagulant use for CRRT in clinical practice. The current guideline recommended CRRT proceed without anticoagulation in patients with contraindication to citrate and increased bleeding risk. Nevertheless, the efficacy of anticoagulation-free CRRT remains inconsistent. Therefore, the purpose of our present systematic review is to evaluate the efficacy and safety of anticoagulant-free CRRT based on the current literatures.

Methods: We conducted a comprehensive search of PubMed (US National Library of Medicine, Bethesda, MD, USA), Cochrane Library databases and EMBASE from database inception to January 12, 2019 for potential candidate studies. Studies included adult critically ill (age > 18 years) patients with increased bleeding risk, and underwent CRRT without anticoagulation were considered for the inclusion.

Results: Finally, 17 observational studies and 3 randomized controlled trials with 1615 patients were included in our present meta-analysis. There was no significant difference in filter lifespan between the anticoagulation-free and systemic heparin group. The filter lifespan was significantly prolonged in the citrate (WMD -23.01, 95%CI [-28.62, -17.39], P < 0.001; I 2 = 0%, P = 0.53) and nafamostat (WMD -8.4, 95%CI [-9.9, -6.9], P < 0.001; I 2 = 33.7%, P = 0.21) groups, compared with anticoagulation-free group. The averaged filter lifespan of the anticoagulation-free CRRT ranged from 10.2 to 52.5 hours.

Conclusion: The filter lifespan in anticoagulation-free patients with increased bleeding risk was comparable to that in patients without increased bleeding risk underwent systemic heparin anticoagulation CRRT. Nafamostat was not recommended for CRRT anticoagulation due to its drawbacks. Currently, the optimal choice of anticoagulation strategy for critically ill patients without citrate contraindications at high risk of bleeding should be regional citrate anticoagulation. Further studies should focus on the special cut-off value of activated partial thromboplastin time (APTT), international normalized ratio (INR) and platelet (PLT) count, at which the anticoagulation-free CRRT would be beneficial.

Key words: Anticoagulation, critically ill patients, continuous renal replacement therapy, filter failure, bleeding

Background

Renal replacement therapy (RRT) has emerged as an important therapeutic tool for critically ill patients. In clinical practice, 8–10% of critically ill patients required RRT, and the rate of RRT application in critically ill patients has increased by 10% per year over the past decade [1]. Continuous renal replacement therapy (CRRT), which accounts for more than 75% of initial strategies, is the commonly used RRT modality in the critical care setting [2, 3]. In order to maintain adequate running time of the extracorporeal circuit, which is one of the important quality indicators of CRRT [1], anticoagulation is usually necessitated for CRRT [4]. However, critically ill patients are commonly associated with coagulation abnormalities, including thrombocytopenia, prolonged prothrombin time (PT) and APTT, and decreased antithrombin or protein C, which indicate high risk of bleeding [5–8]. The increased bleeding risk contributed to the hesitation of anticoagulant use for CRRT in clinical practice. In 2007, a worldwide survey [9] demonstrated that approximately one-third of patients did not receive any anticoagulants during CRRT. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline recommended CRRT proceed without anticoagulation in patients with contraindication to citrate and increased bleeding risk [10]. Nevertheless, compared to circuits managed with anticoagulation, the averaged circuit lifespan of anticoagulation-free CRRT was significantly shorter [11]. Premature circuit failure due to clotting could lead to blood loss, insufficient therapeutic efficacy, increased workload of nurses, and increased cost of CRRT [4, 12, 13]. However, in some patients with prolonged APTT and/or thrombocytopenia, anticoagulation-free CRRT could proceed effectively [14]. Therefore, the purpose of our present systematic review is to evaluate the efficacy and safety of anticoagulant-free CRRT and the risk factors of circuit premature clotting based on the current literatures.

Methods

We performed our present systematic review and meta-analysis with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) statement [15].

Search strategy

We conducted a comprehensive search of PubMed (US National Library of Medicine, Bethesda, MD, USA), Cochrane Library databases and EMBASE from database inception to January 12, 2019 for potential candidate studies. The following terms were employed for the searching: “continuous renal replacement therapy”, “continuous venovenous hemofiltration (CVVH)“, “continuous venovenous hemodialysis (CVVHD)“, “continuous venovenous hemodiafiltration (CVVHDF)“, “Anticoagulation-free”, “No-anticoagulation”, “Without anticoagulation”, and “heparin-free”. The searching of different terms were combined by Boolean Logic. The searching was limited in human subjects without the employment of any language restriction. We also manually searched the reference lists of the articles which underwent full-text review for possible additional studies.

Inclusion and exclusion criteria

Studies included adult critically ill (age > 18 years) patients with increased bleeding risk, and underwent CRRT without anticoagulation were considered for the inclusion. Studies with any of the following characteristics were excluded: (1) full text was not available; (2) the safety and efficacy of anticoagulation-

free protocol was not reported; (3) no sufficient data on the endpoints and outcomes of the anticoagulation-free CRRT were available; (4) animal experiments; (5) intermittent RRT; (6) the following article types: review, case report, letter, conference abstract, and commentary.

Study quality assessment

The risk of bias in the randomized controlled trials were assessed by the use of "the Cochrane collaboration's tool for assessing risk of bias," [16] which including 6 items: (1) allocation concealment; (2) blinding of participants and personnel; (3) blinding of outcome assessment; (4) incomplete outcome data; (5) selective reporting and (6) other bias. For observational studies, a modified version of the Newcastle-Ottawa Scale [17] was employed for the study quality assessment (Additional file 1: Table S1). According to the 8 items of this scale, three aspects of study quality were evaluated: subject selection, comparability of cohorts, and assessment of outcomes. Two investigators (WZ and MB) independently evaluated the studies and disagreements were resolved through discussion and consensus.

Study selection and data extraction

Two reviewers (WZ and YY) screening the identified studies independently. The article type, title, and abstract were reviewed first. Thereafter, the studies that passed initial screening underwent full-text review for the final exclusion. Two of our authors (XLC and LJZ) independently extracted the following data using pre-determined forms: (1) characteristics of the included studies (e.g. first author, publication year, study design, setting, exclusion criteria, sample size, interventions, and number of filters); (2) characteristics of the patients (e.g. demographic characteristics, severity, diagnosis on admission, baseline coagulation parameters); and (3) information related to the safety and efficacy of anticoagulation-free strategy. Disagreements were resolved by discussion and consensus. The observed outcomes included filter lifespan, bleeding complications, mortality, coagulation parameters, and renal and liver function.

Statistical analysis

For continuous variables, mean (95% CI [confidence interal]) was converted to mean ± standard deviation (SD) by using the calculator attacted in the Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. The median (interquartile range [IQR] or range) was converted to mean ± SD by using the online calculator [18], which was programmed according to the methods reported by Wan, X. *et al.* [19] and Luo, D. *et al.* [20].

Weighted mean difference (WMD) and risk ratio (RR) (or odds ratio [OR] where appropriate) were pooled for continuous variables and categorical variables, respectively. Heterogeneity across the included studies was evaluated by the I^2 statistic and chi-square test. A I^2 value of more than 50% was considered as significant heterogeneity. The potential source of heterogeneity was explored by meta-regression and sensitivity analysis. Subgroup analysis was performed to minimize the heterogeneity among the studies with different characteristics. A P value less than 0.05 was considered as statistical significance. P value was assessed using random effects model for $I^2 > 50\%$ ($P < 0.01$) and fixed effects model for $I^2 \leq 50\%$ ($P > 0.01$) [21]. All meta-analyses were performed using the Stata software version 12.0 (Stata Corporation, College Station, TX, USA).

Evaluation of publication bias

The Begg's [22] and Egger's [23] tests were used to evaluate the potential publication bias for primary outcomes.

Results

Study enrolment and characteristics

A total of 565 studies were retrieved and screened according to the pre-defined inclusion and exclusion criteria. The inclusion flow chart are showed in Figure 1. Finally, 20 studies [14, 24–42] with 1615 patients were included in our present meta-analysis.

The characteristics of the 20 included studies and the demographic data were summarized in Table 1. There are 3 (15%) randomized controled trials [24, 39, 40] and 17 observational studies. Of these 17 studies, 7 (35%) [25, 29, 31, 34–36, 38], and 10 (50%) [14, 26–28, 30, 32, 33, 37, 41, 42] were retrospectively and prospectively designed, respectively. The included studies were published between 1993 and 2017. The sample size of the included studies varied greatly (14–255) and only 4 studies [25, 34, 35, 38] enrolled more than 100 patients. The total number of circuits were reported in 12 studies [14, 26–29, 32, 35–39, 42]. The most concerned endpoints for safety were bleeding episodes and transfusion requirements. For efficacy, filter lifespan and azotemic control were the foci of attention.

All studies included critically ill patients with acute kidney injury (AKI) requiring CRRT and a majority of the included patients had high risk of bleeding. Sepsis (43.8%, 381/870 patients) was the most common cause of AKI. The most common indications for CRRT were fluid overload and electrolyte imbalance.

The definitions of high risk of bleeding of the included studies were listed in Table 2. The most frequently used coagulation parameters for the identification of high bleeding risk were APTT, PLT, and INR. Eight studies [14, 26–31, 35] reported the causes of increased risk of bleeding (Table 3). The reported tools for

illness severity evaluation included Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II, and SAPS III score.

The CRRT protocols with or without anticoagulation in the included studies were detailed in Additional file 2: Table S2. The CRRT modality was CVVH in 10 (50%) studies, CVVHDF in 10 (50%) studies, and CVVHD in 4 (20%) studies. As a control, the anticoagulation-free group was compared with heparin group in 9 studies [14, 24–28, 33, 36, 42], citrate group in 1 study [30], heparin and citrate groups in 4 studies [29, 32, 37, 41], and nafamostat mesilate group in 4 studies [35, 38–40], respectively. One study [34] conducted comparison between two anticoagulation-free groups with or without saline flush and the remaining 1 study [31] compared the efficacy of anticoagulation-free CRRT in liver failure patients with sepsis and hematological disease patients.

Quality of studies

The bias risk of the 3 randomized controlled trials [24, 39, 40] were illustrated in Figure 2. Allocation concealment and blinding were not performed in all of these studies, which perhaps were attributed to the nature of the intervention and the critical condition. The results of the methodological quality assessment of the 17 observational cohort studies using the Newcastle-Ottawa Scale were detailed in Additional file 3: Table S3. Eight studies [14, 30–32, 34–36, 38] were awarded 6 scores and were considered to be moderate quality study. The remaining 9 studies [25–29, 33, 37, 41, 42] earned 7 scores, which were considered to be high quality study.

Anticoagulation-free versus systemic heparin

Both the anticoagulation-free and heparin groups included critically ill patients requiring CRRT and were not signifcinatly different in age, gender, and sepsis. However, the patients in the anticoagulation-free group had either developed bleeding tendency (i.e. prolonged coagulation parameters or thrombocytopenia) or already been on active bleeding before CRRT. Therefore, the comparability between anticoagulation-free and heparin group was poor.

Coagulation parameters before CRRT

The patients' PLT count was significantly lower in anticoagulation-free group than that in heparin group (WMD −75.86, 95%CI [−98.32, −53.41, $P < 0.001$; $I^2 = 77.9\%$, $P < 0.001$, Figure 3A), whereas the INR was the opposite (WMD 0.41, 95%CI [0.26, 0.57], $P < 0.001$; $I^2 = 58.3\%$, $P = 0.035$, Figure 3B). No significant difference was observed in APTT between these two groups (WMD 10.66, 95%CI [−0.95, 22.27], $P = 0.07$; $I^2 = 90.5\%$, $P < 0.001$, Figure 3C). The baseline mean INR and PLT in heparin-free and heparin groups of the included studies were summarized in Additional file 4: Table S4.

Mortality

Five studies [25, 26, 33, 38, 41] reported the intensive care unit (ICU) mortality and the data were collected from the latest follow-up time points. The overall mortality in the 5 studies was 58.6% (281/479). The rate in the anticoagulation-free and heparin group were 65.9% (147/223) and 52.3% (134/256), respectively. The pooled mortality in the anticoagulation-free group was significantly higher than that in the heparin group (RR 1.31, 95 % CI [1.09, 1.58], $P = 0.005$; $I^2 = 41.6\%$, $P = 0.14$, Figure 3D).

Filter lifespan

The filter lifespan was available in 11 studies [24–29, 33, 37, 38, 41, 42]. The averaged filter lifespan in the anticoagulation-free groups ranged from 16.7 to 52.5 hours. There was no significant difference in filter lifespan between the anticoagulation-free and heparin group (WMD −1.55, 95%CI [−3.71, 0.60], $P = 0.15$; $I^2 = 14\%$, $P = 0.31$, Figure 4A). In CVVH [25, 26, 28, 29, 41] (WMD −1.43, 95%CI [−7.24, 4.39], $P = 0.63$; $I^2 = 52.5\%$, $P = 0.07$), CVVHD [24, 27] (WMD −0.46, 95%CI [−14.38, 13.46], $P = 0.94$; $I^2 = 0\%$, $P = 0.85$), and CVVHDF [33, 37, 38] (WMD −2.18, 95%CI [−4.63, 0.28], $P = 0.08$; $I^2 = 0\%$, $P = 0.68$) subgroups, the filter lifespan was also comparable between these two groups.

Bleeding

Four studies [24, 25, 29, 33] reported the number of new bleeding episodes after CRRT commencement. The overall bleeding incidence in these studies was 9.8% (36/367). The incidence in anticoagulation-free and heparin groups were 8.5% (9/106) and 10.3% (27/261), respectively. There was no significant difference in bleeding incidence between these two groups (RR 0.72, 95% CI [0.22, 2.35], $P = 0.58$; $I^2 = 60.3\%$, $P = 0.039$, Figure 4B).

Anticoagulation-free versus regional citrate anticoagulation (RCA)

The baseline characteristics between anticoagulation-free and RCA groups were comparable in 3 [30, 37, 41] of the 5 related studies. The patient baseline characteristcs, especially the coagulation parameters, of the remaining 2 studies [29, 32] were not comparable because the anticoagulation-free group included liver failure patients and the citrate group did not.

Filter lifespan

The filter lifespan were reported in 4 studies [29, 30, 37, 41]. The pooled data showed filter lifespan was significantly longer in the RCA group than the anticoagulation-free group (WMD −23.01, 95%CI [−28.62, −17.39], $P < 0.001$; $I^2 = 0\%$, $P = 0.53$, Figure 4C).

Filter clotting

The incidence of filter clotting during CRRT were reported in 4 studies [29, 30, 32, 41]. Compared with RCA group, the filters in anticoagulation-free group had increased clotting risk (RR 1.92, 95%CI [1.27, 2.90], $P = 0.002$; $I^2 = 0\%$, $P = 0.53$, Figure 4D).

Complications of citrate

Of the included studies, 5 studies included patients accepted RCA. Of these studies, 2 [30, 37] reported 2 cases (1/20, 1/33, respectively) of citrate accumulation, and the remaining 3 studies did not report any patients with citrate accumulation or citrate induced complications (e.g. metabolic acidosis/alkalosis, hypernatremia, or hypocalcemia) during RCA-CRRT.

Anticoagulation-free versus nafamostat

Baseline characteristics

Three studies [38–40] reported the APACHE II score before CRRT. There was no difference in APACHE II score between the anticoagulation-free and nafamostat groups (WMD 0.27, 95%CI [−1.48, 2.03], $P = 0.76$; $I^2 = 0\%$, $P = 0.47$, Figure 5A). The serum creatinine and blood urine nitrogen (BUN) were compared at baseline in 3 studies [38–40]. There were no differences in these two parameters between the anticoagulation-free and nafamostat groups. Only 1 study [35] reported the proportion of patients with liver disease, and the two groups was comparable at this parameter. The data of APTT and PLT were pooled in 2 [38, 40] and 3 [38–40] studies, respectively. There were no differences in APTT (WMD −4.72, 95%CI [−13.81, 4.37], $P = 0.31$; $I^2 = 0\%$, $P = 0.85$, Figure 5B) and PLT (WMD 7.25, 95%CI [−39.97, 54.48], $P = 0.76$; $I^2 = 76.5\%$, $P = 0.014$, Figure 5C) between these two groups.

Filter lifespan

The pooled results showed the filter lifespan was significantly prolonged in the nafamostat group compared with anticoagulation-free group (WMD −8.45, 95%CI [−9.96, −6.93], $P < 0.001$; $I^2 = 33.7\%$, $P = 0.21$, Figure 5D).

Mortality

The mortality rates were reported in 3 studies [38–40]. The pooled results showed there was no significant difference in mortality between the anticoagulation-free and nafamostat groups (RR 1.12, 95% CI [0.91, 1.36], $P = 0.28$; $I^2 = 29.7\%$, $P = 0.24$, Additional file 7: Figure S1A).

Bleeding

Bleeding episodes during CRRT was reported in 2 studies [39, 40]. There was no difference in bleeding risk between the anticoagulation-free and nafamostat groups (RR 0.85, 95%CI [0.30, 2.43], $P = 0.76$; $I^2 = 0\%$, $P = 0.38$, Additional file 7: Figure S1B).

Risk factors of filter lifespan

The risk factors of filter lifespan were reported in 7 studies [14, 27, 31, 32, 36, 38, 40] and were summarized in Additional file 5: Table S5 and Additional file 6: Table S6. The most frequently included variables in the anlaysis of filter lifespan were coagulation parameters and CRRT protocol. In univariate analysis, low APTT, high PLT count, thrombelastogram (TEG) K value, and high bilirubin level were reported to be the risk factors of filter failure. Low APTT, high PLT, low circuit INR, low blood flow rate, high fluid removal, high bilirubin level, and mechanical ventilation (MV) were reported to be the risk factors of filter failure in multivariate analysis. Of note, none of the aforementioned analyses were performed exclusively in anticoagulation-free group.

Publication bias

The baseline characteristics between anticoagulation-free and heparin groups were not comparable, therefore, the publication bias test, which otherwise was not effective, was not performed. Due to the small numbers of included studies, publication bias tests were not performed in studies that employed RCA or nafamostat protocol.

Discussion

Our present systematic review found out that (1) the most common causes of bleeding risk in critically ill patients who underwent anticoagulation-free CRRT were coagulopathy and post-surgery; (2) compared with systemic heparin anticoagulation in cricitcally ill patients without increased bleeding risk, anticoagulation-free CRRT in the patients with high bleeding risk yielded similar filter lifespan; (3) In patients at high risk of bleeding requiring CRRT, the filter lifespan was significantly prolonged in RCA group compared with anticoagulation-free group, the rate of citrate accumulation in RCA groups was relatively low and no citrate induced metabolic complications were reported; and (4) nafamostat was superior to anticoagulation-free protocol in terms of filter lifespan, however, this drug was used as anticoagulant for CRRT dominantly in Japan and Korea and was not recommended partly due to it's potential side effects.

Anticoagulation-free versus heparin

The overall mortality in the present systematic review was consistent with the results reported by Nash, D. M. *et al* [43], who summarized that the overall ICU mortality in critically ill patients underwent CRRT was more than 50%. Higher mortality in the anticoagulation-free group, most likely, was not directly caused by bleeding per se, which only reflected the pathophysiology of the underlying disease. Lauzier, F. *et al.* [44] reported that the ctitically ill patients with major bleeding compared with those without had a twofold increased risk of ICU mortality, despite the underlying pathophysiology leading to death remains unclear.

According to the inclusion criteria, a majority of patients in anticoagulation-free group had developed coagulopathy such as thrombocytopenia or prolonged APTT/INR before CRRT, which are non anti-coagulant factors with a positive association with filter lifespan [45]. In addition, the probable heparin resistance in the critically ill patients, especially Antithrombin III (AT III) deficiency, could attenuate the anticoagulant effect of heparin [46, 47]. A combination of the aforementioned conditions might contribute to the similarity of filter lifespan between anticoagulation-free and heparin groups.

Anticoagulation-free versus citrate

In the KDIGO guideline [10], anticoagulation-free protocol was recommended for the critically ill patients requiring CRRT with increased bleeding risk and contraindications to citrate (i.e. liver failure and shock with skeletal muscle hypoperfusion).

Of the 5 studies that compared RCA with anticoagulation-free protocol in our systematic review, 2 studies [30, 41] routinely employed anticoagulation-free CRRT in high bleeding risk patients until the availability of custom-made citrate-based replacement fluid, 2 studies [29, 32] employed anticoagulation-free protocol because of bleeding tendency or liver failure, and the remaining 1 study [37] included post-cardiac surgery patients with AKI and high risk of bleeding, who initially underwent anticoagulation-free CRRT and switched to RCA-CRRT if the filters clotted within 24 hours. In fact, most of these patients in the anticoagulation-free arms, except for a small number of liver failure patients, could theoretically tolerate and benefit from RCA-CRRT. Of note, all of the 5 studies were conducted before the issue of the 2012 KDIGO guideline. In addtion, new evidence suggested that, under strict protocol and colsely monitoring, RCA might be safe for CRRT in liver failure patients [48].

The averaged filter lifespan (range 33–49.8 hours) of RCA-CRRT in the present systematic review were consistent with the results (range 29.5–78 hours) in other studies [49–53]. The prolongation of filter lifespan and reduction of clotting events in the RCA-CRRT were also reported in previously published literatures [52, 54, 55]. In our systematic review, both the citrate and anticoagulation-free groups were with increased bleeding risk, the prolonged filter lifespan were most likely attributed to the use of anticoagulants [4].

Citrate accumulation was reported in 2 studies [30, 37] and both of which did not exclude patients with liver failure, a pathological condition that could theoretically impair citrate metabolism and increase the risk of citrate accumulation [56, 57]. The incidence of citrate accumulation in these 2 studies (5% and 3%, respectively) were slightly higher than that (2.99%) reported by Khadzhynov, D. *et al.* [58] in a large retrospective study which also did not exclude liver failure patients. However, patients with hypoperfusion shock, the other contraindication to citrate and a risk factor of citrate accumulation [59, 60], were not excluded from the RCA groups in most of these 5 studies.

Anticoagulation-free versus nafamostat

Nafamostat, a inhibitor of serine proteases, can also act as an anticoagulant by inhibiting coagulation factors (including thrombin, Xa and XIIa). It has short duration of action in blood due to a 5–8 minutes elimination half-life and has the theoretical advantage of extracorporeal elimination coupled with reduced systemic anticoagulation [61]. This drug, dominantly available in Japan and Korea, had been safely used in the critically ill with high bleeding risk in some observational studies [62–64]. The reported filter lifespan of nafamostat-anticoagulated CRRT ranged from 22 to 25.5 hours and the bleeding incidence ranged from 4% to 6.6% [65, 66]. In our systematic review, the filter lifespan was significantly prolonged in nafamostat group (range 19–31 hours) and the bleeding incidence was not increased, compared with anticoagulation-free group. However, because of the absence of antidotes and the potential side-effects including agranulocytosis, anaphylaxis, hyperkalemia, and bone marrow suppression, nafamostat was not recommended for CRRT anticoagulation by the KDIGO guideline [10].

Risk factors of filter lifespan

The impact of blood flow rate on filter lifespan remained controversial in the previous studies [67, 68]. The negative effect of high fluid removal on filter lifespan has been demonstrated in 2 large multi-centre trials of RRT intensity [69, 70]. Lower APTT and INR, higher PLT counts and bilirubin level, and the usage of MV had been reported as factors with negative association with filter lifespan in a meta-analysis [71], despite very low evidence level. These findings suggested that, in order to maintain sufficient circuit patency, the intensity of anticoagulation-free CRRT should be targeted at appropriate range, and in addition, patients with these risk factors who underwent anticoagulation-free CRRT should be monitored closely and switch to protocols with anticoagulation if the filter clotted within a short period of time.

Limitations

There are some limitations in our present systematic review. First, most of the included studies were observational study with potential selective bias and confounding factors. Second, the guidelines and clinical practice had changed greatly across the long time span of the included studies, so that there are great differences in patient population and CRRT protocols among these studies, which could contribute to the significant inter-study heterogenicity. Third, we tried to performe meta-regression analysis to indentify the cut-off value of coagulation parameters at which patients could benefit from anticoagulation-free CRRT, however, no significant results were obtained. Further studies should be carried out under the latest guideline and focus on the specific cut-off point for coagulation factors that would indicate the possibility to perform CRRT without anticoagulation. Therefore, we are performing a retrospective cohort study to evaluate the effecacy of anticoagulation-free CRRT and and risk factors of filter lifespan in critically ill patients with high bleeding risk and try to find out a model to predict the filter lifespan in patients who underwent anticoagulation-free CRRT.

Conclusions

Anticoagulation in critically ill patients requiring CRRT at high risk of bleeding is a challenging work for clinicians. The filter lifespan in anticoagulation-free patients with increased bleeding risk was comparable to that in patients without increased bleeding risk underwent systemic heparin anticoagulation CRRT. Compared to the anticoagulation-free protocol, RCA could significantly prolong the filter lifespan without incremental bleeding risk and citrate-related metabolic complications. Nafamostat's advantage on filter lifespan were weighed out by its drawbacks and was not recommended for anticoagulation of CRRT. Currently, the optimal choice of anticoagulation strategy for critically ill patients without citrate controindications at high risk of bleeding should be RCA. High bleeding risk patients with low APTT and INR, high PLT and bilirubin, or usage of MV requiring CRRT could have procoagulant tendency and should be treated with appropriate anticoagulation measures. Further studies should focus on the special cut-off value of APTT, INR and PLT, at which the anticoagulation-free CRRT would be feasible and beneficial.

Abbreviations

AUS: Australia; APTT: activated partial thromboplastin time; APACHE: Acute Physiology and Chronic Health Evaluation; ARF: acute renal failure; ACT: activated clotting time; AKI: acute kidney injury; APC-PCI: activated protein C-protein C inhibitor; AV: arteriovenous; BB: bicarbonate buffered solution; BUN: blood urine nitrogen; CB: citrate buffered solution; CHE: Switzerland; CVVH: continuous venovenous hemofiltration; CVVHD: continuous venovenous hemodialysis; CVVHDF: continuous venovenous haemodiafiltration; CRRT: continuous renal replacement therapy; CCU: cardiac care unit; C: citrate, DIC: disseminated intravascular coagulation; DBP: diastolic blood pressure; ESP: Spain; FDP: fibrinogen degradation product; F: female; FV: femoral vein; Hb: hemoglobin; H: heparin; Hae: Hematological; HIT: heparin induced thrombopenia; INR: international normalized ratio; ICU: intensive care unit; ITA: Italy; IND: India; IJV: internal jugular vein; KOR: Republic of Korea; LF: liver failure; LB: lactate buffered solution; M: male; MODS: multiple organ dysfunction syndrome; MELD: model for end-stage liver disease; MV: mechanical ventilation; NR: not reported; N: no anticoagulation; NLD: Netherlands; NF: no flush; NM: nafamostat; PLT: platelet; PCS: prospective cohort study; POS: prospective observational study; PTT: partial thromboplastin time; PT: prothrombin time; PAI: plasminogen activator inhibitor; RCT: randomized controlled trial; RCA: regional citrate anticoagulation; ROS: retrospective observational study; RH: regional heparin; S: sepsis; SAPS: simplified acute physiology score; SBP: systolic blood pressure; SF: saline flush; SOFA: sequential organ failure assessment; SH: systemic heparin; SV: subclavian vein; TEG: thrombelastogram; TAT: thrombin-antithrombin; UK: United Kingdom; UFH: unfractionated heparin

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are from published articles.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WZ and MB contributed equally to this work. WZ, MB, and XMC conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. YY, XLC, and LJZ performed statistical analyses and helped to draft the manuscript. MB collected the data and revised the manuscript critically for important intellectual content. XMC collected the data, performed statistical analyses and helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of the included studies

Source	Design	Setting	Exclusion of patients/ circuits	Patients included	Endpoints	Patients (M/F)/ circuits number	Mean age (year)	Illness severity	Laboratory tests
R.Bellomo *et al* [24] (AUS, 1993)	RCT	University Hospital ICU	NR/NR	Patients with ARF	Filter lifespan, bleeding	64 (NR)/NR	NR	NR	Hb, PLT, INR, APTT, FDP
Martin, P. Y. *et al* [25] (CHE, 1994)	ROS	University Hospital medical and surgery ICU	NR/NR	Critically ill patients treated by CVVH	Filter survival, coagulation parameters evolution of the patients	255 (203/52)/NR	58..2±16.3[a]	NR	PLT, PT, APTT, creatinine, BUN
Tan, H. K. ***et al*** [26] (AUS, 2000)	PCS	Tertiary multidisciplinary ICU	NR/NR	Patients with severe ARF deemed at high risk of bleeding	Circuit life, bleeding, azotemic control	N: 12 (8/4)/40 H: 14 (9/5)/40	N: 57.7(50.9-64.5)[b] H: 61.1(57.1-64.1)[b]	N: 28.1(23.1-33.1) (APACHE II) [b] H: 26.7(23.2-30.2) (APACHE II) [b]	Urea, Creatinine, APTT, INR, PLT
Holt, A. W.***et al*** [27] (AUS, 2002)	POS	General ICU of a tertiary hospital	NR/ Replaced electively	Consecutive patients requiring CRRT	Conventional coagulation parameters, TEG and circuit lifespan	14 (NR)/47	NR	NR	TEG, APTT, INR, PLT
Morabito, S. ***et al*** [14] (ITA, 2003)	PCS	Surgical ICU	NR/ NR	Critically ill patients required CRRT for ARF and MODS following cardiac surgery	Filter life; filter pressure drop, bleeding	59 (46/13)/170	64.9±10.1[a]	30.1±6.4 (APACHE II)[a]	APTT, PLT, Hb, hematocrit
Uchino, S. *et al* [28] (AUS, 2004)	POS	ICU	NR/NR	Critically ill patients with ARF treated with CVVH	Circuit life; coagulation parameters, bleeding	48 (33/15)/300	65 (46-77)[b]	22 (18-26) (APACHE II)[b]	PT, INR, APTT, PLT
Palsson, R. ***et al*** [29] (USA, 2006)	ROS	Medical ICU	NR/ Non-clotting events for cessation of CVVH	Critically ill adult patients with renal failure who received CVVH	Filter lifespan, complications of CVVH, and patient outcomes	29 (14/15)/76	61.9±12.9[a]	30±6.4 (APACHE II)[a]	Serum electrolytes, BUN, creatinine,complete blood count; systemic PTT, ACT
Nurmohamed, S. A. *et al* [30] (NLD, 2007)	PCS	Adult ICU of a University medical center	NR/NR	Critically ill patients with ARF and high bleeding risk	Filter life, azotemic control and cost	N: 31(14/17)/NR C: 20 (13/7)/NR	N: 70 (59-75)[b] C: 64 (55-75)[b]	N: 24 (18-30) (APACHE II)[b] C: 24 (22-28) (APACHE II)[b]	Creatinine, BUN, PLT, APTT, INR, electrolytes and acid-base status
Agarwal, B.*et al* [31] (UK, 2009)	ROS	ICU of a tertiary referral center	CRRT less than 48h; Initially given anticoagulation; not be sedated during CRRT/ NR	Liver failure patients with AKI requiring CRRT	Filter life, azotemic control and the total number of filters used	LF: 40(26/14)/NR S: 10(7/3)/NR Hae: 10(7/3)/NR	LF: 46.4±12.1[a] S: 57.1±21.4[a] Hae: 40.5±15.5[a]	LF: 21±6.8 (APACHE II)[a] S: 29.1±5.7 (APACHE II)[a] Hae: 30.1±12.7 (APACHE II)[a]	Urea, Creatinine, PLT, PT, APTT, INR
Kleger, G.	POS	Medical ICU of	NR/ filters	Adult patients	Circuit	38	64.3±13.3[a]	82.3±18.1	Creatinine

R.*et al* [32] (CHE, 2010)		a teaching hospital	terminated selectively	receiving CRRT	lifetime and reasons for circuit change	(23/15)/167		(SAPS III)[a]	
Nagarik, A. P.*et al* [33] (IND, 2010)	PCS	ICU	NR/NR	Critically ill patients with ARF underwent CRRT	Filter life, bleeding episodes, transfusion requirements and mortality	N: 35 (22/13)/NR H: 30 (20/10)/NR	N: 58±16.03[a] H: 63.25±15.24[a]	NR	Hb, PLT, APTT
Panphanpho, S.*et al* [34] (THA, 2011)	RCS	ICU, CCU of a tertiary care academic center	NR/ access malfunction or unrelated patient issues	Critically ill patients with severe AKI requiring CRRT	Circuit survival and clotting rates	NF: 43(25/18)/NR SF: 78(38/40)/NR	NF: 58.6±17.4[a] SF: 64.1±13.7[a]	NF: 13.9±2.9 (SOFA score)[a] SF: 14±2.8 (SOFA score)[a]	APTT, PT, PLT, creatinine, BUN
Baek, N. N.***et al*** [35] (KOR, 2012)	ROS	ICUs of an university-affiliated, tertiary referral hospital	began CRRT before the study, received standard heparin anticoagulation/ NR	Patients with high risk of bleeding and received CRRT more than 48 hours	Filter lifespan and bleeding	N: 181 (114/67)/543 NM: 62 (40/22)/124	N: 55.5±12.7[a] NM: 59.3±15.9[a]	13 (10-16) (SOFA score)[b]	INR, APTT, PLT
Chua, H. R.*et al* [36] (AUS, 2012)	ROS	ICU of a regional tertiary referral center	NR/ terminated prematurely due to elective indications	Adults with acute liver failure or decompensated cirrhosis who received CRRT	Circuit lifespan, bleeding	71(26/45)/539	45.9±11.2[a]	100±30 (APACHE III)[a] 37±8 (MELD score)[a]	Hb, PLT, INR, APTT
Morabito, S. *et al* [37] (ITA, 2012)	POS	Cardiac surgery ICU	NR/ terminated prematurely due to elective indications	High bleeding-risk cardiac surgery patients who received CRRT	Filter lifespan, bleeding, and citrate related complications	N:33 (NR/NR)/77 H: 16 (NR/NR)/73 C: 33 (NR/NR)/152	70.8±9.5[a]	32.1 ± 4.6 (APACHE III)[a] 13.9 ± 2.5 (SOFA score)[a] 18.7 ± 4.7 (MELD score)[a]	Creatinine, BUN, bilirubin, electrolytes and acid-base status
Hwang, S. D.*et al* [38] (KOR, 2013)	ROS	ICUs of an university hospital	Died within the first filter use, patients who ingested paraquat/ NR	Patients treated with CRRT	Filter life span, hemorrhagic episodes and survival	N: 131 (77/54)/640 H: 56 (25/31)/341 NM: 25 (16/9)/204 SH: 10 (5/5)/51	N: 66.2±15[a] RH: 69.5±13[a] NM: 65.2±11[a] SH: 73.6±10.1[a]	N: 24.9±6.1 (APACHE II)[a] H: 24.3±5.8 (APACHE II)[a] NM: 25.6±7.1 (APACHE II)[a] SH: 26.2±6.2 (APACHE II)[a]	BUN, creatinine, PLT, PT, APTT
Lee, Y. K.*et al* [39] (KOR, 2014)	RCT	ICU	Pregnant, breast feeding, allergic to nafamostat mesilate/ NR	Patients requiring CRRT with hemorrhagic tendency	Mortality, filter life span, and adverse events	N: 37 (20/17)/94 NM: 36 (24/12)/138	N: 57.54±13.04[a] NM: 52.97±13.9[a]	N: 26.84±6 (APACHE II)[a]	hematologic, biochemical, coagulation tests

								NM: 26.72±5.26 (APACHE II)[a]	
Choi, J. Y. *et al* [40] (KOR, 2015)	RCT	ICU of an University Hospital	Pregnant or possibly pregnant women; allergic to NM or were hypercoagulable/ NR	Patients with AKI receiving CRRT at high risk of bleeding;	Filter lifespan, safety and patient survival rates	N: 24 (15/9)/NR NM: 31 (21/10)/NR	N: 58.6±18[a] NM: 36.6±11.5[a]	N: 35.9±8.4 (APACHE II)[a] NM: 23.5±6.2 (APACHE II)[a]	complete blood count, BUN, serum creatinine, electrolyte, PT, APTT
Schilder, L.*et al* [41] (NLD, 2015)	POS	ICU	NR/NR	Critically ill patients with AKI necessitating CVVH	Filter lifespan, markers of thrombin generation, ICU mortality	N: 13 (7/6)/NR H: 8 (6/2)/NR C: 17 (11/6)/NR	N: 70(34-84)[c] H: 57(23-81)[c] C: 61(32-79)[c]	N: 75 (43-112) (SAPS II)[c] H: 47 (37-77) (SAPS II)[c] C: 52 (32-86) (SAPS II)[c]	Creatinine, APTT, INR, PLT, TAT, APC-PCI, PAI-1
Sanz Ganuza, M.*et al* [42] (ESP, 2017)	POS	ICU of an university hospital	Active bleeding, history of HIT and patients with circuits changed electively/NR	Patients with AKI requiring CRRT	Filter lifespan	N:29(NR)/67 H:21(NR)/55	N: 64±13.5[a] H: 64±12.4[a]	N: 61.3±16.9 (SAPS III)[a] H:59.1±19.2 (SAPS III)[a]	Hb, PLT; INR; PT; APTT,

Abbreviations: AUS Australia, APTT activated partial thromboplastin time, APACHE Acute Physiology and Chronic Health Evaluation, ARF acute renal failure, ACT activated clotting time, AKI acute kidney injury, APC-PCI activated protein C-protein C inhibitor, BUN blood urine nitrogen, CHE Switzerland, CRRT continuous renal replacement therapy, CVVH continuous veno-venous hemofiltration, CCU cardiac care unit, C citrate, ESP Spain, FDP fibrinogen degradation product, F female, Hb hemoglobin, H heparin, Hae Haematological, HIT heparin induced thrombopenia, INR international normalized ratio, ICU intensive care unit, ITA Italy, IND India, KOR Republic of Korea, LF liver failure, M male, MODS multiple organ dysfunction syndrome, MELD model for end-stage liver disease, NR not reported, N no anticoagulation, NLD Netherlands, NF no flush, NM nafamostat, PLT platelet, PCS prospective cohort study, POS prospective observational study, PTT partial thromboplastin time, PT prothrombin time, PAI plasminogen activator inhibitor, RCT randomized controlled trial, ROS retrospective observational study, RH regional heparin, S sepsis, SAPS simplified acute physiology score, SF saline flush, SOFA sequential organ failure assessment, SH systemic heparin, TEG thrombelastogram, TAT thrombin-antithrombin, UK United Kingdom. [a]Mean ± standard deviation, [b]Median (interquartile range), [c]Median (range)

Table 2. The criteria of high risk of bleeding employed by the included studies

Study	Criteria of high risk of bleeding
R.Bellomo *et al* [24]	1. PLT < 60×10^9/L;
	2. APTT > 60s;
	3. INR > 2;
	4. FDP > 50μg/L;
	5. Spontaneous bleeding
Martin, P. Y. *et al* [25]	Coagulation abnormalities (low platelet counts and prolonged APTT)
Tan, H. K.*et al* [26]	1. On going bleeding;
	2. Major hemorrhage in the last 48h;
	3. Surgery in the last 24h;
	4. INR > 2;
	5. APTT > 60s;
	6. PLT < 60×10^9/L
Holt, A. W.*et al* [27]	1. Postoperative;
	2. Percutaneous tracheostomy;
	3. Severe liver disease
Morabito, S. *et al* [14]	1. Presence of spontaneous bleeding;
	2. APTT > 45s;
	3. PLT < 50×10^9/L;
	4. Recent surgery < 48 hours
Uchino, S. *et al* [28]	1. INR > 2.5;
	2. APTT > 60s;
	3. PLT < 60×10^9/L
	4. Active bleeding;
	5. In the 24 hour postsurgery period
Palsson, R. *et al* [29]	1. Active or recent bleeding;
	2. Thrombocytopenia/suspected HIT;
	3. Coagulopathy associated with liver failure;
	4. Other known risks of bleeding
Nurmohamed, S. A. *et al* [30]	1. PLT < $40\times10^{9/}$L;
	2. APTT > 60s;
	3. INR > 2;
	4. Recent major bleeding;
	5. Significant active bleeding
Agarwal, B.*et al* [31]	1. Liver failure;
	2. The reduction in platelet count;
	3. Prolongation of conventional coagulation tests (PT, APTT)
Kleger, G. R.*et al* [32]	1. Major disruption of the coagulation system;
	2. Liver failure
Nagarik, A. P.*et al* [33]	1. Baseline APTT > 55s;

	2. PLT < 40×10^9/L;
	3. Heparin induced thrombocytopenia;
	4. Intracranial hemorrhage within three months;
	5. Gastrointestinal hemorrhage requiring a transfusion of greater than two units of blood within three months;
	6. Active bleeding within three days;
	7. Significant trauma within three days;
	8. Evidence of irreversible coagulopathy as a result of liver failure;
	9. DIC or a coagulation factor deficiency
Panphanpho, S.*et al* [34]	1. Ongoing bleeding;
	2. Major hemorrhage in the last 48 h;
	3. Surgery in the last 24 h;
	4. APTT > 60 s;
	5. INR > 2;
	6. PLT < 60×10^9/L
Baek, N. N.*et al* [35]	1. Spontaneous bleeding;
	2. Major surgery within 7 days before CRRT;
	3. Brain hemorrhage, or operation within 14 days before CRRT;
	4. Coagulopathy (INR >2, APTT > 60s, or PLT < 50×10^9/L)
Chua, H. R.*et al* [36]	1. Coagulopathy;
	2. Elevated INR, APTT;
	3. Thrombocytopenia
Morabito, S. *et al* [37]	1. PLT < 50×10^9/L;
	2. heparin induced thrombocytopenia;
	3. spontaneous or heparin associated bleeding;
	4. APTT > 45s;
	5. surgery in the last 48 hours
Hwang, S. D.*et al* [38]	Obvious or suspicious bleeding
Lee, Y. K.*et al* [39]	1. PLT < 100×10^9/L;
	2. APTT < 60s;
	3. INR > 2.0;
	4. Active hemorrhage;
	5. Surgery within the past 48 hours;
	6. Cerebral hemorrhage within the past 3 months or history of a major cerebral bleeding;
	7. Septic shock or DIC
Choi, J. Y. *et al* [40]	1. Active bleeding;
	2. APTT > 60s;
	3. INR > 2;
	4. PLT < 100×10^9/L;
	5. Surgery within 48 hours before CRRT;

Schilder, L.*et al* [41]	1. PLT < 40 × 10^9/L; 2. APTT > 60s; 3. INR > 2; 4. Recent or active bleeding
Sanz Ganuza, M.*et al* [42]	1. PLT < 50×10^9/L; 2. INR > 2; 3. HIT

Abbreviations: APTT activated partial thromboplastin time, CRRT continuous renal replacement therapy, DIC disseminated intravascular coagulation, FDP fibrin degradation products, HIT heparin induced thrombopenia, INR international normalized ratio, PLT platelet, PT prothrombin time

Table 3. The cause of high risk of bleeding for patients receiving anticoagulation-free CRRT

Study	Thrombocytopenia	Prolonged APTT	Increased INR	Postoperative	Active bleeding	Severe liver disease	Severe coagulopathy	Percutaneous tracheostomy	Total
Tan, H. K. *et al* [26]	--	--	--	7	--	--	2	--	9
Holt, A. W. *et al* [27]	--	--	--	5	--	1	--	4	10
Morabito, S. *et al* [14]	9	13	--	5	5	--	--	--	32
Uchino, S. *et al* [28]	98	31	20	36	10	--	--	--	195
Palsson, R. *et al* [29]	1	--	--	--	2	5	5	--	13
Nurmohamed, S. A. *et al* [30]	9	13	--	3	18	--	--	--	43
Agarwal, B.*et al* [31]	--	--	--	--	--	30	10	--	40
Baek, N. N.*et al* [35]	--	--	--	76	25	--	140	--	241
Summary n (%)	117 (17.8)	57 (8.7)	20 (3)	132 (20)	60 (9)	107 (16.3)	157 (24)	4 (0.6)	654

Abbreviations: APTT activated partial thromboplastin time, CRRT continuous renal replacement therapy, INR international normalized ratio

Figures

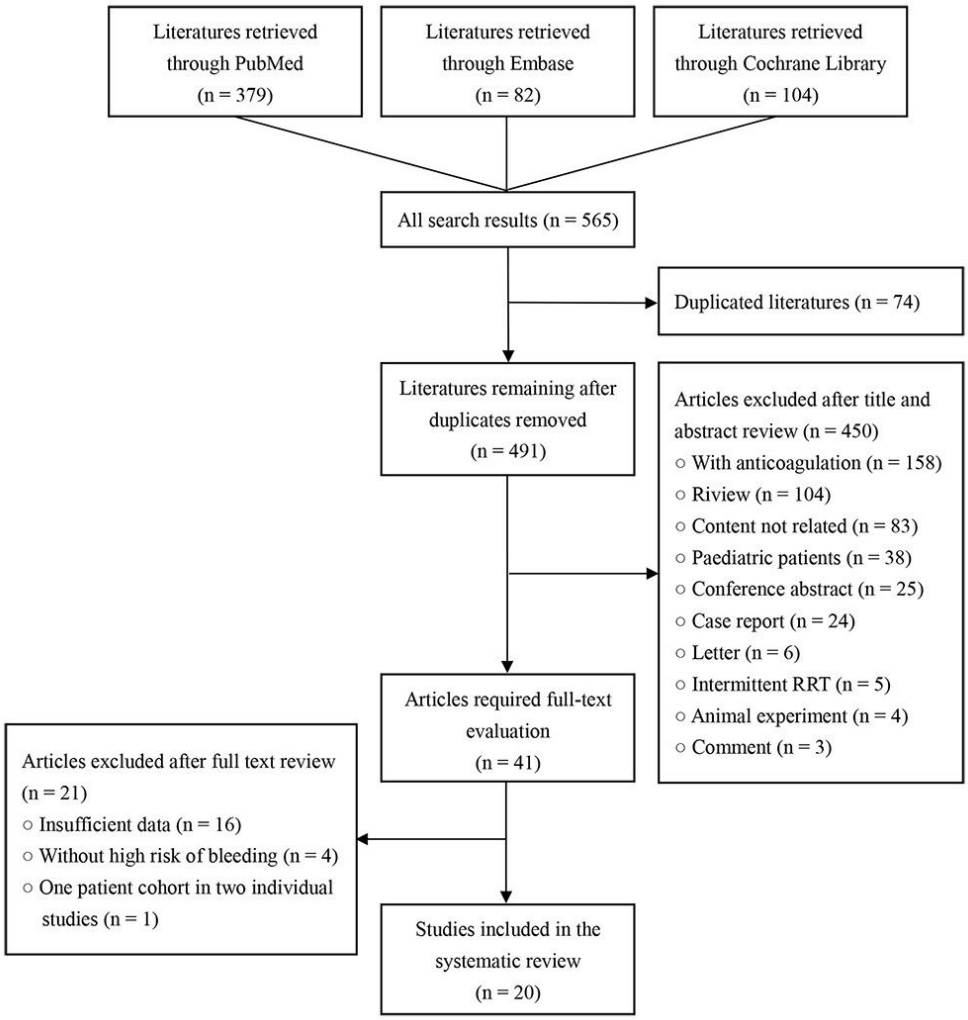

Figure 1

Study inclusion flow chart.

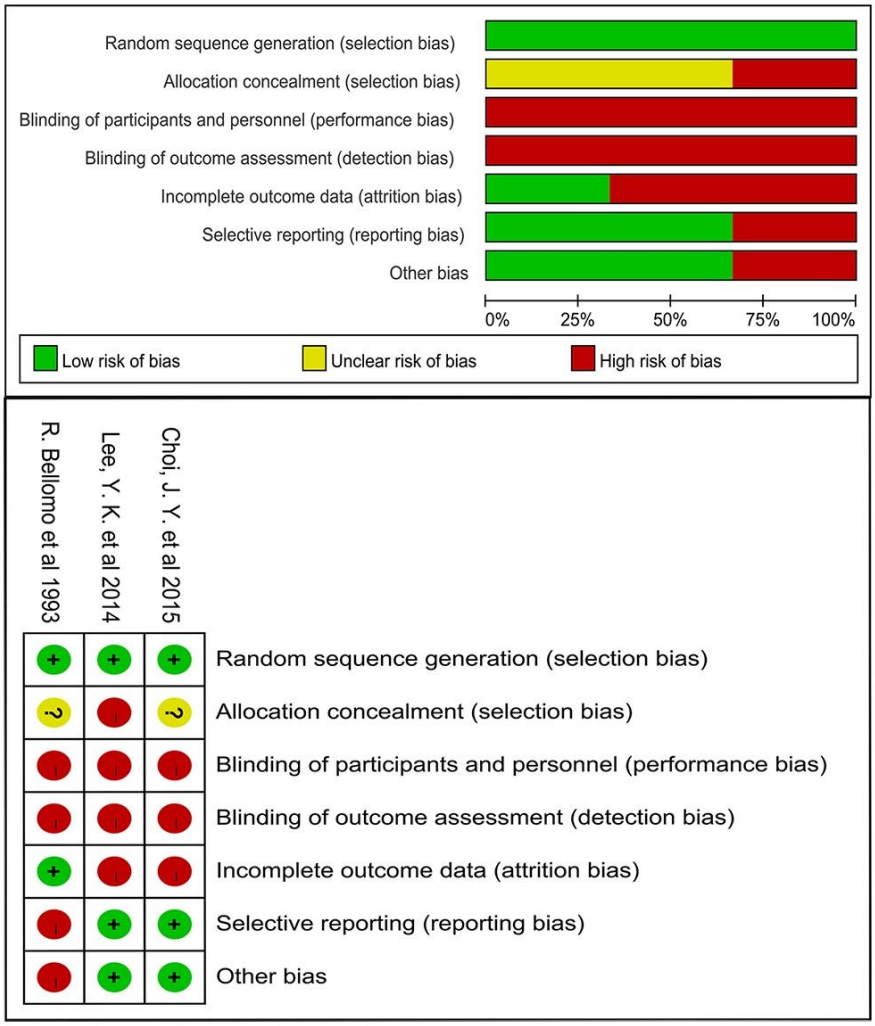

Figure 2

The results of bias risk assessment of the 3 randomized controlled trials.

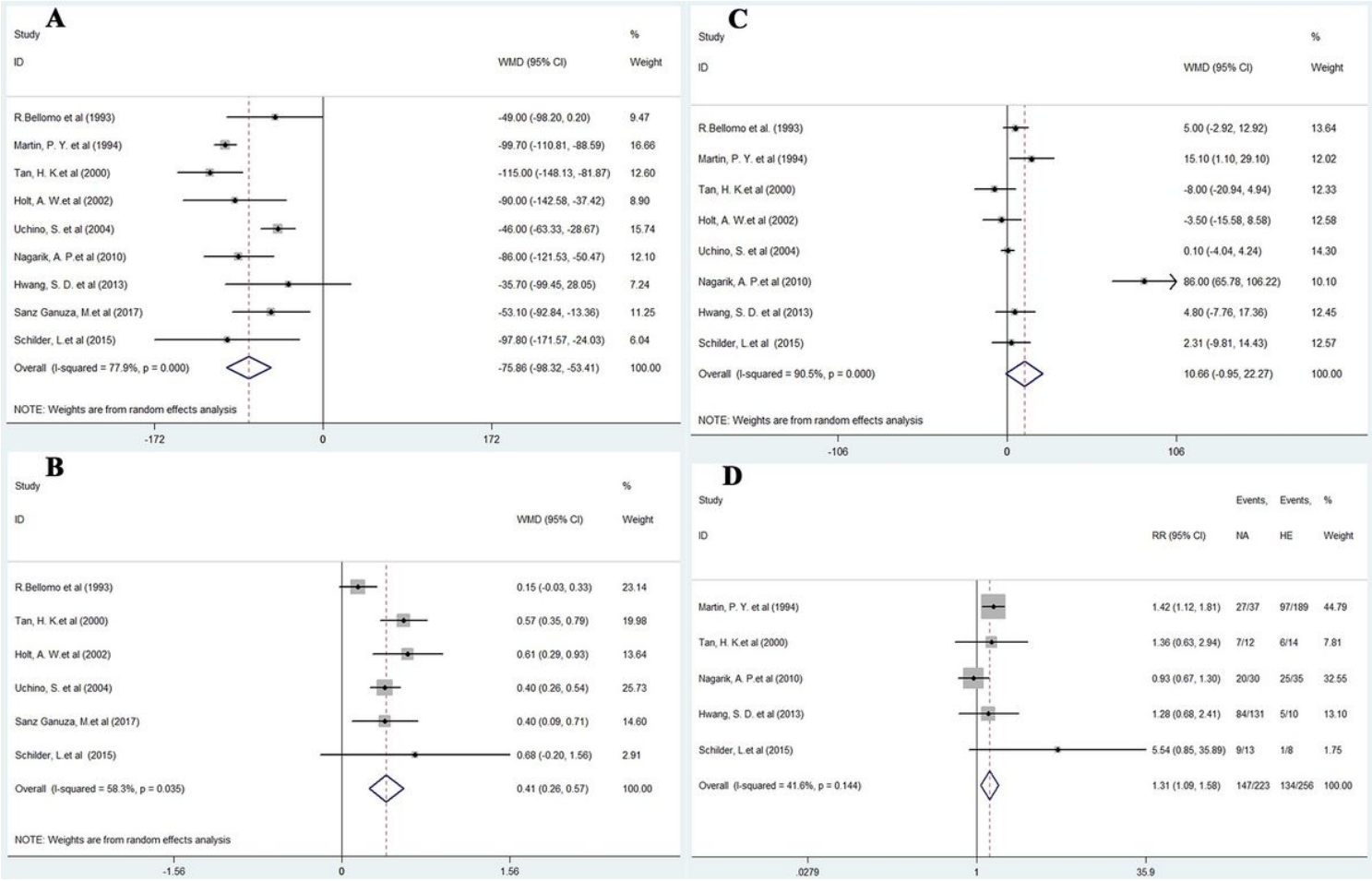

Figure 3

Forest plot of comparison between the anticoagulation-free group and systemic heparin group. Outcomes: patient platelet count (A), INR (B), and APTT (C) before CRRT, and ICU mortality (D). NA, no anticoagulation; HE, heparin; WMD, weighted mean difference; RR, risk ratio

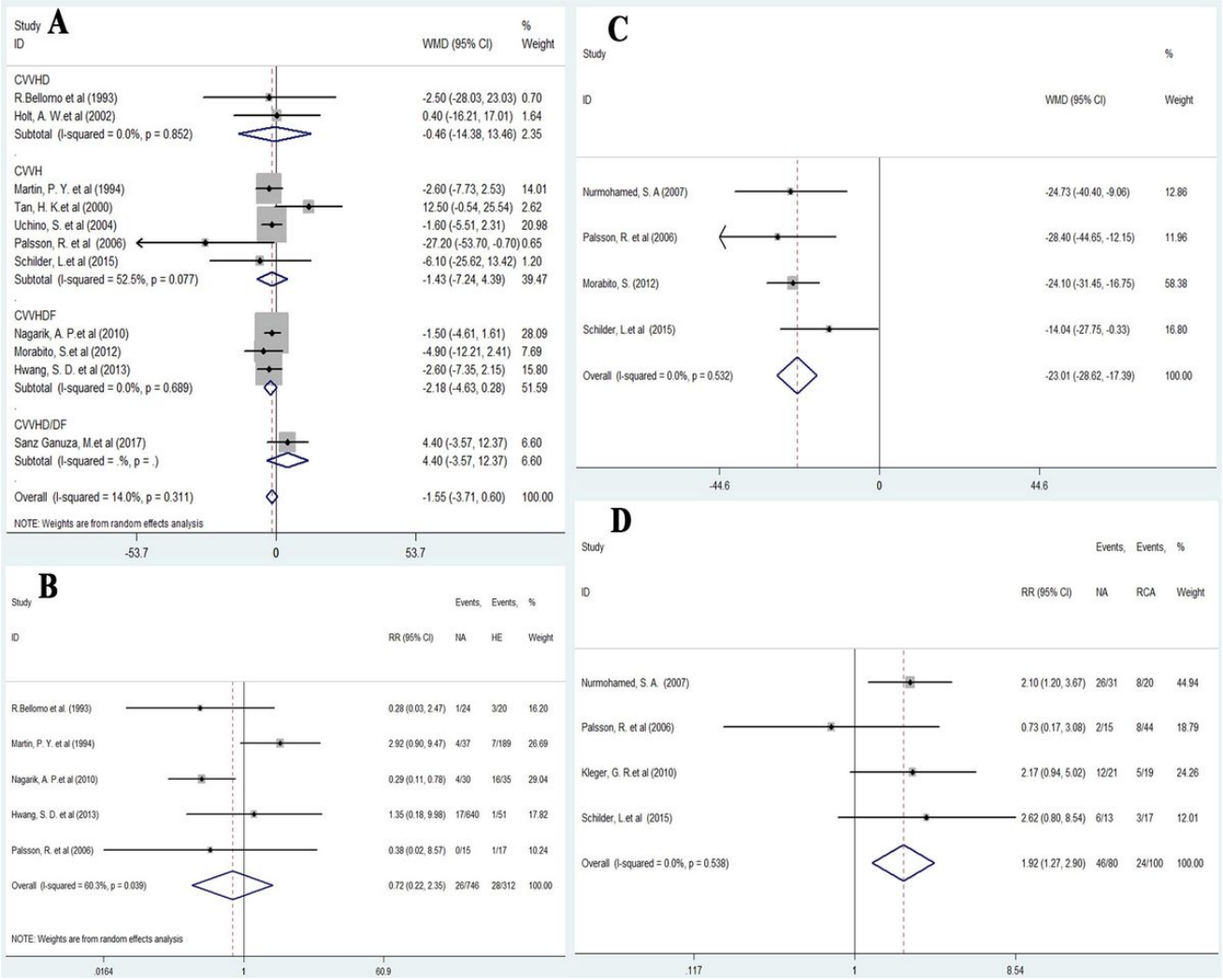

Figure 4

Forest plot of comparison between anticoagulation-free group and systemic heparin group, outcomes: filter lifespan (A), bleeding (B), and between anticoagulation-free group and RCA group, outcomes: filter lifespan (C), filter clotting (D). CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; NA, no anticoagulation; RCA, regional citrate anticoagulation; WMD, weighted mean difference; RR, risk ratio.

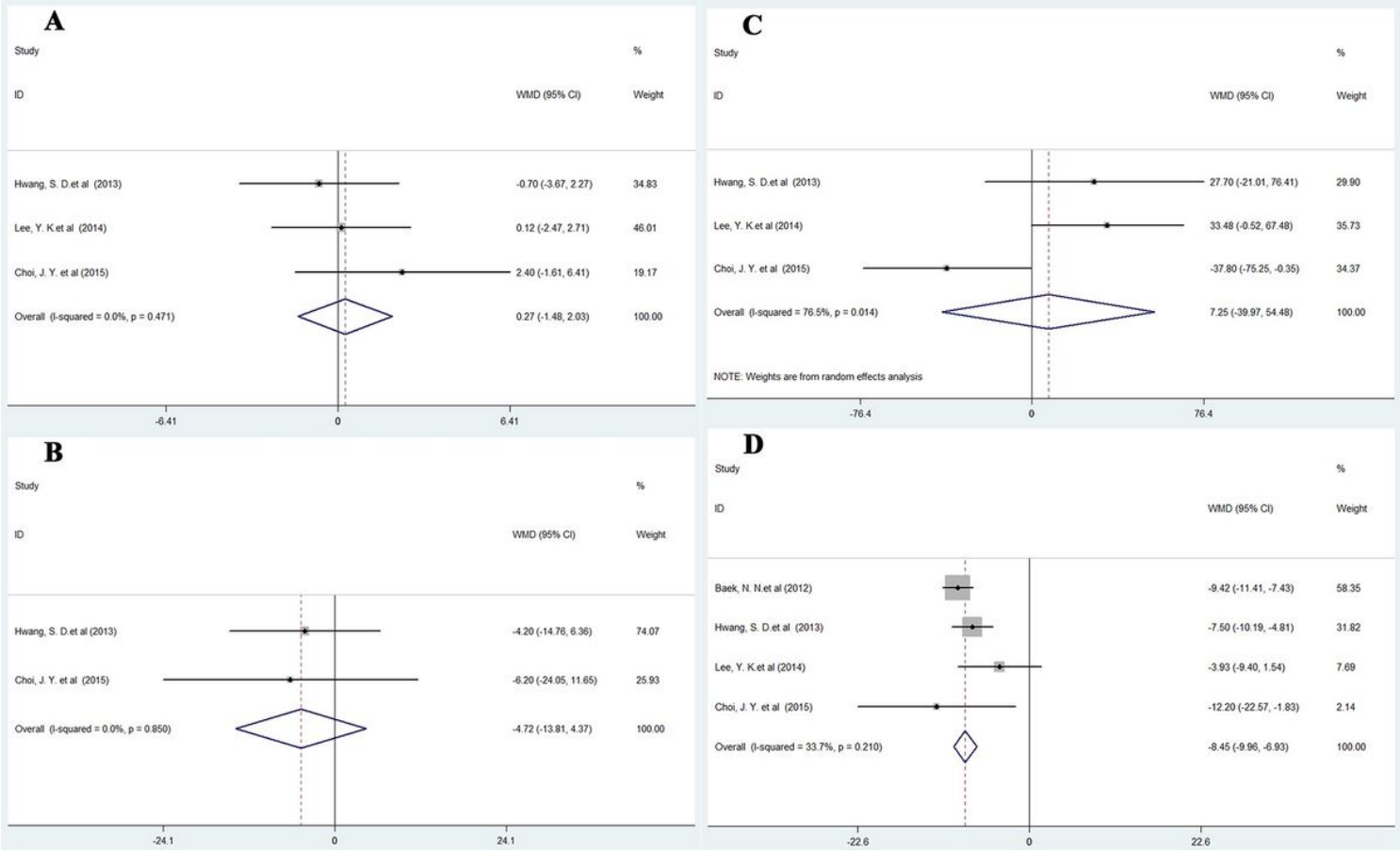

Figure 5

Forest plot of comparison between anticoagulation-free group and nafamostat group. Outcomes: APACHE II score (A), APTT (B), and PLT (C) before CRRT, and filter lifespan (D). WMD, weighted mean difference.

Supplementary Files

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- Additionalfile1TableS1.docx
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- FigureS1.tif
- Additionalfile4TableS4.docx
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- Additionalfile3TableS3.docx