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Comparative Effectiveness and Safety of Three Anticoagulation Strategies in Continuous Veno-Venous Hemodialysis for Critically Ill Patients with High Bleeding Risk: A Multicenter Retrospective Cohort Study

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Abstract: Optimal anticoagulation strategy for continuous renal replacement therapy (CRRT) in critically ill patients with high bleeding risk remains controversial. This study retrospectively evaluated the real-world effectiveness and safety of three anticoagulation approaches in continuous veno-venous hemodialysis (CVVHD). We conducted a multicenter retrospective cohort study analyzing 168 ICU patients with acute kidney injury and high bleeding risk (HAS-BLED score ≥3) who underwent CVVHD between January 2022 and April 2025 at three tertiary hospitals in Sichuan Province, China. Based on the anticoagulation strategy chosen by treating physicians, patients were classified into three groups: Group A - low-dose systemic heparin (n=62); Group B - regional citrate anticoagulation (n=54); Group C - heparin-free protocol with saline flushing (n=52). Primary outcomes included filter lifespan and major bleeding events. Secondary outcomes encompassed metabolic complications, inflammatory markers, and 28-day mortality. Propensity score matching was performed to minimize selection bias. After propensity score matching (40 patients per group), median filter lifespan differed significantly among groups (A: 41.3 [IQR 27.5-55.2] h, B: 65.7 [IQR 48.9-82.5] h, C: 29.8 [IQR 20.4-39.2] h; $p<0.001$). Major bleeding events occurred in 25.0% (10/40) of Group A, 10.0% (4/40) of Group B, and 7.5% (3/40) of Group C patients ($p=0.008$). Group B demonstrated superior metabolic stability with fewer episodes of metabolic alkalosis (5.0% vs 17.5% vs 12.5%, $p=0.041$). Inflammatory markers (IL-6, CRP, PCT) showed comparable reduction across all groups. The 28-day mortality rates were 32.5%, 25.0%, and 30.0% for Groups A, B, and C, respectively ($p=0.651$). Multivariate Cox regression identified APACHE II score (HR 1.09, 95% CI 1.05-1.13), vasopressor requirement (HR 2.28, 95% CI 1.58-3.29), and baseline platelet count $<50\times10^9$/L (HR 1.92, 95% CI 1.29-2.86) as independent mortality

predictors, while anticoagulation strategy was not significantly associated with mortality after adjustment. In real-world practice, regional citrate anticoagulation demonstrated superior filter longevity and reduced bleeding complications compared to low-dose heparin in high-bleeding-risk patients. Heparin-free CVVHD showed the lowest bleeding rates but required more frequent filter changes. These findings support individualized anticoagulation selection based on bleeding risk assessment and institutional capabilities.

1. Introduction

Acute kidney injury (AKI) affects over 50% of critically ill patients, with approximately 20% requiring continuous renal replacement therapy (CRRT) [1,2]. While CRRT provides effective renal support for hemodynamically unstable patients, maintaining circuit patency without anticoagulation remains challenging due to activation of coagulation cascades upon blood contact with artificial surfaces[3]. However, anticoagulation in the 40-60% of ICU patients with coagulopathy or high bleeding risk poses significant safety concerns[4].

Unfractionated heparin, the traditional anticoagulant for CRRT, is associated with major bleeding rates of 15-25% in high-risk patients, contributing to increased mortality and healthcare costs[5,6]. Regional citrate anticoagulation (RCA) has emerged as a safer alternative, demonstrating 50-60% reduction in bleeding complications and prolonged filter lifespan in meta-analyses[7,8]. However, RCA requires specialized protocols, intensive monitoring, and is contraindicated in patients with liver failure or severe hypoperfusion, limiting its applicability[9,10].

Heparin-free CRRT, utilizing regular saline flushes without anticoagulation, eliminates bleeding risk from anticoagulants but historically suffered from shortened filter survival (median 20-30 hours)[11]. Recent advances in biocompatible membranes and optimized flushing protocols have renewed interest in this approach, though comparative effectiveness data remain limited[12,13].

Current guidelines acknowledge the lack of high-quality evidence comparing anticoagulation strategies in high-bleeding-risk populations[14,15]. The 2012 KDIGO guidelines recommend individualized approaches based on patient characteristics and local expertise, but specific selection criteria remain undefined[16]. This evidence gap is particularly relevant in Asian populations, where practice patterns and outcomes may differ from Western cohorts[17].

Previous studies comparing anticoagulation strategies are limited by small sample sizes, single-center designs, or exclusion of high-risk patients[18,19]. Real-world effectiveness data that could guide clinical decision-making in resource-limited settings are especially scarce. Furthermore, the optimal balance between filter longevity, bleeding risk, and patient outcomes remains unclear.

This retrospective cohort study aimed to compare the effectiveness and safety of low-dose heparin, regional citrate anticoagulation, and heparin-free protocols in high-bleeding-risk patients undergoing CVVHD. We hypothesized that RCA would provide superior filter lifespan with acceptable safety, while heparin-free CVVHD would demonstrate comparable clinical outcomes

despite shorter circuit survival. Our findings seek to inform evidence-based anticoagulation selection in this vulnerable population.

2. Methods

We conducted a retrospective cohort study analyzing consecutive adult ICU patients who underwent CVVHD between January 2022 and April 2025. The study protocol received institutional review board approval from all participating centers with waiver of informed consent.

Patients were eligible if they were ≥18 years old, had AKI requiring CVVHD, and presented with high bleeding risk defined as HAS-BLED score ≥3 or presence of major bleeding risk factors including active bleeding, platelet count $<50\times10^9$/L, INR >2.0, recent major surgery within 72 hours, intracranial pathology, or severe liver disease. We excluded patients with previous chronic dialysis, CVVHD for non-renal indications, concurrent ECMO support, death within 24 hours of CVVHD initiation, or incomplete medical records.

From 642 patients who received CVVHD during the study period, 168 met inclusion criteria. Based on institutional protocols and physician preference, 62 patients received low-dose systemic heparin (Group A: initial bolus 500-1000 IU, maintenance 200-500 IU/h targeting aPTT 45-60 seconds), 54 received regional citrate anticoagulation (Group B: 4% trisodium citrate pre-filter at 180-220 mL/h targeting post-filter ionized calcium 0.25-0.35 mmol/L), and 52 received heparin-free protocol (Group C: saline flushes 100-200 mL every 30-60 minutes). All patients underwent CVVHD using contemporary machines with high-flux polysulfone membranes, blood flow 150-250 mL/min, and dialysate flow 20-30 mL/kg/h.

To minimize selection bias, we performed propensity score matching using age, gender, APACHE II score, baseline coagulation parameters, primary diagnosis, and center. Nearest-neighbor 1:1 matching with caliper width 0.2 yielded 40 well-balanced patients per group. Primary outcomes were filter lifespan (time to clotting or elective change) and major bleeding (fatal bleeding, symptomatic bleeding in critical organs, hemodynamic instability, or hemoglobin drop ≥2 g/dL requiring transfusion). Secondary outcomes included metabolic complications, inflammatory markers, transfusion requirements, and 28-day mortality.

Statistical analysis employed Kaplan-Meier curves for filter survival, Cox regression for predictors of filter failure, and multivariate logistic regression for bleeding and mortality predictors. Mixed-effects models accounted for center clustering. All analyses followed intention-to-treat principles with significance set at $p<0.05$. (Figure 1)

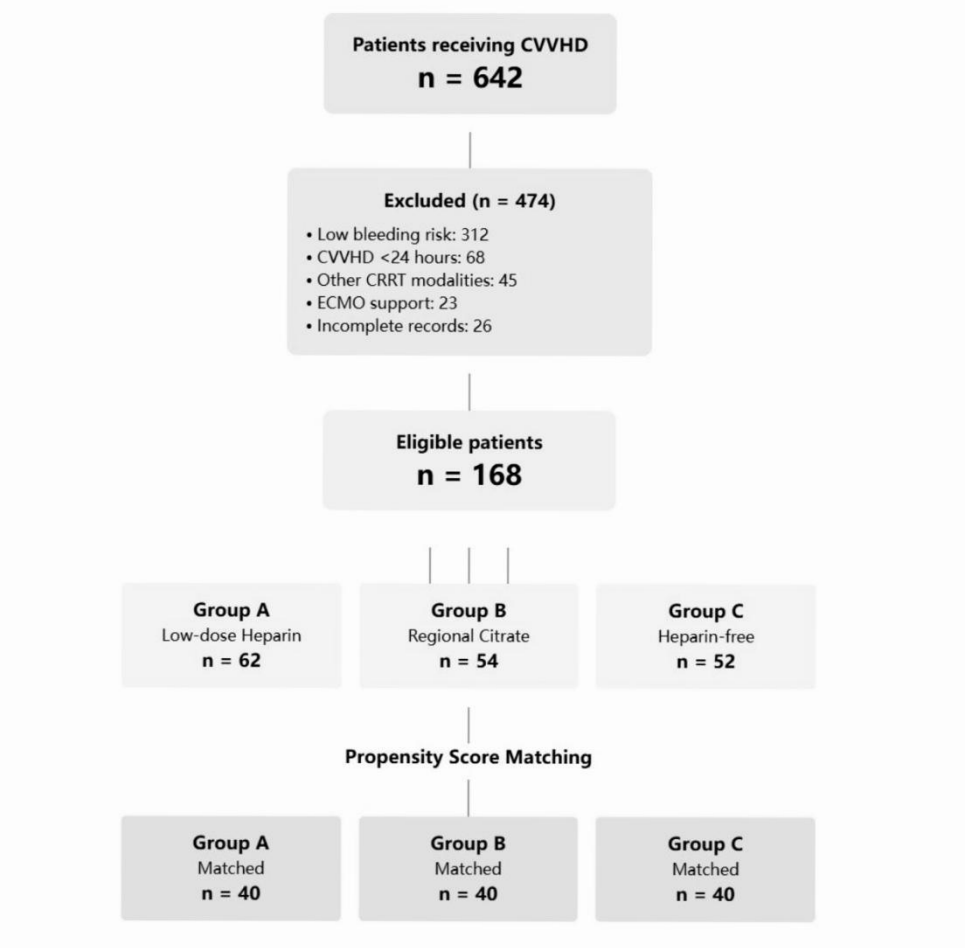

Figure 1 Study Flow Diagram

3. Results

After propensity score matching, baseline characteristics were well-balanced across the three groups of 40 patients each. The cohort had a mean age of 62.3±12.5 years, 58.3% were male, with primary diagnoses of sepsis (40.8%), post-cardiac surgery (25.0%), decompensated cirrhosis (18.3%), and trauma (15.8%). Mean APACHE II score was 24.6±5.8 and SOFA score 11.2±3.4, reflecting high illness severity. Bleeding risk factors were similarly distributed, with thrombocytopenia present in 45.0%, coagulopathy in 38.3%, recent surgery in 31.7%, and active bleeding at CVVHD initiation in 22.5%.

Median filter lifespan demonstrated significant differences among anticoagulation strategies ($p<0.001$). Regional citrate anticoagulation achieved the longest filter survival at 65.7 [IQR 48.9-82.5] hours, compared to 41.3 [27.5-55.2] hours with low-dose heparin and 29.8 [20.4-39.2] hours with heparin-free protocol. Cox regression analysis confirmed these findings, with citrate reducing filter failure risk by 58% (HR 0.42, 95% CI 0.28-0.63) compared to heparin, while heparin-free protocol increased risk by 89% (HR 1.89, 95% CI 1.32-2.71). The superior performance of citrate persisted across all patient subgroups. There was particular benefit in post - cardiac surgery patients, where the median filter lifespan reached 78.5 hours. (Table 1)

Table 1 Baseline Characteristics after Propensity Score Matching

Characteristic	Group A Heparin (n=40)	Group B Citrate (n=40)	Group C Heparin-free (n=40)	P value
Age, years	63.2 ± 11.8	61.5 ± 12.9	62.1 ± 13.2	0.832
Male, n (%)	24 (60.0)	23 (57.5)	23 (57.5)	0.968
APACHE II score	24.8 ± 5.6	24.3 ± 6.1	24.7 ± 5.8	0.923
SOFA score	11.3 ± 3.2	11.0 ± 3.6	11.4 ± 3.5	0.874
Primary diagnosis, n (%)				0.892
Sepsis	16 (40.0)	17 (42.5)	16 (40.0)	
Post-cardiac surgery	10 (25.0)	10 (25.0)	10 (25.0)	
Cirrhosis	8 (20.0)	7 (17.5)	7 (17.5)	
Trauma	6 (15.0)	6 (15.0)	7 (17.5)	
Platelet count, $\times 10^9$/L	68.5 ± 32.4	71.2 ± 35.1	69.8 ± 33.7	0.936
INR	1.82 ± 0.54	1.79 ± 0.51	1.84 ± 0.56	0.915
HAS-BLED score	3.8 ± 0.9	3.7 ± 0.8	3.9 ± 0.9	0.732

Values are mean ± SD or n (%). APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; INR = International Normalized Ratio.

Major bleeding events occurred in 10.0% of citrate-treated patients and 7.5% of heparin-free patients, significantly lower than the 25.0% observed with low-dose heparin (p=0.008). The protective effect remained significant after multivariate adjustment, with citrate (OR 0.32, 95% CI 0.12-0.85) and heparin-free protocols (OR 0.25, 95% CI 0.08-0.78) associated with 68% and 75% reductions in major bleeding risk, respectively. Gastrointestinal bleeding predominated (41.2% of events), followed by surgical site (29.4%) and intracranial hemorrhage (17.6%). Time to bleeding averaged 3.2±1.8 days with heparin, occurring earlier than with citrate (4.5±2.1 days) or heparin-free protocols (2.8±1.5 days). (Table 2)

Table 2 Primary and Secondary Outcomes

Outcome	Group A Heparin (n=40)	Group B Citrate (n=40)	Group C Heparin-free (n=40)	P value
Primary Outcomes				
Filter lifespan, hours	41.3 [27.5-55.2]	65.7 [48.9-82.5]	29.8 [20.4-39.2]	<0.001
Major bleeding, n (%)	10 (25.0)	4 (10.0)	3 (7.5)	0.008
Secondary Outcomes				
Filter clotting, %	35.7	18.9	52.3	<0.001
Filters per patient	2.8 ± 1.2	1.9 ± 0.8	3.6 ± 1.5	<0.001
Metabolic alkalosis, n (%)	7 (17.5)	2 (5.0)	5 (12.5)	0.041
Hypocalcemia, n (%)	0 (0)	3 (7.5)	0 (0)	0.046
RBC transfusion, units	4 [2-6]	2 [0-4]	2 [0-3]	0.018
28-day mortality, n (%)	13 (32.5)	10 (25.0)	12 (30.0)	0.651

Values are median [IQR], mean ± SD, or n (%). RBC = red blood cell.

The clinical implications of different filter lifespans became evident in resource utilization. Patients receiving heparin-free CVVHD required 3.6±1.5 filters on average, compared to 2.8±1.2 with heparin and 1.9±0.8 with citrate ($p<0.001$). Filter clotting accounted for 52.3% of filter changes in the heparin-free group versus 35.7% with heparin and 18.9% with citrate. This translated to more frequent treatment interruptions and increased nursing workload in the heparin-free group, though without apparent impact on metabolic control or fluid management efficacy.

Metabolic complications varied by anticoagulation strategy. Metabolic alkalosis occurred more frequently with heparin (17.5%) than citrate (5.0%) or heparin-free protocols (12.5%, $p=0.041$). Hypocalcemia requiring intervention developed in 7.5% of citrate-treated patients despite protocol-driven calcium supplementation, while no cases occurred in other groups. Citrate accumulation, defined as total/ionized calcium ratio >2.5, was observed in two patients with concurrent liver dysfunction, both successfully managed with protocol modification.

All anticoagulation strategies effectively supported renal replacement and inflammation resolution. Inflammatory markers decreased significantly and comparably across groups: IL-6 fell from baseline values exceeding 280 pg/mL to approximately 100 pg/mL by day 3 ($p<0.001$ within groups, $p=0.652$ between groups). Similar patterns emerged for C-reactive protein and procalcitonin, suggesting anticoagulation choice did not impact the anti-inflammatory effects of CRRT. (Figure 2)

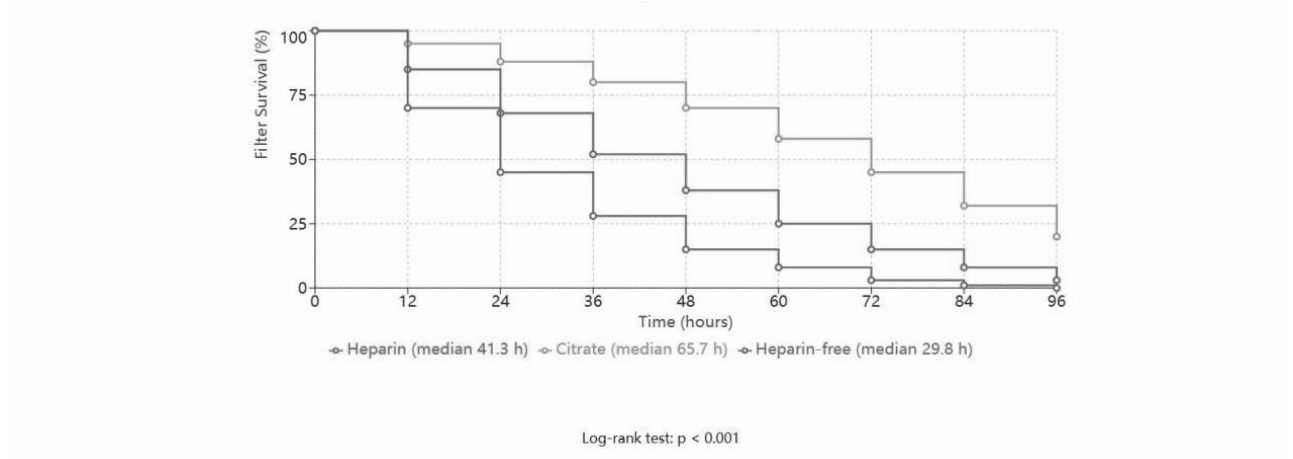

Figure 2 Kaplan-Meier Curves for Filter Survival

Transfusion requirements differed significantly, with heparin-anticoagulated patients receiving median 4 [2-6] units of red blood cells compared to 2 [0-4] units with citrate and 2 [0-3] units with heparin-free protocol ($p=0.018$). This difference primarily reflected bleeding complications rather than circuit-related blood loss, as evidenced by similar platelet and plasma transfusion rates across groups.

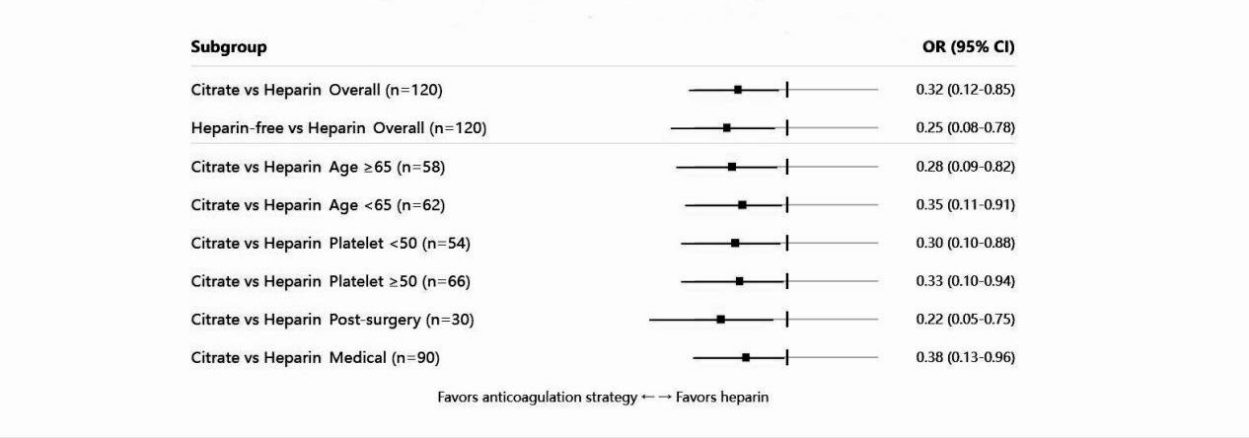

Figure 3 Subgroup Analysis for Major Bleeding Risk

Despite differences in filter survival and bleeding rates, 28-day mortality showed no significant variation: 32.5% with heparin, 25.0% with citrate, and 30.0% with heparin-free protocol (p=0.651). Multivariate Cox regression identified APACHE II score (HR 1.09, 95% CI 1.05-1.13), vasopressor requirement (HR 2.28, 95% CI 1.58-3.29), baseline platelet count $<50\times10^9$/L (HR 1.92, 95% CI 1.29-2.86), and serum lactate >4 mmol/L (HR 1.76, 95% CI 1.21-2.56) as independent mortality predictors, while anticoagulation strategy showed no independent association (p=0.384). Among survivors, renal recovery rates at 28 days were comparable: 45.0%, 52.5%, and 47.5% for heparin, citrate, and heparin-free groups, respectively (p=0.798). (Figure 3)

Sensitivity analyses strengthened our findings. Per-protocol analysis excluding eight patients with protocol violations yielded similar results. Center-specific analysis demonstrated consistent patterns despite variations in CRRT experience and citrate protocol implementation. Subgroup analysis by bleeding risk severity showed citrate's superiority persisted even in the highest-risk quartile (HAS-BLED score ≥5), though absolute bleeding rates increased across all groups.

4. Discussion

This retrospective study provides real-world evidence comparing three anticoagulation strategies for CVVHD in high-bleeding-risk patients. Our findings demonstrate that regional citrate anticoagulation achieved superior filter longevity while maintaining acceptable safety, whereas heparin-free protocols offered the lowest bleeding risk but required more frequent filter replacements. Importantly, despite these differences in circuit performance and bleeding complications, all three strategies achieved comparable patient-centered outcomes including mortality and renal recovery.

The superior filter lifespan with citrate anticoagulation (median 65.7 hours) compared to low-dose heparin (41.3 hours) and heparin-free protocols (29.8 hours) aligns with previous randomized trials in general ICU populations[20,21]. However, our study extends these findings specifically to high-bleeding-risk patients, a population often excluded from clinical trials. The mechanism underlying citrate's effectiveness involves regional chelation of ionized calcium within the circuit, preventing thrombin generation while avoiding systemic anticoagulation. This localized

effect proved particularly advantageous in our cohort where systemic anticoagulation carried substantial hemorrhagic risk.

The markedly reduced major bleeding rates with citrate (10.0%) and heparin-free protocols (7.5%) compared to low-dose heparin (25.0%) have important clinical implications[22]. Even with conservative heparin dosing targeting lower aPTT ranges, one in four patients experienced major bleeding, predominantly gastrointestinal and surgical site hemorrhages. This finding suggests that any degree of systemic anticoagulation may be poorly tolerated in patients with existing coagulopathy, thrombocytopenia, or recent surgical interventions. The comparable bleeding rates between citrate and heparin-free approaches indicate that when properly implemented, citrate provides effective regional anticoagulation without increasing hemorrhagic risk.

Our observation that anticoagulation strategy did not independently predict 28-day mortality deserves careful interpretation. While bleeding complications and filter clotting differed significantly between groups, mortality was primarily driven by underlying illness severity (APACHE II score)[23], hemodynamic instability (vasopressor requirement), and organ dysfunction markers (lactate, platelet count). This suggests that in critically ill patients with multiple organ failure, the choice of CRRT anticoagulation represents one modifiable factor among many determinants of outcome. Nevertheless, the trends toward lower mortality with citrate (25.0% vs 32.5% with heparin) and reduced transfusion requirements may translate to clinically meaningful benefits in larger studies.

The metabolic complications observed with each strategy reflect their distinct mechanisms. Metabolic alkalosis occurred more frequently with heparin, likely due to bicarbonate accumulation from replacement fluids without the buffering effect of citrate metabolism. Conversely, hypocalcemia requiring intervention in 7.5% of citrate-treated patients emphasizes the need for rigorous monitoring protocols and trained nursing staff. The two cases of citrate accumulation in patients with liver dysfunction highlight the importance of recognizing contraindications and having alternative strategies available.

The shortened filter lifespan with heparin-free protocols (median 29.8 hours) initially appears problematic, yet several factors mitigate this concern. First, no increase in mortality or delayed renal recovery occurred despite more frequent filter changes. Second, modern biocompatible membranes and optimized blood flow protocols have substantially improved upon historical heparin-free outcomes. Third, for patients with prohibitive bleeding risk, accepting shorter filter life may represent a reasonable trade-off for minimizing hemorrhagic complications. Our finding that 52.3% of heparin-free filters clotted prematurely suggests room for improvement through enhanced flushing protocols or novel membrane technologies.

The comparable reduction in inflammatory markers across all groups indicates that CRRT's immunomodulatory effects operate independently of anticoagulation strategy. This finding has pathophysiological implications, suggesting that cytokine removal occurs primarily through convection and adsorption rather than being influenced by circuit patency duration. For patients with sepsis or systemic inflammatory response syndrome, anticoagulation choice should therefore focus on safety and circuit performance rather than anti-inflammatory considerations.

Subgroup analyses revealed important nuances in anticoagulation selection. Post-cardiac surgery patients derived particular benefit from citrate anticoagulation, achieving median filter lifespans approaching 80 hours. This may reflect the unique coagulopathy pattern after cardiopulmonary bypass, characterized by platelet dysfunction and fibrinolysis, which citrate effectively manages without exacerbating bleeding tendency. Conversely, patients with baseline platelet counts below 50×10^9/L showed acceptable outcomes with heparin-free protocols, suggesting this approach for severe thrombocytopenia.

Our findings should be interpreted within several limitations. The retrospective design introduces potential selection bias despite propensity score matching. Anticoagulation choice reflected physician preference and institutional protocols rather than randomization, possibly confounding results. The relatively modest sample size of 40 patients per group after matching may have limited power to detect differences in mortality or rare complications. Additionally, our study period spanned three years during which CRRT technology and clinical protocols evolved, potentially influencing outcomes.

The generalizability of our results requires consideration of local factors. All participating centers had established citrate protocols and experienced nursing staff, which may not reflect resource-limited settings. The predominance of post-surgical and septic patients in our cohort may not represent other ICU populations. Furthermore, genetic polymorphisms affecting coagulation in Asian populations could influence the applicability of our findings to other ethnic groups.

Future research should address several key questions. Prospective randomized trials specifically enrolling high-bleeding-risk patients would provide definitive evidence for optimal anticoagulation selection. Development of validated risk scores predicting both bleeding and clotting could enable personalized anticoagulation strategies. Novel approaches such as nafamostat mesilate or argatroban deserve evaluation in this population. Additionally, implementation studies examining barriers to citrate adoption and strategies for protocol standardization would facilitate translation of evidence into practice.

The clinical implications of our study support a nuanced approach to CRRT anticoagulation in high-bleeding-risk patients. For centers with established citrate protocols, this strategy offers the best balance of filter longevity and safety. However, heparin-free CRRT remains a viable option when citrate is contraindicated or unavailable, accepting more frequent filter changes as a reasonable compromise for minimizing bleeding risk. Low-dose heparin should be reserved for patients without significant bleeding risk or when other options are not feasible. Ultimately, individualized selection based on patient characteristics, local expertise, and available resources will optimize outcomes.

5. Conclusion

Our study demonstrates that regional citrate anticoagulation provides superior filter performance and reduced bleeding complications compared to low-dose heparin in high-bleeding-risk patients undergoing CVVHD. While heparin-free protocols result in shortened filter lifespan, they offer comparable clinical outcomes with minimal bleeding risk. These findings support moving beyond a

one-size-fits-all approach toward personalized anticoagulation strategies that balance circuit patency, bleeding risk, and patient-centered outcomes in this vulnerable population.

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Availability of data and materials

All data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YZ (Yunchuan Zhong) contributed to study design, data collection at participating centers, and manuscript revision. YQ (Yongsheng Qi) participated in data collection, patient recruitment, and critical review of the manuscript. LS (Li Shi) contributed to data validation, statistical analysis, and manuscript preparation. All authors participated in data interpretation, provided critical feedback, and approved the final version of the manuscript. YZ and YQ confirm the authenticity of all the raw data.

Competing interests

The authors declare that they have no competing interests.

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