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Original article

Effects of continuous venous-venous hemofiltration with or without hemoperfusion on patients with hypertriglyceride acute pancreatitis

Ying Wang [a,b], Gao-fan Dai [a,b], Wen-biao Xiao [a,b], Jing-shi Shi [a,b], Bing-wen Lin [a,b], Jian-dong Lin [a,b,*], Xiong-jian Xiao [a,b,*]

[a] Department of Intensive Care Units, the First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China
[b] Department of Intensive Care Units, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou 350212, China

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ABSTRACT

Background: The role of continuous venous-venous hemofiltration (CVVH) and combined CVVH with hemoperfusion (HP) in patients with acute pancreatitis (AP) is diverse. We hypothesized HP+CVVH, rather than CVVH alone, could have significant benefits in hypertriglyceridemia (HTG)-AP patients.
Methods: This single-center retrospective study included 347 patients with hypertriglyceride (HTH) -AP treated from January 2020 to December 2023. We assessed the association of short- and long-term outcomes (including incidence of systemic and local complications, length of ICU and hospital stays, and costs) between the HP+CVVH and CVVH groups. A subgroup analysis was performed to explore the effects of heterogeneity upon the incidence of severe AP (SAP).
Results: Among 86 included patients, 40 received HP+CVVH therapy, and 46 received CVVH. Subgroup analysis revealed a lower incidence of severe AP after HP+CVVH therapy in patients with high procalcitonin, C-reactive protein, and interleukin-6 levels (46.4 % vs. 80.0 %, $p = 0.019$; 33.3 % vs. 72.7 %, $p = 0.010$; 37.5 % vs. 79.2 %, respectively). A significantly decreased hospital length of stay (LOS) in the HP+CVVH group was observed (10.40 [8.63–12.17] vs. 15.48 [13.02–17.94] days, $p = 0.001$). Furthermore, HP+CVVH showed a tendency towards lower hospital costs than CVVH ($5128 [4312–5943] vs. $8168 [6416–9920], $p = 0.001$). No significant differences were observed in the incidence of systemic or local complications, recurrence rates, or quality of life.
Conclusions: The use of HP+CVVH yielded superior outcomes in terms of the incidence of SAP compared to that of CVVH, for HTG-AP patients with a high inflammatory burden.

Introduction

Acute pancreatitis (AP) is a common gastrointestinal disorder that warrants hospitalization, with a mortality rate of 20–40 % in moderate or severe cases [1]. Gallstones and alcohol abuse remain the most frequent etiologies of AP worldwide [1,2]. As hypertriglyceridemia (HTG) is considered to be associated with AP, a clear upward tendency has been observed, and it is the second leading cause of AP in certain countries [3].

Cytokine cascades and oxidative stress play prominent roles in AP [4]. Patients with HTG-AP are more likely to develop persistent systemic inflammatory response syndrome (SIRS) [5,6], thereby inducing a higher incidence of multiple organ dysfunction syndrome (MODS) and mortality [7]. The pathogenesis of HTG-AP has not yet been clarified, although it is suspected that inflammatory changes and capillary injury mediated by free fatty acids (triglyceride degradation products), hyper-viscosity, and ischemia resulting from chylomicrons are involved [8]. Rapid control of serum triglyceride (TG) levels and blocking the systemic inflammatory response are critical for HTG-AP treatment. A triglyceride reduction below 5.65 mmol/L is recommended to prevent further episodes of AP [9].

Continuous venous-venous hemofiltration (CVVH), one of the most widely used blood purification procedures, can reduce excessive levels of inflammatory cytokines through convection and adsorption [10], thereby downregulating the hyperactive inflammatory cascade. When high-volume CVVH is employed, trials have demonstrated a significant linear improvement in visceral functions, such as hemodynamics [11], arterial oxygenation, and lung function [12]. However, owing to the limitation of the transient phenomenon of adsorption and the variable cut-off of highly permeable membranes, CVVH has a restricted range of

* Corresponding authors.
E-mail addresses: linjd01680067@sina.com (J.-d. Lin), xxj1495@163.com (X.-j. Xiao).

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action. Hemoperfusion (HP) holds promise for compensating for CVVH deficiency. HP is shown to effectively reduce pro-inflammatory cytokines in patients with severe AP (SAP) [13,14]. Although the routine use of renal replacement therapy in AP is not recommended except for complicated by acute kidney injury (AKI), abdominal compartment syndrome (ACS), restrictive fluid management [15], recent studies imply good application prospects. A meta-analysis concluded that high-volume hemofiltration may reduce short-term mortality by decreasing the incidence of infection [16]. Compared to CVVH alone, HP+CVVH has been clinically demonstrated to decrease the concentration of pro-inflammatory cytokines and increase the 28-day survival rate in patients diagnosed with MODS [14].

To date, little is known about the contrast between HP+CVVH and CVVH in HTG-AP. Hence, we conducted a single-center retrospective cohort study to explore this question, with a particular focus on both clinical and economic outcomes.

Materials and methods

Study design and population

This retrospective study was conducted from January 2020 to December 2023, and data were consecutively obtained from a tertiary teaching hospital. Patients who met the diagnostic criteria of HTG-AP [17] and were admitted to the intensive care unit (ICU) were enrolled. The exclusion criteria were as follows: 1) prehospital hypolipidemic therapy with serum TG levels lower than 5.65 mmol/L on admission, 2) <48 h of hospital stay, 3) recurrent episodes of pancreatitis or acute attack of chronic pancreatitis, 4) with other etiologies of AP like gallstones and alcohol abuse and et al., and 5) pregnancy or age < 18 years. The local institutional review board approved the protocol (MTCA, ECFAH of FMU [2015]084–1).

Patient managements

Conventional treatment for AP was administered to all individuals, including fasting, controlled fluid resuscitation, antispasmodics and pain relief, and heparin administration. Low molecular weight heparin was subcutaneous injected at 5000 U once every 12 h starting from the admission day and lasting 14 days or until discharge [18]. For patients who could not tolerate minimal enteral feeding, parenteral nutrition support was provided until the acute gastrointestinal injury was graded as levels I-II. Antibiotics were administered if there were unambiguous signs of an intra- or extra-pancreatic infection. The initial empirical antibiotic regimen was cefoperazone-sulbactam based on the results of the antibiotic phase briefings at the hospital. Patients with acute respiratory failure (ARF) received either oxygen therapy (including high-flow oxygen therapy) or intubation and mechanical ventilation, based on the degree of respiratory failure. Mangiferin umbilical compress and rhubad enema therapy were administered to relieve abdominal distension.

In addition to conventional treatment, patients in the CVVH group received cycles of CVVH (changed every 24 h or at the occurrence of filter dysfunction) until triglyceride levels decreased to <5.65 mmol/L, while the HP+CVVH group received one cycle of HP (approximately 2–2.5 h), followed by cycles of CVVH. The treatment was initiated at the discretion of the treating physicians. Signed informed consent was obtained before renal replacement therapy (RRT). An HA330-type microporous resin cartridge (Zhuhai Jafron Biomedical Materials Co., Ltd., Zhuhai, China) and RENAFLO HF1200 filter were used. Blood flow was set at 180–250 mL/min. The CVVH dose was ≥ 35 ml/kg/hour, which was calculated on the basis of total effluent with correction for percentage predilution [19]. Heparin anticoagulation was administered unless contraindicated.

Data collection and outcomes

Outcomes included the incidence of systemic and local complications, hospital length of stay (LOS), ICU LOS, and hospitalization costs. Demographic characteristics, severity scores, and medical history were collected at baseline. During hospitalization, clinical, laboratory, and radiological findings were recorded. The collected data were verified for consistency.

The definition of SAP was according to the Atlanta classification and definitions [20]. The average number of hospitalizations were nearly 9 days based on our annual average LOS and as reported [21]. We defined short hospital LOS as < 9 days and prolonged hospital LOS as ≥ 9 days. A subgroup analysis was performed to explore the effects of heterogeneity. There was a gap in the cut-off of interleukin-6 (IL-6) in sepsis patients, varying from 273.8 to 310 pg/ml, as reported previously [22,23]. A previous study demonstrated that procalcitonin (PCT) ≥ 0.5ng/mL and C-reactive protein (CRP) ≥ 150 mg/L showed the highest sensitivity in predicting SAP [24]. Therefore, PCT ≥ 0.5 ng/mL, CRP ≥ 150 mg/L, and IL-6 ≥ 300 pg/ml were defined as high levels, otherwise as low levels. A score of 22.4 mmol/L of TG is considered the cut-off of severe and very severe hypertriglyceridemia [25]. TG level of 37.7 mmol/L have been proposed as the cut-off for predicting SAP [26]. Based on these findings, TG levels were classified as low (≤20 mmol/L), moderate (20 <TG >40 mmol/L), and high (≥ 40 mmol/L). Nucleic acid testing combined with clinical symptoms were used for the diagnosis of COVID-19 [27].

Statistical analysis

Statistical analysis was performed using IBM SPSS 27.0. After Kolmogorov–Smirnov test for normality was performed, continuous variables were compared via Student's t-test or one-way ANOVA followed by Tukey's multiple comparison test and expressed as the mean with standard deviations (SDs), while categorical parameters were compared via χ^2 test or Fisher's exact test and presented as frequencies and proportions, unless stated otherwise. Missing data were handled as lost without data imputation. Changes in data were analyzed by applying repeated-measures analysis of variance between the groups. All elements included in the study tended to show an association with hospital LOS, with a P value of <0.10 in univariate logistic regression, and were transferred to multivariate logistic regression to identify the significance of the association [28]. Statistical significance was defined as a two-sided p value < 0.05.

Results

Baseline characteristics

The enrollment process is schematically presented in Fig. 1. The total number of patients with AP in the hospital throughout the study period was 1311, of which 347 (26.47 %) had HTG-APs. The proportional increase, more prominent in patients admitted to the ICU, was clearly visible (accounting for 58.19 %). For patients admitted to the hospital more than once, only data on the first hospital stay during the first AP attack were included. There were 46 participants in the CVVH group and 40 in the HP+CVVH group. Surprisingly, all patients included received RRT. The most frequent reasons for initiating RRT were restrictive fluid management (43.5 %) in the CVVH group and inflammatory load (42.5 %) in the HP+CVVH group (Table 1). The time from the initial attack to the administration of therapy was indistinguishable (31.10 [26.25–35.95] vs. 32.04 [26.48–37.60] h, $p = 0.05781$; Table 1). The HP+CVVH group had higher triglyceride levels (37.79 [32.91–42.66] vs. 30.99 [24.00–37.96] mmol/L, $p < 0.001$; Table 1) and greater PCT concentrations (3.13 [1.25–4.99] vs. 2.93 [1.20–4.65] mmol/L, $p = 0.017$; Table 1) at admission than the CVVH group. Though not statistically significant, the HP+CVVH group tended to have higher IL-6 levels (429.90 [330.08–529.72] vs. 394.02 [290.15–497.90] mmol/L,

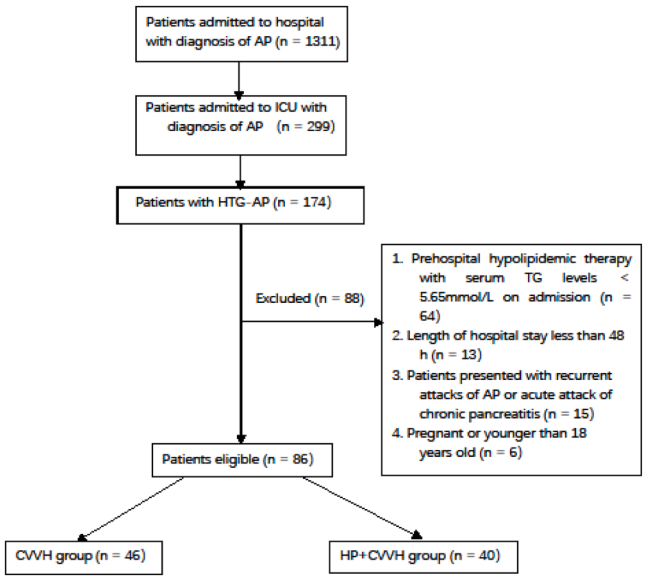

Fig. 1. Flow chart of enrollment.
AP: Acute Pancreatitis. HTG-AP: Hypertriglyceride Acute Pancreatitis. CVVH: Continuous Venous-Venous Hemofiltration. HP: Hemoperfusion. *The numbers of patients in line with items 1 and 2 were 6, with items 1 and 3 were 2, with items, with items 3 and 5 were 2.

p = 0.382; Table 1). No statistically significant differences were observed with respect to acute physiology and chronic health evaluation (APACHE) II scores (6.40 [5.43–7.37] vs. 5.46 [4.46–6.45], p = 0.097; Table 1) and Ranson scores (1.73 [1.44–2.01] vs. 1.67 [1.42–1.92], p = 0.868; Table 1).

Short-term outcomes

Systemic and local complications

The incidence of systemic complications, including ARF, acute kidney injury, shock, sepsis, gastrointestinal bleeding, and intra-abdominal hypertension (IAH), did not differ between the groups. A stress ulcer was confirmed as the cause of bleeding via gastroscopy. A comparable proportion of patients in both groups had SAP (21 % (52.5) vs. 29 % (63.0), p = 0.323; Table 2). The incidence of local complications was similar between the groups.

Subgroup analyses demonstrated dissimilar outcomes in terms of the incidence of SAP across different subgroups. Patients with high PCT, CRP, and IL-6 levels receiving HP+CVVH therapy had a decreased incidence of SAP compared with the CVVH group (46.4 % vs. 80.0 %, p = 0.019; 33.3 % vs. 72.7 %, p = 0.010; 37.5 % vs. 79.2 %, p = 0.003, respectively; Fig. 2). Results for high TG levels showed that CVVH resulted in a lower incidence of SAP than HP+CVVH (100.0 % vs. 42.9 %, p = 0.003; Fig. 2). Neither CVVH nor CVVH+HP group had significant influence on the incidence of SAP given COVID-19 negative and positive group (63.4 % vs. 58.3 %, p = 0.648; 60.0 % vs. 50.0 %, p = 0.764; Fig. 2).

Hospital LOS and ICU LOS

No remarkable between-group difference in length of ICU stay (ICU LOS) was observed (5.20 [4.37–6.03] vs. 5.85 [4.58–7.11] days, p = 0.860; Table 2); however, total hospital LOS was significantly shorter in the HP+CVVH group than in the CVVH group (10.40 [8.63–12.17] vs. 15.48 [13.02–17.94] days, p = 0.001; Table 2).

Predictors of hospital LOS

The results of the univariate and multivariate logistic regression analyses to detect the association between hospital LOS and clinical factors are presented in Table S1. The modalities of HP+CVVH, TG, blood glucose, urea nitrogen, and lactic acid were significant predictors of hospital LOS among patients with HTG-AP (area under the curve 0.899, 95 % confidence interval 0.823–0.976, p < 0.001; Fig. 3). The decision curve analysis for predicting hospital LOS is shown in Fig. 3. When the threshold probability was approximately 5–100 % predicted by the nomogram, the use of our predictors of hospital LOS would provide more benefits.

Table 1
Baseline patient characteristics.

	CVVH (n = 46)	HP+CVVH (n = 40)	P value
Age (yr.)	40.11 [36.51–43.71]	37.63 [35.77–39.48]	0.621
Male sex, n (%)	31 (67.4 %)	32 (80.0 %)	0.188
BMI (kg/cm^2)	25.67 [24.91–26.43]	25.21 [24.69–25.72]	0.893
Time from symptom onset to RRT (h)	32.04 [26.48–37.60]	31.10 [26.25–35.95]	0.078
Medical history			
Hypertension (%)	6 (13.0 %)	10 (25.0 %)	0.155
Diabetes (%)	14 (30.4 %)	7 (17.5 %)	0.164
Hyperlipidemia (%)	8 (17.4 %)	15 (37.5 %)	**0.036**
Smoking (%)	11 (24.4 %)	16 (40.0 %)	0.124
Cancer (%)	5 (10.9 %)	3 (7.5 %)	0.719
Laboratory Examination			
COVID-19 positive	5 (10.9 %)	4 (10.0 %)	0.895
CTSI scores	3.09 [2.48–3.69]	2.78 [2.56–2.99]	0.247
Hct (%)	0.44±0.05	0.45±0.06	0.363
LDH (U/L)	534.24 [400.93–667.55]	378.30 [326.23–430.37]	0.185
Triglyceride (mmol/L)	30.99 [24.00–37.96]	37.79 [32.91–42.66]	**<0.001**
Cholesterol (mmol/L)	13.93 [12.08–15.77]	16.61 [14.94–18.29]	**0.024**
BUN (mmol/L)	4.39 [3.82–4.96]	4.38 [3.79–4.97]	0.815
TBIL (μmol/L)	15.08 [12.68–17.47]	12.77 [11.04–14.49]	0.524
Procalcitonin (ng/ml)	2.93 [1.20–4.65]	3.13 [1.25–4.99]	**0.017**
CRP (mg/L)	177.23 [136.30–218.17]	172.07 [130.60–213.54]	0.972
IL-6 (pg/mL)	394.02 [290.15–497.90]	429.90 [330.08–529.72]	0.382
D-Di (mg/L)	1.43 [0.88–1.98]	1.16 [0.65–1.66]	0.151
Lactate (mmol/L)	2.35 [2.02–2.70]	2.75 [1.94–3.57]	0.876
SOFA scores	2.02 [1.52–2.53]	1.90 [1.60–2.20]	0.662
APACHE II scores	5.46 [4.46–6.45]	6.40 [5.43–7.37]	0.097
mMarshall scores	1.63 [1.27–1.99]	1.23 [1.04–1.41]	0.085
BiSAP scores	0.98 [0.78–1.18]	1.02 [0.80–1.25]	0.670
Ranson scores	1.67 [1.42–1.92]	1.73 [1.44–2.01]	0.868
VAS scores	4.70 [4.33–5.07]	4.38 [3.85–4.90]	0.302
SIRS (%)	34 (73.9 %)	30 (75.0 %)	0.908
Reasons for RRT start			
Inflammatory load	13 (28.9 %)	17 (42.5 %)	0.190
Restrictive fluid management	20 (43.5 %)	8 (20 %)	**0.020**
Severe acidosis	9 (19.6 %)	4 (10.0 %)	0.217

RRT: Renal replacement therapy (including HP+CVVH and CVVH only); CTSI: CT severity index; SOFA: sequential organ failure assessment; APACHE II: Acute physiology and chronic health evaluation II; VAS: visual analog scale. * Restrictive fluid management: Early fluid resuscitation is recommended for acute pancreatitis patients, but for patients with acute respiratory distress syndrome or intra-abdominal hypertension or some conditions, restrictive fluid management is an optimal regimen.

Therapy

After therapy, the null hypothesis of TG clearance within 24 h showed a difference between the groups (61.6 % [56.7–66.5] vs. 51.0 % [41.7–60.2], p = 0.225; Table 2). The HP+CVVH group had a shorter time of initiation of enteral nutrition than the CVVH group (3.10 [2.41–3.79] vs. 4.32 [3.48–5.16] days, p = 0.007; Table 2). Though the number of patients applying antibiotic in both groups were poorly differentiated, the HP+CVVH group had fewer time of antibiotic dosage

Table 2
The efficacy and prognostic outcomes of CVVH with or without HP on patients with HTG-AP.

	CVVH ($n = 46$)	HP+CVVH ($n = 40$)	*P*
Systemic Complications			
Respiratory failure (%)	29 (63. %)	29 (72.5 %)	0.357
AKI (%)	5 (10.9 %)	5 (12.5 %)	0.814
Shock (%)	3 (6.5 %)	1 (2.5 %)	0.620
Sepsis (%)	30 (65.2 %)	33 (82.5 %)	0.071
GI bleeding (%)	3 (6.5 %)	2 (5.0 %)	0.764
IAH (%)	10 (21.7 %)	6 (15.0 %)	0.423
SAP (%)	29 (63.0 %)	21 (52.5 %)	0.323
Local Complications			
Pancreatic and peripancreatic collections (%)	25 (54.3 %)	20 (50.0 %)	0.687
Acute necrotic collection (%)	0	3 (7.5 %)	0.097
Pancreatic pseudocyst (%)	1 (2.2 %)	2 (5.0 %)	0.595
Walled-off necrosis (%)	2 (4.3 %)	1 (2.5 %)	0.641
RRT Related Complications			
Thrombocytopenia (%)	4 (8.7 %)	3 (7.5 %)	0.840
Therapy			
Clearance rate of TG within 24 h (%)	51.0 [41.7–60.2] %	61.6 [56.7–66.5] %	0.225
Number of patients using antibiotic (%)	40 (87.0 %)	33 (82.5 %)	0.565
Average time of antibiotic (days)	8.89 [7.26–10.52]	6.35[4.85–7.85]	**0.029**
Average time of antibiotic use in regular wards (days)	4.13 [2.92–5.38]	2.10 [1.11–3.09]	**0.020**
Time of initiation of enteral nutrition (days)	4.32 [3.48–5.16]	3.10 [2.41–3.79]	**0.007**
Liquid balance of Day 1 (ml)	1707.16±909.76	2373.54±1072.95	**0.003**
Liquid balance of Day 2 (ml)	258.35±926.53	177.98±896.64	0.685
Sets of RRT	3.17 [2.69–3.66]	2.45 [2.23–2.67]	**0.010**
Duration of RRT (hours)	45.27 [34.97–55.57]	28.58 [23.92–33.23]	**<0.001**
ICU LOS (days)	5.85 [4.58–7.11]	5.20 [4.37–6.03]	0.860
Hospital LOS (days)	15.48 [13.02–17.94]	10.40 [8.63–12.17]	**0.001**
hospitalization costs ($)	8168 [6416–9920]	5128 [4312–5943]	**0.001**
Prognosis			
Recurrence (%)	6 (13.0 %)	6 (15.0 %)	0.794
GIQLI	121.93 [118.09–125.78]	123.30 [118.61–127.99]	0.438

AKI: Acute kidney injury; GI Bleeding: Gastrointestinal bleeding; IAH: Intra-. abdominal hypertension; SAP: Sever acute pancreatitis; DM: Diabetes; RRT: Renal replacement therapy; LOS: Length of stays; GIQLI: Gastrointestinal quality of life index.

and shorter duration of antibiotic use in regular wards (6.35 d [4.85–7.85] vs. 8.89 d [7.26–10.52], $p = 0.029$; 2.10 d [1.11–3.09] vs. 4.13 d [2.92–5.38], $p = 0.020$; Table 2). The fluid balance was measured daily, and results varied in Day 1 and Day 2 in groups (2373.54 ±1072.95 vs. 1707.16±909.76 ml, $p = 0.003$; 177.98±896.64 vs. 258.35±926.53 ml, $p = 0.685$; Table 2). Notably, the HP+CVVH intervention resulted in sets (2.45 [2.23–2.67] vs. 3.17 [2.69–3.66] days, $p < 0.010$; Table 2) and decreased time (28.58 [23.92–33.23] vs. 45.27 [34.97–55.57] hours, $p < 0.001$; Table 2) of RRT compared to the CVVH group.

Repeated-measures analysis of variance was performed (Supplementary Table S2). There was a significant and sharp drop in TG and IL-6 levels after the first day of RRT treatment (Fig. S1), which then decreased gradually with time. PCT and CRP levels increased early, peaked at 1 day, and then showed a progressive and significant decrease over time. There was a progressive decline in APACHE II and Sequential Organ Failure Assessment (SOFA) scores. No statistically significant differences were obtained among intergroup effect except for the APACHE II scores ($p = 0.033$; Supplementary Table S2).

Safety

Thrombocytopenia was detected in seven patients (four in the CVVH group and three in the HP+CVVH group; Table 2); however, once RRT was stopped, the platelet counts rapidly increased to normal. No other RRT-related adverse events were related to RRT.

Economic effectiveness

The HP+CVVH group showed a tendency toward lower hospitalization costs when compared with the CVVH group ($5128 [4312–5943] vs. $8168 [6416–9920], $p = 0.001$; Table 2).

Long-term outcomes

Recurrence rate

No patients were lost to follow-up; the average follow-up duration was 24.02±10.09 months. No significant difference was observed in terms of recurrence rate between groups (6 % (15.0) vs. 6 % (13.0), $p = 0.794$; Table 2).

Quality of life

Gastrointestinal quality of life index (GIQLI) scores was obtained in all participants, and the results were similar between the two groups (123.30 [118.61–127.99] vs. 121.93 [118.09–125.78], $p = 0.438$; Table 2).

Discussion

To the best of our knowledge, this is the first observational trial to compare the effects of CVVH and HP+CVVH treatment among patients with HTG-AP. Reductions in TG, PCT, CRP, IL-6, and SOFA scores were observed without differences between the groups. However, the HP+CVVH group had fewer time of antibiotic dosage, shorter duration of antibiotic use in regular wards, shorter initiation of enteral nutrition, decreased hospital LOS, and lower hospital costs. In patients with a high inflammatory load (high PCT, CRP, or IL-6 levels), a lower incidence of SAP attacks was observed.

AP is an acute inflammatory process of the pancreas of which 25 % are severe cases linked to systemic organ dysfunction and high mortality [29–31]. HTG-AP is associated with a greater prevalence of complications and patients are more likely to develop persistent SIRS [5,32]. To rapidly regulate TG levels below 5.65 mmol/L, taking a step further, a key to successful treatment is to block the cascade of inflammatory reactions [9,33]. In our study, the clearance rate of TG within 24 h in both CVVH group and HP+CVVH group were higher than 50 % without significant difference. But the mechanism is still unclear.

The most frequent reasons for initiating RRT in our study were restrictive fluid management (like AKI and ARDS) in the CVVH group and inflammatory load in the HP+CVVH group as recorded. We observed reductions in PCT, CRP and IL-6 without differences between the groups, which is similar with studies have reported. CVVH is initially recommended for the treatment of sepsis because of its potential action in the non-selective removal of pro- and anti-inflammatory mediators, thus protecting visceral functions [34,35]. SAP may mimic sepsis despite the absence of an infection site [36]. Pupelis et al. performed CVVH in 111 patients with SAP and found that it was safe and feasible [37]. Jiang et al. investigated the efficacy of eliminating cytokines using different CVVH filtration rates and found that high-volume and early CVVH application was associated with improved hemodynamic and survival rates in patients with AP [38]. Despite its promising avenues, CVVH does not allow macromolecules to penetrate a continuous hemofilter. “The peak concentration hypothesis,” which implies a cutting peak of soluble mediators, restricts the use of CVVH [34]. HP, as a scavenger, can adsorb hydrophobic substances bound to serum proteins and lipids and increase the clearance of inflammatory mediators, which compensates for the

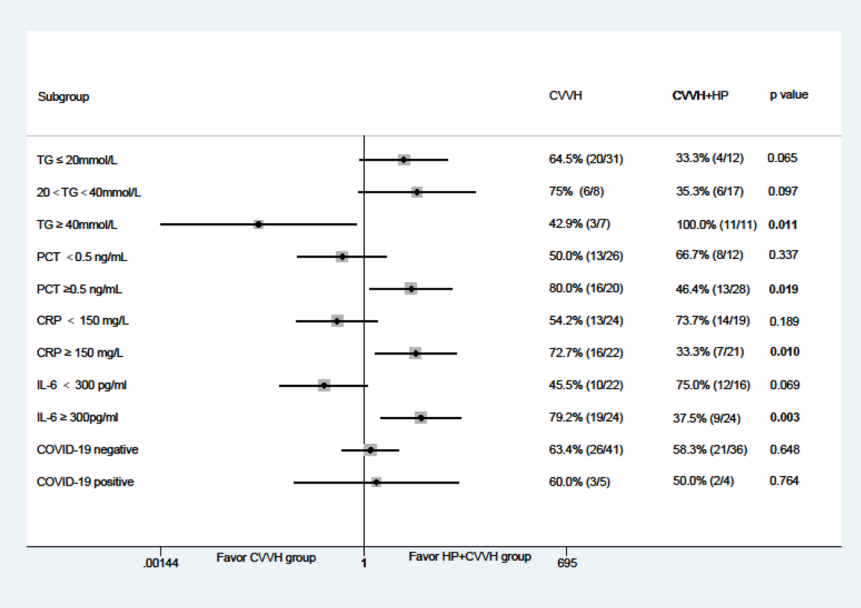

Fig. 2. Forest plots of subgroup analyses.
PCT ≥ 0.5ng/mL, CRP ≥ 150 mg/L or IL-6 ≥ 300 pg/ml was defined as high levels, otherwise as low levels. TG levels were classified as low (≤ 20 mmol/L), moderate (20 <TG >40 mmol/L), and high (≥ 40 mmol/L). Nucleic acid testing combined with clinical symptoms were used for the diagnosis of COVID-19.

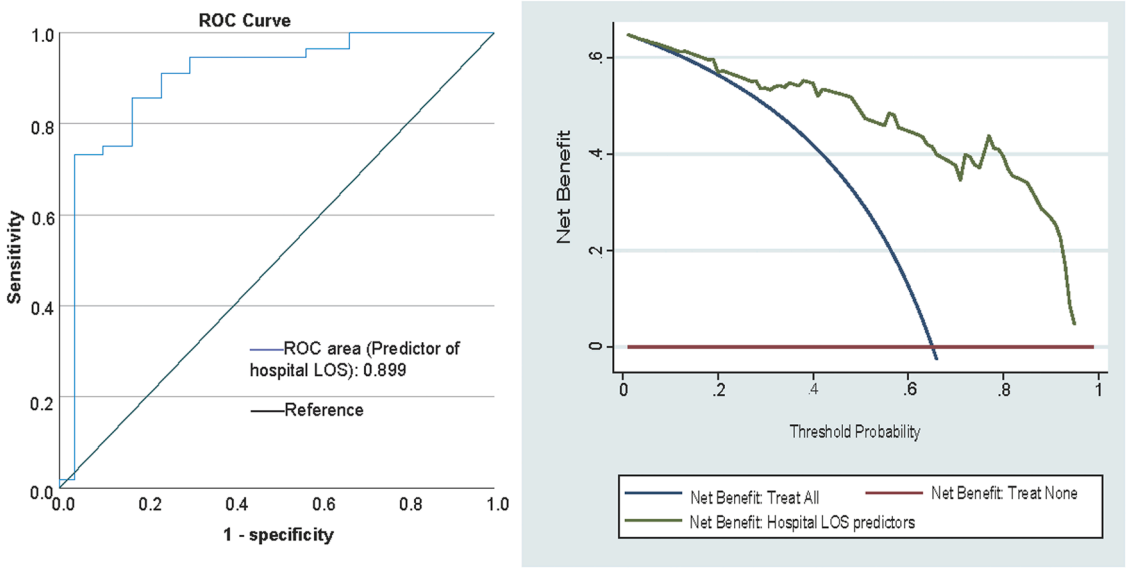

Fig. 3. ROC curve and DCA curve for predicting hospital LOS.
We defined short hospital LOS as <9 days while prolonged hospital LOS as ≥ 9 days. All elements included in the study tend to show an association with hospital LOS with a *P* value of <0.10 in univariate logistic regression were transferred to multivariate logistic regression to identify the significance of the association. The curve shows C-statistic of the five significant predictors (HP+CVVH therapy, TG, Glu, BUN and Lac) of short hospital LOS; predictive performance of 0.899. When the threshold probability was approximately 5–100 %, the DCA analysis indicated that the use of the five predictors (HP+CVVH therapy, TG, Glu, BUN and Lac) was beneficial than the mere treat-all-patients or treat-no-patients scheme. *TG: triglyceride; Glu: blood glucose; BUN: blood urea nitrogen; Lac: lactic acid.

shortcomings of CVVH [39,40]. In an observational trial of patients with SAP, a combination of hemodialysis and HP has been demonstrated to effectively remove toxic metabolites and decrease the incidence of complications and mortality [41].

We observed a decrease in the incidence of SAP following HP+CVVH therapy in patients with a high inflammatory load (with a high level of PCT, CRP, or IL-6) at admission. This discrepancy can be attributed to several factors. First, inflammatory mediators have been reported to be important in the development of AP and resulting MODS [42]. Targeting the reduction in pro-inflammatory mediators and blocking the progression of inflammation are crucial for the treatment of AP. As inflammatory markers, CRP and PCT have shown promising outcomes in predicting the severity of AP [24,43,44]. Liu et al. performed a prospective, randomized clinical trial, which came to the conclusion that after HP+CVVH rather than CVVH treatment only, the plasma concentrations of TNF-α, IL-1β and IL-6 were lower on the 5th day [14]. In our trial, we observed a continuously decreasing trend in PCT, CRP, and IL-6 concentrations with CVVH or HP+CVVH intervention over time. Second, previous trials regarded APACHE II as a suggestive and predictive tool for assessing AP severity and prognosis [45]. In our trial, a

significant downward trend in APACHE II scores was confirmed in the HP+CVVH group. The absence of severe underlying diseases and the young or middle-aged condition could be the causes of the lower APACHE II scores observed in our trial.

There is a high incidence of IAH in patients with SAP, usually occurring after extensive fluid resuscitation [46]. The prevention of progression to abdominal compartment syndrome (ACS) is a therapeutic strategy for IAH. Although we reported an IAH proportion of 18.6 %, no one developed ACS. The improved fluid balance observed in both groups implied less fluid accumulation, resulting in a lower incidence of ACS. The CVVH group reported a lower fluid balance on the first day of our trial, which could be partially due to the higher rate of restrictive fluid management in the group at admission.

Studies have shown that enteral nutrition can reduce the incidence of infectious complications, MODS, and mortality [47,48]. Compared to delayed enteral nutrition, early enteral nutrition started within 48 h after admission improves clinical outcomes [49]. We reported a decreased time to initiation of enteral nutrition and a shorter duration of antibiotic therapy after HP+CVVH therapy. The length of hospital rather than ICU stays in the HP+CVVH group was shorter than that in the control group. Shortened antibiotic usage in regular wards and decreased APACHE II scores in the HP+CVVH group may account for this phenomenon. As reported, AP is increasingly prevalent, costing approximately $2.6 billion annually and $6279 per capita in the United States [50]. HP+CVVH treatment in the trial showed a decline in hospitalization costs compared with CVVH treatment alone. Decreased costs have been associated with a shorter length of hospital stay, reduced duration of RRT, and a less time of antibiotic use.

Clotting, vascular access problems and bleeding are the most frequent risk of disadvantages of RRT [51]. In our study, only thrombocytopenia was detected in seven patients (four in the CVVH group and three in the HP+CVVH group); however, once RRT was stopped, the platelet counts rapidly increased to normal.

Limitations

Our study had several notable limitations. First, the observational and retrospective nature of the data limits causal inference owing to the potential for unmeasured confounding. We lacked data comparing the conservation and RRT (including CVVH and HP+CVVH groups) + conservation treatments. However, an effective role in clinical outcomes has been demonstrated previously when compared to conservation therapy with HP+CVVH or only CVVH [52–54]. Furthermore, the retrospective design has the potential for selection bias. Third, while cost data were not inflation-adjusted due to negligible price fluctuations (0.2 % annual inflation) [55], future multi-year studies should incorporate economic normalization methods. Finally, we reported a significantly less SAP in the subgroup with TG $\geq$ 50 mmol/L in CVVH group; however, the samples were very small, and further studies are required to clarify the effect.

Conclusions

No significant differences were observed in the incidence of systemic or local complications, recurrence rates, or quality of life. However, the HP+CVVH group was associated with less time of antibiotic use, a shorter duration of antibiotic dosage in regular wards, a shorter initiation of enteral nutrition, a decreased hospital LOS, and lower hospital costs. In patients with a high inflammatory load (high PCT, CRP, or IL-6 levels), a lower incidence of SAP attacks was observed. Further randomized controlled studies are required to clarify these effects in patients with HTG-AP.

List of abbreviations

HTG-AP: Hypertriglyceride acute pancreatitis
CVVH:Continuous venous-venous hemofiltration
HP: Hemoperfusion
AP: Acute pancreatitis
SIRS:Systemic inflammatory response syndrome
TG: Triglyceride
ARF: Acute respiratory failure
RRT: Renal replacement treatment
APACHE II: Acute physiology and chronic health evaluation II
LOS: Length of stay
PCT: Procalcitonin
CRP: C-reactive protein
AKI: Acute kidney injury
IAH: Intra-abdominal hypertension
GIQLI: Gastrointestinal quality of life index
DCA: Decision curve analysis
ACS: Abdominal compartment syndrome

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee of First Affiliated Hospital of Fujian Medical University (MTCA, ECFAH of FMU [2015]084–1). All study participants, or their legal guardian, provide informed written consent prior to study enrollment.

Availability of data and materials

No additional data are available.

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CRediT authorship contribution statement

Ying Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gao-fan Dai:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Wen-biao Xiao:** Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation. **Jing-shi Shi:** Writing – review & editing, Software, Project administration, Methodology, Investigation. **Bing-wen Lin:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation. **Jian-dong Lin:** Writing – review & editing, Writing – original draft, Project administration. **Xiong-jian Xiao:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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

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Supplementary materials

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