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Effect of high volume hemodiafiltration on oxygenation and ventilatory function in mechanically ventilated patients with Sepsis: a randomized controlled trial.

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Abstract:

Background: High volume hemodiafiltration (HVHDF) has been used in patients with sepsis to potentially improve hemodynamics and increase survival rates. We aimed to assess the effect of HVHDF on oxygenation in mechanically ventilated septic patients. We hypothesized that HVHDF could improve oxygenation. **Methods:** In this prospective, non-blinded, single-institution randomized trial, forty patients were randomly assigned to receive HVHDF (n = 20) or not (n = 20). Patients in the HVHDF group received HVHDF at a prescribed dose of 70 ml/kg/ hours for 48 hours in addition to their usual treatments. **Results:** At 24 hours and 48 hours after the initiation of HVHDF, the arterial oxygen pressure (PaO_2), the ratio of arterial oxygen pressure to the fraction of inspired oxygen (PaO_2/ FiO_2 ratio), and jugular venous oxygen saturation ($S_{JV}O_2$) were all significantly higher in the HVHDF group compared to the non-HVHDF group ($P < 0.05$). Compared to the non-HVHDF group, the alveolar-arterial oxygen pressure difference ($P_{A-a}O_2$) and serum Interleukin- 6 were significantly lower, dynamic compliance increased more significantly, and plateau pressure decreased more significantly in the HVHDF group ($P < 0.05$) at 48 hours after initiation of HVHDF.

Duration for weaning from mechanical ventilation (MV) was significantly shorter in the HVHDF group ($P = 0.001$). However, serum lactate levels, success of weaning from MV, and 28-day survival were not different between the groups ($P > 0.05$).

Conclusions: In mechanically ventilated septic patients, treatment with HVHDF, in addition to standard therapies, improved oxygenation and ventilatory function, and reduced the duration of MV.

Keywords: Septic shock, Sepsis, High volume hemodiafiltration (HVHDF), Renal replacement therapy, Sequential organ failure assessment (SOFA)

Trial registration: Clinical Trials.gov, NCT03853005. Registered 10 July 2018, https://clinicaltrials.gov/study/NCT03853005

1. Introduction:

Sepsis is a potentially fatal condition characterized by a dysregulated immunological response to infection [1]. Although the use of antibiotics to treat infections is well-established, controlling systemic inflammation is just as crucial but more challenging to do because of the incredibly complex structure of the reaction and the several mediators involved [2]. It has been proposed that hemofiltration helps to restore immunological homeostasis [3].

High volume hemodiafiltration (HVHDF) is a hybrid intermittent renal replacement treatment [4] that uses high filtration volumes to reduce inflammation and improve patient outcomes, particularly in septic patients [5]. It has been shown to improve survival rates and hemodynamics [6, 7]. Ren et al. suggest that combining HVHDF with fluid resuscitation can improve alveolar-arterial oxygen exchange, thereby increasing patient survival in refractory septic shock patients [8].

Therefore, we aimed to evaluate the impact of HVHDF on the arterial oxygen pressure (PaO_2) at 24 hours after the start of HVHDF in mechanically ventilated patients with sepsis as the primary outcome. Our hypothesis was that it would improve oxygenation. Secondary outcomes included the effects of HVHDF on the ratio of arterial oxygen pressure to the fraction of inspired oxygen (PaO_2/ FiO_2 ratio), ventilatory function, and the duration for weaning from mechanical ventilation (MV).

2. Methods:

2. 1. Study design

This prospective randomized and controlled clinical trial was approved by our local Research Ethics Committee (IRB no: IRB17200208 on November 7, 2016). It was registered on Clinical Trials.gov (NCT03853005 on July 10, 2018) and conducted in accordance with the Helsinki Declaration-2013. Informed consent was

obtained from all patients' relatives before enrollment.

2. 2. Study population

Forty patients, aged 18 years or older, with sepsis (defined by the presence of 2 or more criteria of the Quick Sequential/ Sepsis Organ Failure Assessment (qSOFA) Score) [9] and acute respiratory distress syndrome (ARDS), who were mechanically ventilated with multi-organ dysfunction, including respiratory failure (detected by an increase in Sequential/ Sepsis Organ Failure Assessment (SOFA) Score of >2 points from basal condition) [9], were enrolled between March 20, 2019, and November 10, 2020.

The exclusion criteria included patient relatives' refusal, pregnancy, recent active internal hemorrhage, not being mechanically ventilated, and hypersensitivity to the dialyzer fluid or filter material.

2. 3. General consideration to all patients

The study adhered to the 2016 Surviving Sepsis Campaign bundle guidelines for patients. Patients received a lung-protective strategy with standardized mechanical ventilation (MV) parameters, including Bilevel positive airway pressure (BiPAP) mode, tidal volume adjustments, respiratory rate settings, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FiO_2) to preserve arterial oxygen saturation. A permissive hypercarbia protocol was considered in cases of high plateau pressure, and sodium bicarbonate was used to maintain blood pH levels. Sedation was administered to reduce ventilator-patient dyssynchrony, using propofol or midazolam hydrochloride. Sedation was stopped each morning to assess the patient's highest Glasgow Coma Scale (GCS) score. Renal protective measures were also provided, with hematocrit maintained above 22% and strict glycemic control. Serial blood gases and chest X-rays were routinely performed to optimize mechanical ventilation management.

2. 4. Randomization

Patients were randomly assigned according to computer-generated randomization, to receive HVHDF treatment, (HVHDF group; n=20) or not receive HVHDF treatment (control group, non-HVHDF group; n=20).

2. 5. HVHDF preparation and technique of administration

A 12-gauge central venous catheter was inserted into a central vein (either the internal jugular, femoral or subclavian vein) under complete sterilization. It was then flushed and tested for unrestricted blood flow before starting HVHDF.

The Multifilter apparatus for software version 1.7 from the Fresenius company group was used. The bicarbonate solution for MFT

Model Multipic and the Multifilterate Kit Model 8 CVVHDF 1000 were the specific solution bags and kits used for the apparatus. The AV10000S high-performance filter was also employed.

Hemodiafiltration (HDF) was used to support patients with respiratory failure, starting on the same day as tracheal intubation, regardless of renal function. HDF plus countercurrent dialysis (HVHDF), was utilized to improve small molecule clearance and regulate the sodium load imposed by the circuit anticoagulant, trisodium citrate.

The targeted clearance by HVHDF was set at 70 ml/kg/hour filtration rate for predicted body weight which was calculated by adding the volume of dialysate solution to the volume of ultrafiltrate production. It was designed to promote the clearance of low- and middle-molecular-weight particles, such as proinflammatory mediators.

An intravenous solution was administered to maintain fluid balance, with a net fluid balance of a deficit of 10 to 100 mL/hour. An automated system continuously delivered HVHDF for 48 hours while the patient was on mechanical ventilation. Heparin infusion was employed for anticoagulation, with an initial dose of 2500 units (U) followed by a maintenance dose of 5-10 U /kg/hour [10]. The activated partial thromboplastin clotting time (aPTT) was maintained at 60-80 seconds. In cases where there was a risk of bleeding, heparin was used to flush the tubes and filter before connecting the patient. The dose used was 5 U/kg, with no heparin maintenance utilized thereafter [11].

2. 6. Data collection

The primary outcome was the effect of HVHDF on the PaO_2 at 24 hours after the start of HVHDF.

The secondary outcomes measured in the study were as follows: the effects of HVHDF on the PaO_2/ FiO_2 ratio, ventilatory function, and the duration for weaning from mechanical ventilation (MV).

Age, sex and causes of sepsis were recorded. Measurements were obtained at 0 hours (just before the start of HVHDF), as well as at 24 and 48 hours after the initiation of HVHDF. Changes in arterial oxygen pressure (PaO_2), PaO_2/ FiO_2 ratio, arterial oxygen saturation (SaO_2), and the alveolar-arterial oxygen pressure difference (A-a DO_2) were measured. A 0.5 ml blood sample was taken from the radial artery, and arterial blood gas analyses were conducted after anticoagulation with heparin. The A-a DO_2 was calculated using the following equation: $[P_{(A-a)}O_2] = [(P_a - P_{H2O}) \times FiO_2\% - PaCO_2 - PaO_2] = [(760 - 47) \times FiO_2\% - PaCO_2 - PaO_2] = [713 \times FiO_2\% - PaCO_2 - PaO_2]$. Where P_a=

atmospheric pressure (standard state is 760 mmHg), P_{H2O} = saturated water vapor pressure (standard state is 47 mmHg), FiO_2% = Fraction of inspired O_2, PaO_2 = arterial partial pressure of oxygen, P_AO_2 = alveolar oxygen partial pressure, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood.

Changes in the parameters of ventilatory function, such as static compliance, dynamic compliance, positive end-expiratory pressure (PEEP), plateau pressure, peak airway pressure, and airway resistance, were noted.

The study recorded various outcomes such as tissue perfusion (measured through serum lactate), jugular venous oxygen saturation ($S_{JV}O_2$), interleukin-6 (IL-6) levels, SOFA score, mean arterial pressure (MAP) variations, noradrenaline infusion dosage, urine output (UOP), body temperature, weaning from mechanical ventilation, 28-day survival, and any side effects following HVHDF technology application.

An evaluation was conducted on the leukocyte count, platelet count, international normalized ratio (INR), liver function test, and renal function test as a follow-up to routine investigations.

For serum IL-6 assay: five millilitres of venous blood were withdrawn from patients in a plain vial. At 6000 rpm, centrifugation was carried out. Until analysis, samples were frozen at -20°C. Using an enzyme-linked immunosorbent assay, the serum levels of IL-6 were quantitatively measured.

2. 7. Sample size and statistical analysis

The sample size was calculated based on a pilot study conducted with five patients in each group (HVHDF group versus non-HVHDF group). It was determined that 15 patients per group were needed to compare the efficacy of HVHDF in mechanically ventilated patients with sepsis, with 95% power and a 5 % probability of Type I error. To account for any potential protocol violations, we included 20 patients in each group.

Computerized statistical software, SPSS Version 22.0 (IBM Corporation, Armonk, NY), was utilized for the statistical analysis. The normality of the data distribution was confirmed by the use of the Kolmogorov-Smirnov test. Data were displayed as mean ± standard deviation (SD), median (range), or numbers (%) as appropriate. The Independent sample t-test was employed to compare quantitative variables between groups for parametric data, while the Mann-Whitney U test was employed for nonparametric data. The Chi-square test or Fisher's exact test was used for qualitative variables. Changes in variables over time were analyzed using a 2-way repeated

measures analysis of variance followed by the Bonferroni test. Correlations between serum IL6 levels and $S_{JV}O_2$, as well as serum lactate levels at 24 and 48 hours after the initiation of HVHDF were evaluated using the Spearman rank correlation coefficient. $P < 0.05$ was deemed significant.

3. Results:

Of forty-seven participants, forty fulfilled the eligibility criteria and were randomized and included in the final analysis (Fig. 1).

Age, sex, and etiology of infection were comparable between groups (Table 1).

Changes in respiratory function, ventilatory function, and weaning from mechanical ventilation are listed in Table 2. The PaO_2, PaO_2/FiO_2 ratio, and $S_{JV}O_2$ were all significantly increased at 24 and 48 hours after HVHDF in the HVHDF group compared to the non-HVHDF group.

At 48 hours after HVHDF, the $P_{A-a}O_2$ was significantly lower in the HVHDF group. The dynamic compliance increased more significantly and the plateau pressure decreased more significantly in the HVHDF group versus the non-HVHDF group. Days for weaning from mechanical ventilation was significantly lower in the HVHDF group. There were no significant differences in SaO_2, static compliance, PEEP needed, peak airway pressure, airway resistance, and success of weaning from mechanical ventilation between groups during the whole study period.

Changes in laboratory, physiological, and hemodynamic parameters are shown in Table 3.

There were no significant differences in serum lactate levels, leucocyte count, platelet count, INR, ALT, AST, and MAP between groups during the whole study period.

At 24 hours after HVHDF, UOP and body temperature were significantly lower in the HVHDF group. At 48 hours after HVHDF, serum IL-6, serum creatinine, serum urea, total bilirubin, noradrenaline infusion dosage, and body temperature were all significantly lower in the HVHDF group compared to the non-HVHDF group.

In both groups, $SjvO_2$ and serum lactate were weakly correlated with serum IL-6 levels at 24 and 48 hours after HVHDF (Table 4).

The SOFA scores were significantly lower at 24 and 48 hours after HVHDF in the HVHDF group compared to the non-HVHDF group (Table 5).

There was no significant difference in 28-day survival between the two groups (Table 5).

Recorded adverse effects in HVHDF group:

Three patients experienced bleeding, two from the endotracheal, oral, and nasal cavities, while one had hematuria. All had their heparin infusion stopped during HVHDF.

4. Discussion:

The current study evaluated the impact of HVHDF usage on mechanically ventilated patients with sepsis. Two groups were studied: one receiving HVHDF and the other not receiving HVHDF. The HVHDF group showed improved oxygenation parameters (PaO_2, PaO_2/FiO_2 ratio, and $P_{A\text{-}a}O_2$), ventilatory function (dynamic compliance and plateau pressure), IL-6 clearance, total SOFA score, $SjvO_2$, noradrenaline infusion doses, and days for weaning from mechanical ventilation (MV) compared to those in the non-HVHDF group. 28-day survival was similar between both groups.

The treatment of critically ill patients aims to prevent systemic inflammatory consequences and mortality [12]. In 1992, Grootendorst et al. introduced the concept of HVHDF, which improves hemodynamic parameters in porcine models of sepsis. They hypothesized that HVHDF removes substances that cause cardiac dysfunction and vasodilatation in septic animals [13, 14]. Other studies have confirmed its effectiveness in septic animal models [15, 16], sparking interest in its potential advantages for human health.

Hemofiltration therapy has been utilized in the treatment of systemic infectious diseases and has become essential for saving critically ill patients [17, 18]. Continuous HVHDF has been studied in trials focusing on sepsis complicated by ARDS, with the goal of improving inflammatory factors, pulmonary function, and hemodynamic indices [18].

In a study by Chen et al. on 163 ARDS patients, it was found that HVHDF improved oxygenation (PaO_2/FiO_2 ratio) and lung function. Significant improvements were observed in the HVHDF and pulse-indicated continuous cardiac output (PiCCO) + HVHDF groups. This led to reduced organ failure, shortened MV duration, and decreased hospital mortality compared to the conventional therapy group [19].

A study by You et al. reveals that early application of HVHDF in severe burn patients improves the PaO_2/FiO_2 ratio, reduces sepsis, and decreases mortality due to the early clearance of inflammatory mediators [20]. Hu et al. studied 14 septic patients with MODS and found that coupled plasma filtration adsorption (CPFA) treatment was superior to HVHDF in improving MAP and the PaO_2/FiO_2, as well as in eliminating inflammatory mediators [21]. Xie et al. found that HVHDF significantly improved the PaO_2/FiO_2 ratio, extravascular lung water (EVLW) index, peak airway pressure, dynamic compliance, and serum IL-6 levels in patients with ARDS and MODS using PiCCO

monitoring [22]. Zhang et al. found that continuous HVHDF treatment significantly improved the PaO_2 / FiO_2 ratio and EVLW in severe ARDS patients. This led to a shorter duration of MV and increased success in weaning [23].

The present study found significant improvements in the HVHDF group 24 hours after HVHDF in the PaO_2, PaO_2/FiO_2 ratio, and $S_{JV}O_2$ ratio. Additionally, at 48 hours after HVHDF, improvements were found in the PaO_2, PaO_2/FiO_2 ratio, $P_{A\text{-}a}O_2$ differences, $S_{JV}O_2$, dynamic compliance, and plateau pressure compared to the non-HVHDF group. HVHDF improves lung oxygenation in critically ill patients by reducing lung edema content and removing inflammatory markers, such as cytokines, that contribute to the pathogenesis of sepsis [24]. HVHDF operates through convection, which increases the sieving coefficient for larger molecules, facilitating the effective clearance of cytokines and inflammation mediators. Modern hemofiltration membranes have a cut-off of 30-50 kD, allowing for significant removal of smaller cytokines [25]. The reduction of cytokines or complement factors levels significantly depends on production rates, endogenous half-life, serum levels at the beginning of therapy, and extracorporeal therapy elimination rate [25]. Low production rates, longer half-lives, and higher initial serum levels may improve the reduction of plasma levels. Cytokines' plasma half-lives are extremely short, making plasma levels likely only influenced by extremely high clearances and membranes with high sieving coefficients [26].

Junhai et al.'s meta-analysis suggests that HVHDF can effectively reduce plasma levels of IL-6 in critically ill patients [27]. The focus has shifted from solely removing cytokines to immunomodulation [28], which entails lowering peak levels of both proinflammatory and anti-inflammatory mediators. Other theories propose that increased excretion of cytokines from the blood impacts interstitial cytokine levels and associated pathophysiological processes by creating a drag from extracellular and intracellular spaces [29]. Consequently, there was a notable influx of inflammatory mediators into the blood compartment, where they could be cleared [30]. Furthermore, HVHDF may boost the immune response by modulating neutrophils and monocytes [30]. In the current study, a significant decrease in IL-6 was observed 48 hours after HVHDF in the HVHDF group compared to the non-HVHDF group.

Several scoring systems have been used to assess organ dysfunction in septic patients

undergoing HVHDF [8]. Ghani et al.'s study found that the SOFA score for septic patients using intermittent HVHDF and standard volume hemodiafiltration (SVHDF) groups showed similar scores at baseline but decreased by day seven, with a significant decrease in the SVHDF group [31]. Joannes-Boyau et al. found no significant difference in median SOFA scores between the HVHDF and SVHDF groups over a 96-hour period [32]. Hu et al. found significant reductions in both SOFA and the acute physiology and chronic health evaluation II (APACHE II) scores after coupled plasma filtration adsorption (CPFA), with only the SOFA score significantly decreased after HVHDF [21]. The current study showed a significant decrease in total SOFA scores at 24 and 48 hours after HVHDF in the HVHDF group compared to the non-HVHDF group.

Lactate is a significant indicator of illness severity and mortality in sepsis. The 2014 Australasian Resuscitation in Sepsis Evaluation (ARISE trial) found that patients with isolated hyperlactatemia had a 1.7 times higher risk of 90-day mortality and were less likely to be discharged alive from the ICU and hospital [33]. The Sepsis-3 consensus definition of shock, which necessitates the presence of hyperlactatemia, highlights this prognostic value [34]. The analysis of three flow-sensitive parameters, including central venous oxygen saturation, central venous-arterial carbon dioxide pressure gradient, and peripheral perfusion, can help identify hypoperfusion in hyperlactatemia [35].

Levraut et al.'s 1997 study on critically ill patients found that continuous venovenous hemofiltration (CVVHF) with dialysis cannot mask lactate overproduction, and its blood concentration remains a reliable marker of tissue oxygenation in patients receiving this renal replacement therapy [36]. Liu et al. conducted a study on 15 critically ill patients, comparing three doses of CVVHF based on plasma lactate concentrations. They found that CVVHF is capable of reducing plasma lactate levels, with varying doses leading to different rates of lactate clearance [37]. Cheungpasitporn et al. found that HVHDF is not effective for severe lactic acidosis and should not be considered a non-renal indication for continuous renal replacement therapy (CRRT) [38]. Meanwhile, Salaman et al. evaluated the impact of hemofiltration on lactate levels during cardiopulmonary bypass (CPB) in adult patients. They observed that hemofiltration during CPB leads to hemoconcentration, raised lactate levels, and increased need for inotropic support [39]. The present study found no significant changes in serum lactate levels between groups at 0, 24

and 48 hours after HVHDF. However, a negative correlation was observed between serum lactate levels and serum IL-6 at 48 hours after HVHDF in the HVHDF group, which could be explained by the ability of HVHDF to reduce cytokine levels [23].

A meta-analysis revealed that the HVHDF group had a significantly higher MAP compared to the non-HVHDF group [27]. In the current study, we did not observe a significant difference in MAP between the groups. However, the HVHDF group did show a significantly lower dose of noradrenaline support, which could potentially suggest improved hemodynamics.

Additionally, a meta-analysis found that HVHDF significantly improved ICU survival in critically ill patients with sepsis and ARDS compared to the non-HVHDF group [25]. The meta-analysis highlights the importance of HVHDF in improving ICU survival. In contrast, we did not find a significant difference in mortality between the two groups studied. This could be explained by the fact that 28-day survival was not our primary outcome.

HVHDF can have a negative impact on outcomes and hemodynamics. Additionally, there is an increased risk of electrolyte disturbances, particularly hypophosphatemia, which has been linked to higher mortality rates in critically ill patients [29]. High drugs dosing during hemofiltration can increase antibiotic clearance, but it may decrease plasma levels, especially in sepsis patients where adequate antibiotic treatment is crucial. No studies have reported adjusting dosing for enhanced clearances [40].

Rickard et al. conducted a study comparing 60 circuits in CVVHF mode with or without an intravenous fluid warmer set at 38.5 °C on the dialysate and 1 L/hour of replacement fluid lines. They found that fluid warmers did not prevent hypothermia (defined as a core temperature <36.0 °C) during CVVHF [41]. In Santiago et al.'s study on critically ill children treated with CRRT to determine complications related to the technique, they found significant hemorrhage in 10.3% of patients. There was no relation between hemorrhage and age, weight, diagnosis, or clinical severity. Hemorrhage patients had higher mortality rates, with hypotension at connection and electrolyte disturbances (especially in serum phosphate, potassium, and calcium) being the most common complications [42]. In the current study, bleeding was observed in three patients in the HVHDF group.

Limitations

The study has several limitations, including a small sample size, a short follow-up period,

diverse sepsis etiology, and only investigating serum IL-6. Further research with larger samples and longer follow-ups is needed. Additionally, evaluating more precise and sensitive sepsis biomarkers, such as micro-RNAs and PCT, could be beneficial.

In conclusion

HVHDF improved oxygenation, jugular venous oxygen saturation, dynamic compliance, plateau pressure, SOFA score, reduced serum IL-6 levels, and shortens weaning days in mechanically ventilated septic patients with multi-organ failure.

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Table legends:

Table 1. Patient characteristics and etiology of infection in the two groups. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; HELLP: hemolysis, elevated liver enzymes and low platelets; MODS: multiple organ dysfunction syndrome. Data are shown as median (range) or number. P < 0.05 was considered significant.

Table 2. Changes in respiratory function, ventilatory function, and weaning from mechanical ventilation between the two studied groups. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; PaO_2: arterial oxygen pressure; FiO_2: fraction of inspired Oxygen; PaO_2/FiO_2 ratio: ratio of arterial oxygen pressure to the fraction of inspired oxygen; $P_{A-a}O_2$: alveolar arterial oxygen pressure difference; SaO_2: arterial oxygen saturation; $SjvO_2$: jugular venous oxygen saturation; PEEP: positive end-expiratory pressure. Data are shown as mean ± SD or number (percentage). P < 0.05 was considered significant.

Table 3. Changes in laboratory, physiological, and hemodynamic parameters between the two groups. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration. Data are shown as mean ± SD. P < 0.05 was considered significant.

Table 4. Correlations between serum IL-6 levels and both SjvO2 and serum lactate. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; IL-6: interleukin-6; $SjvO_2$: jugular venous oxygen saturation. Data are expressed as correlation coefficient (P- value). Spearman rank correlation coefficients were calculated. P < 0.05 was considered statistically significant.

Table 5. SOFA score and 28-day survival in the two groups. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; SOFA: Sequential/ Sepsis Organ Failure Assessment. Data are shown as mean ± SD or number (percentage). P < 0.05 was considered significant.

Figure legends:

Fig 1. CONSORT flow diagram of participants. HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration.

Highlights

- Sepsis is a potentially fatal condition characterized by a dysregulated immunological response to infection.
- High volume hemodiafiltration (HVHDF) has been used in patients with sepsis to

potentially improve hemodynamics and increase survival rates.

- Treatment with HVHDF, in addition to standard therapies, in mechanically ventilated patients with sepsis, improved oxygenation and ventilatory function, and reduced the duration of MV.
- HVHDF can be incorporated as part of a routine management for various intensive care mechanically ventilated patients with sepsis to enhance oxygenation and ventilatory function.

Table 1 Patient characteristics and etiology of infection in the two groups.

	HVHDF (n= 20)	**non-HVHDF (n= 20)**	**P-value**
Age (years)	53 (29-78)	55 (20-75)	0.903
Sex (male/female)	10/10	12/8	0.527
Etiology of infection			0.528
- Peritonitis (severe acute pancreatitis and neglected perforated viscus)	7	9	
- Severe pneumonia	4	3	
- Metastasis	1	1	
- Polytrauma	0	2	
- Acute fatty liver of pregnancy	2	0	
- Severe preeclamptic toxemia and HELLP syndrome	1	2	
- Massive pulmonary embolism and myocardial infarction	2	0	
- Fournier's gangrene on legs, scrotum and the back	2	1	
- Hepatorenal syndrome and end stage liver disease	1	1	
- Rupture uterus and massive blood transfusion with MODS	0	1	

HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; HELLP: hemolysis, elevated liver enzymes and low platelets; MODS: multiple organ dysfunction syndrome. Data are shown as median (range) or number. $P < 0.05$ was considered significant.

Table 2 Changes in respiratory function, ventilatory function, and weaning from mechanical ventilation between the two studied groups.

	HVHDF (n=20)	**non-HVHDF (n=20)**	**P-Value**
PaO_2			
0 hour	104.7 ± 29.2	103.9 ± 38.8	0.941
24 hours	156.2 ± 55	86 ± 14.4	0.002
48 hours	144.4 ± 27.3	95.8 ± 26.8	0.001
PaO_2/FiO_2 ratio			
0 hour	163 ± 53.3	167.6 ± 65.84	0.989
24 hours	296 ± 70.04	192.3 ± 51	0.003
48 hours	324.96 ± 73.71	198.7 ± 69.83	0.001
$P_{A-a}O_2$			
0 hour	345.8 ± 122.8	326.7 ± 153	0.433
24 hours	183.9 ± 56	209 ± 66	0.203
48 hours	158 ± 107.5	241.9 ± 141.8	0.014
SaO_2			
0 hour	95.3 ± 3	96.3 ± 3.2	0.226
24 hours	97.6 ± 2.3	97.2 ± 2.5	0.639
48 hours	98 ± 2.5	96.9 ± 2.2	0.088
$SJVO_2$			
0 hour	77.5 ± 17.1	78 ± 13.2	0.626
24 hours	88.4 ± 8	81.4 ± 11.6	0.033
48 hours	90 ± 8.25	81.9 ± 11.3	0.007
Static Compliance (ml/cmH_2O)			
0 hour	30 ± 12.1	30.9 ± 11.1	0.820
24 hours	37.2 ± 15.6	35.1 ± 14.8	0.662
48 hours	45.2 ± 23.1	33.3 ± 15.2	0.060
Dynamic Compliance (ml/cmH_2O)			
0 hour	29.8 ± 5.3	29 ± 8	0.730
24 hours	35.8 ± 10.3	30.2 ± 6.7	0.056
48 hours	39.6 ± 10.4	31 ± 10.8	0.014
PEEP needed (cmH_2O)			
0 hour	8.1 ± 2.1	7.7 ± 3.3	0.335
24 hours	8 ± 2.3	7.7 ± 2.5	0.453
48 hours	7.2 ± 4.1	7.4 ± 2.6	0.614
Plateau pressure (cmH_2O)			
0 hour	22.7±2.97	22.8 ± 4.86	0.938
24 hours	20.6 ± 3.39	22.4 ± 4.9	0.195
48 hours	18.6 ± 4.3	22.4 ± 6.2	0.031

Peak airway pressure (cmH_2O)			
0 hour	31.4 ± 4.83	30.8 ± 6.2	0.735
24 hours	32.8 ± 5.83	30.3 ± 5.73	0.180
48 hours	30.4 ± 6.92	31.1 ± 7.12	0.193
Airway resistance (cmH_2O/L/sec)			
0 hour	13.9 ± 6.2	13 ± 9	0.721
24 hours	11.9 ± 7.8	11.4 ± 7.1	0.914
48 hours	10.8 ± 6.8	13.9 ± 8.5	0.206
Success of weaning from mechanical ventilation	12 (60%)	7 (35%)	0.113
Days for weaning from mechanical ventilation	2 ± 1.2	7 ± 4.4	0.001

HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; PaO_2: arterial oxygen pressure; FiO_2: fraction of inspired Oxygen; PaO_2/FiO_2 ratio: ratio of arterial oxygen pressure to the fraction of inspired oxygen; $P_{A\text{-}a}O_2$: alveolar arterial oxygen pressure difference; SaO_2: arterial oxygen saturation; $SjvO_2$: jugular venous oxygen saturation; PEEP: positive end-expiratory pressure. Data are shown as mean ± SD or number (percentage). $P < 0.05$ was considered significant.

Table 3 Changes in laboratory, physiological, and hemodynamic parameters between the two groups.

	HVHDF (n=20)	non-HVHDF (n=20)	P-Value
Interleukin-6 (IL-6) (ng/dL)			
0 hour	5.3 ± 1.8	4.9 ± 0.9	0.291
24 hours	3.8 ± 1.7	4.6 ± 1.3	0.089
48 hours	2.7 ± 1.5	4.2 ± 1.9	0.009
Serum lactate (mmol/L)			
0 hour	5.3 ± 3.2	4.7 ± 4.1	0.148
24 hours	3.4 ± 3.1	3 ± 2.9	0.409
48 hours	2.3 ± 1.7	3 ± 2.8	0.704
Leukocyte count (X 10^3/ml)			
0 hour	20.2 ± 10.4	15.5 ± 6.7	0.128
24 hours	17.2 ± 7.6	14.7 ± 7.4	0.417
48 hours	14.1 ± 6.7	17.9 ± 10.2	0.175
Platelet count (X 10^3/ml)			
0 hour	160.8 ± 96.3	120.4 ± 46.2	0.176
24 hours	127.2 ± 64.6	166.2 ± 69.5	0.074
48 hours	115.2 ± 73	153.1 ± 80.8	0.089
International normalized ratio (INR)			
0 hour	1.6 ± 0.6	1.4 ± 0.4	0.176
24 hours	1.7 ± 0.9	1.4 ± 0.2	0.882
48 hours	1.5 ± 0.5	1.4 ± 0.2	0.925
Serum creatinine (umole/L)			
0 hour	271.7 ± 147.9	233.7 ± 231	0.133
24 hours	142.3 ± 82.1	233.3 ± 251.7	0.745
48 hours	104.4 ± 74.7	221.1 ± 195.5	0.027
Serum urea (mmole/L)			
0 hour	26.5 ± 14.1	24.9 ± 8.5	0.671
24 hours	21.6 ± 12.3	27.5 ± 10.9	0.121
48 hours	16.6 ± 11.1	28.1 ± 11.7	0.002
Alanine Amino Transferase (ALT) (U/L)			
0 hour	84.8 ± 61.7	60.8 ± 64.5	0.055
24 hours	70.9 ± 57.6	106.3 ± 94.4	0.409
48 hours	461.5 ± 918.5	110.9 ± 84.8	0.164

Aspartate Amino Transferase (AST) (U/L)			
0 hour	149.8 ± 106.1	123.9 ± 82.6	0.395
24 hours	132.5 ± 119.3	142.3 ± 75.2	0.323
48 hours	119.3 ± 81	143.6 ± 89.2	0.626
Total Bilirubin (mmol/L)			
0 hour	51 ± 46.9	71.2 ± 95.2	0.543
24 hours	28.2 ± 20.7	57.9 ± 64.4	0.167
48 hours	19.4 ± 13	53.1 ± 57.2	0.025
Mean arterial pressure (MAP) (mmHg)			
0 hour	81.1 ± 14.5	80.35 ± 9	0.860
24 hours	83.5 ± 15.7	76.9 ± 10.3	0.116
48 hours	81.75 ± 16.4	78.65 ± 13.8	0.523
Noradrenaline (ng/kg/minute)			
0 hour	95 ± 82.5	93.5 ± 111.2	0.716
24 hours	73.5 ± 77.4	110 ± 86.75	0.236
48 hours	72.5 ± 99.3	166 ± 140	0.029
Urine output (UOP) (ml/day)			
0 hour	1320 ± 1220.6	1752.5 ± 949.9	0.126
24 hours	1352.5 ± 1195.8	2117.5 ± 967	0.023
48 hours	1337.5 ± 954.2	2025 ±1207.8	0.053
Body temperature (ºC)			
0 hour	38.2 ± 0.8	38.2 ± 1	0.987
24 hours	37.1 ± 0.8	37.9 ± 0.7	0.001
48 hours	36.8 ± 0.4	37.8 ± 0.7	0.001

HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration. Data are shown as mean ± SD. $P < 0.05$ was considered significant.

Table 4 Correlations between serum IL-6 levels and both SjvO2 and serum lactate.

Serum IL-6 (ng/ ml)	**HVHDF (n=20)**	**non-HVHDF (n=20)**
24 hours		
vs. $SjvO_2$ (%)	0.328 (0.159)	0.242 (0.317)
vs. serum lactate (mmol/ l)	0.003 (0.99)	0.32 (0.182)
48 hours		
vs. $SjvO_2$ (%)	0.013 (0.956)	0.073 (0.765)
vs. serum lactate (mmol/ l)	-0.302 (0.196)	0.276 (0.253)

HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; IL-6: interleukin-6; $SjvO_2$: jugular venous oxygen saturation. Data are expressed as correlation coefficient (P- value). Spearman rank correlation coefficients were calculated. $P < 0.05$ was considered statistically significant.

Table 5 SOFA score and 28-day survival in the two groups.

	HVHDF (n=20)	**non-HVHDF (n=20)**	**P-Value**
SOFA score			
0 hour	12.5 ± 2.4	12 ± 2.4	0.513
24 hours	7.5 ± 2.7	9.3 ± 2.3	0.027
48 hours	7.4 ± 3.8	11.6 ± 4.9	0.004
28-day survival	10 (50%)	6 (30%)	0.197

HVHDF: high volume hemodiafiltration; non-HVHDF: non-high volume hemodiafiltration; SOFA: Sequential/ Sepsis Organ Failure Assessment. Data are shown as mean ± SD or number (percentage). $P < 0.05$ was considered significant.

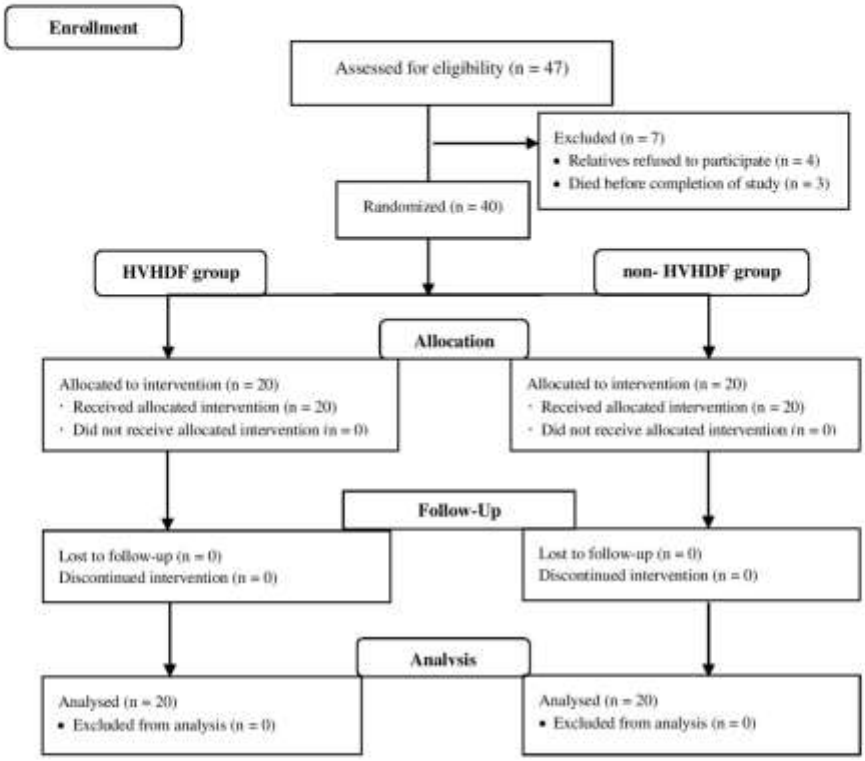

Figure 1. CONSORT flow diagram of participants.