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Research article

The role of polymyxin B-immobilized hemoperfusion in reducing mortality and enhancing hemodynamics in patients with sepsis and septic shock: A systematic review and meta-analysis

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ABSTRACT

Purpose: Polymyxin B-immobilized hemoperfusion (PMX-HP) is a therapeutic strategy for removing circulating endotoxins from patients with sepsis or septic shock. However, the survival advantage of PMX-HP treatment remains controversial for patients with sepsis/septic shock. Therefore, this study collected all the clinical trials to assess the effect and the safety of PMX-HP treatment.

Methods: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for eligible trials fromtheir inception through June 30, 2023. All clinical trials that investigated the effect of polymyxin B hemoperfusion in patients who died with sepsis or septic shock within 28-day mortality were eligible. The Cochrane Risk of Bias Assessment instrument and the ROBINS-I tool were used to assess the risk of bias.

Results: A total of 30 trials, including 25680 adult patients, were included. PMX-HP decreased 28-day mortality (OR 0.75, 95 % CI 0.65–0.88; $p < 0.00001$). Subgroup analysis revealed that 28-day mortality was significantly reduced after PMX-HP treatment in the mixed infection site group and in the age under 70 years old group. PMX-HP might also lower endotoxin levels (MD -1.22, 95 % CI -1.62 – 0.81, $p < 0.00001$) and improve SOFA scores (MD -2.11, 95 % CI -3.80- 0.43, $p = 0.01$). PMX-HP was not linked to the development of significant adverse events ($p = 0.05$).

Conclusion: Our findings suggest that PMX-HP therapy can reduce 28-day mortality in individuals with sepsis or septic shock. The therapeutic effect may be due to the ability of PMX-HP to lower endotoxin levels and enhance hemodynamics. However, further assessment of the clinical effects of PMX-HP on sepsis or septic shock is required.

1. Introduction

Sepsis and septic shock are life-threatening organ dysfunctions induced by an aberrant host response to infection [1]. Every year, millions of people worldwide die from sepsis and septic shock, resulting in one death for every three to six individuals [2–4]. A sepsis epidemiology study on the mainland revealed that the frequency and mortality of sepsis and septic shock in China greater than those in North America and Europe [5]. We require an effective therapy for sepsis and septic shock that will improve people's quality of life while reducing the strain on the healthcare budget.

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Abbreviations

APACHE II score	Acute Physiology, and Chronic Health Evaluation
MAP	mean arterial pressure
ORs	Odds ratios
Pao2/Fio2 ratio	pulmonary oxygenation
PMX-HP	Polymyxin B-immobilized hemoperfusion
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SOFA	Sequential Organ Failure Assessment
RRT	renal replacement therapy
CVVH	continuous venovenous hemofiltration

Endotoxin, a major component of the outer membrane of gram-negative bacteria, has been identified as a powerful modulator of the host response to infection and the development of sepsis [6]. Endotoxemia activates several cellular and hematogenous mediators, which can cause organ damage and cascade of inflammatory reactions [7]. Endotoxin levels are directly related to increas mortality in patients with septic shock [6,8,9].

Polymyxin B (PMX), a circular cationic polypeptide antibiotic produced from Bacillus polymyxa, binds to and neutralizes endotoxin [10]. In Japan, a unique technique for binding and immobilizing PMX to polystyrene fibershemoperfusion devices have been developed [11,12]. PMX hemoperfusion (PMX-HP) can lower circulating endotoxin levels in sepsis patients, modulating and limiting the maladaptive host response to infection and the advancement of the organ damage cascade in sepsis [13].

Although several systematic reviews have been conducted to assess the efficacy and safety of PMX-HP in the treatment of sepsis or septic shock, the findings are inconsistent, and none of them include all RCTs conducted to date [14–20]. The majority of the systematic reviews concentrated on mortality and adverse events, but they did not explain why the outcomes of earlier studies were varied differed. A patient's status, such as age, source of infection, and degree of disease, may presumably impact results.

As a result, we conducted a recent systematic review and evidence synthesis to assess the impact of PMX-HP as an adjuvant treatment for critically sick adults patients with sepsis or septic shock on clinical outcomes and health-care usage. We anticipate that using PMX-HP will enhance survival in adults with sepsis or septic shock by removing inflammatory cytokines.

2. Materials and methods

2.1. Protocol and registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews [21].The protocol was registered at PROSPERO (CRD42022347290).

2.2. Systematic search

We searched PubMed, EMBASE and the Cochrane Library from inception until June 2022 by using MESH terms and synonyms of "polymyxin B hemoperfusion", "sepsis" and "septic shock". We did not apply any language restriction. We additionally reviewed the references of the retrieved articles for probably eligible trials. The electronic search strategies are given in Appendix. 1.

2.3. Selection of studies

The study inclusion criteria are described below. 1) Population: adult patients with sepsis or septic shock. 2) Intervention: patients who received at least one course of PMX-HP treatment. 3) Comparison: patients who received standard therapy. 4) Outcome: included the outcomes of the investigation of the prognostic and hemodynamic variables.

The exclusion criteria were as follows: 1) inadequate study type or modality; 2) animal studies; 3) trials involving neonates or pediatric patients.

2.4. Data extraction and quality assessment

The data were independently and redundantly aggregated by two reviewers (C.L., J-L. Z.) using a modified version of the data extraction template of the Cochrane Consumers and Communication Review Group. In the event of disagreement: A third reviewer (P. Y.) was consulted for any best opinion. Forty-one articles, which included trial characteristics, 28-day mortality, Acute Physiology and Chronic Health evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, pulmonary oxygenation (Pao2/Fio2 ratio), mean arterial pressure (MAP), and blood endotoxin and cytokine levels. Any concurrent interventions were retrieved and documented accordingly.

For RCTs, we assessed the risk of bias using the tool of risk of bias summary according to Review Manager software, version 5.3 (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark). For non-RCTs, we also assessed the risk of bias using the tool

of Risk of Bias in Nonrandomized Studies of Interventions [22]. Publication bias was assessed by visual evaluation of a funnel plot. Two investigators independently performed extraction and risk of bias assessment.

2.5. Data synthesis and analysis

The primary outcome was 28-day mortality between the PMX-HP and standard therapy groups. The secondary outcomes were changes in the levels of endotoxin and humoral cytokines in the PMX-HP and standard therapy groups. The consequences were analysed using random effect models, regarding possible excessive heterogeneity among studies. Odds ratios (ORs) for 28-day mortality, with a 95 % CI, forPMX-HP and standard therapy groups have been calculated and introduced as precision statistics.

To account for clinical heterogeneity among the populations included in the studies and other sources of variation, a meta-analysis was conducted to investigated the effects of PMX-HP therapy on 28-day mortality. This analysis included disease severity, infection site, and age subgroup stratification. Summary statistics, in the form of odds ratios with 95 % confidence intervals were calculated and are presented for the mortality-stratified comparison between the PMX-HP and standard treatment groups.

3. Results

3.1. Selection and characteristics of trials

Fig. 1 depicts the outcomes of the literature search and screening procedure in this study, which used predeveloped search strategies to retrieve 4597 articles from the Pubmed, Embase, and Cochrane Library databases (PubMed (1579), Embase (2630), and the Cochrane Library (388). 612 duplicate publications were eliminated. We rejected 3773 papers primarily based on the inclusion and exclusion standards through reviewing the titles and abstracts. After reviewing the complete textual content of the last 212 papers, only 35 studies were included, comprising 14 RCTs and 21 non-RCTs.

The 35 qualifying items were published between 1998 and 2021, as shown in Table 1. The research comes from a variety of nations and populations, including Japan, France, Italy, North America, Thailand, and Europe. A total of 28291 patients with sepsis/septic shock were included, with 1340 patients in the PMX-HP group and 14846 patients in the standard therapy group; the ages were mostly middle-aged and elderly, with no significant difference in age between groups. There was also no significant difference in the SOFA and

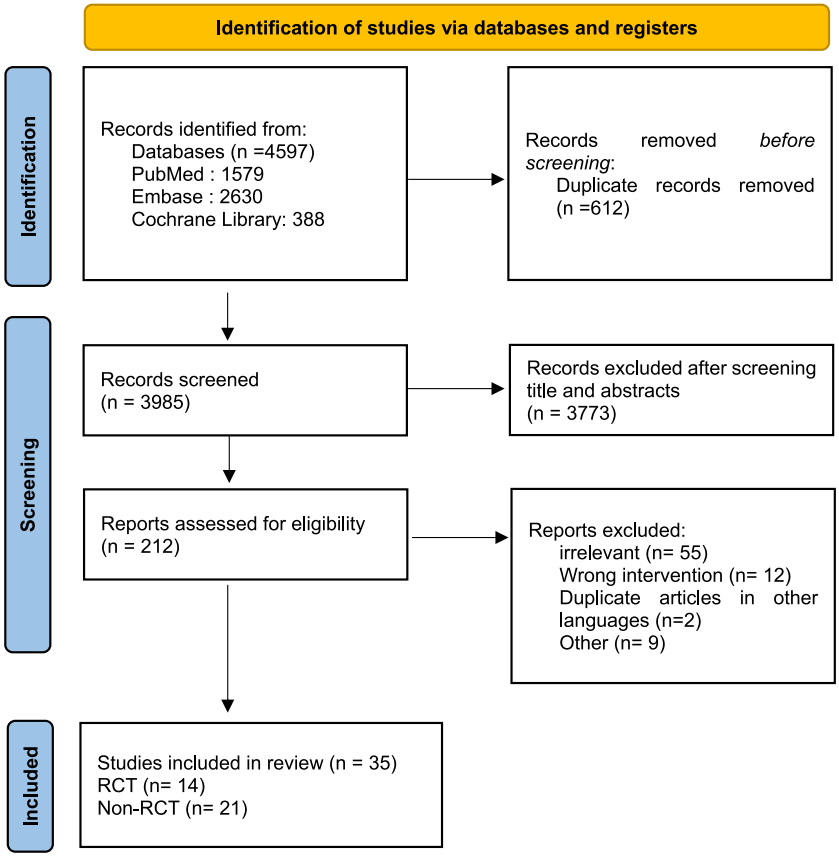

Fig. 1. Flowchart of study selection. RCT = randomized controlled trial.

Table 1
Characteristics of the trials included in the meta-analysis.

Source	Country	Total no. of patients	Age, mean (SD), years	Sex, male, female, *n*	Patient status	Infection site	APACHE II, mean (SD)
Cantaluppi 2008 [23]	Italy	16	60(11.25)	12,4	sepsis	Mixed	20.8(3.9)
Chen 2020 [24]	China Taiwan	28	68(12.4)	13,15	septic shock	abdominal	19(5.4)
Chen-Tse 2018 [25]	Taiwan	48	69.1(10.8)	26,22	septic shock	Mixed	23.1(6.1)
Coudroy 2017 [26]	Europe/ France	213	72.5(11.8)	93,120	septic shock	abdominal	NA
Cruz 2009 [27]	Italy	64	63.8(14)	42,22	sepsis/septic shock	abdominal	20.5(6.2)
Dellinger 2018 [28]	North America	450	59.8(14.9)	273,177	septic shock	Mixed	28.7(8.8)
Fujimori 2021a [29]	Japan	7502	NA	4705, 2797	sepsis	Mixed	NA
Fujimori 2021b [30]	Japan	8282	NA	4909, 3373	sepsis	Mixed	NA
Fujimori 2021c [31]	Japan	4066	NA	2414, 1652	sepsis	Mixed	NA
Jin 2019 [32]	South Korea	40	67.3(9.9)	24,16	septic shock	abdominal	18.55(5.5)
Klein 2018 [33]	Italy	194	58(14.6)	121, 73	septic shock	Mixed	29.8(7.9)
Lee 2021 [34]	South Korea	231	64.8(14.5)	135,96	sepsis	Mixed	NA
Masao 2014 [35]	Japan	1180	74.7(11)	534, 646	septic shock	abdominal	NA
Masao 2016 [36]	Japan	1956	70.5(12.1)	1157, 799	septic shock	Mixed	NA
Masashi 2014 [37]	Japan	15	66.6(5)	14, 1	severe sepsis/septic shock	Mixed	NA
Massimo 2010 [38]	Italy	64	NA	NA	severe sepsis/septic shock	NA	NA
Nakamura 1999 [39]	Japan	50	53.8(14.5)	30, 20	septic shock	Mixed	24.8(1.3)
Nakamura 2002a [40]	Japan	14	54.5(5.14)	8, 6	sepsis	Mixed	NA
Nakamura 2002b [41]	Japan	18	40(10)	12, 6	sepsis	Mixed	28(3.8)
Nakamura 2003a [42]	Japan	60	55.5(NA)	40, 20	sepsis	Mixed	23.7(4.1)
Nakamura 2003b [43]	Japan	20	63.7(10.2)	12, 8	sepsis	Mixed	27.3(4.5)
Nakamura 2005 [44]	Japan	26	56.5(10.5)	15, 11	septic shock	Mixed	25.3(5.0)
Nakamura 2009 [45]	Japan	50	58(10.1)	35, 15	septic shock	Mixed	21.6(4.6)
Nakata 2020 [46]	Japan	741	73(13.33)	437, 304	severe sepsis/septic shock	Mixed	25(10.37)
Navas 2018 [47]	Spain	18	67.5(9.9)	6, 12	septic shock	Mixed	20.67(4.7)
Nemoto 2001 [13]	Japan	98	61.9(2.68)	60, 38	sepsis	Mixed	22.4(7)
Nobuyuki 2017 [48]	Japan	413	72(12.4)	216, 197	severe sepsis	Mixed	25.32(9)
Payen 2015 [49]	France	232	71.7(15.9)	134, 98	septic shock	abdominal	NA
Rachoin 2020 [50]	North America	194	58.04(14.6)	121, 73	septic shock	Mixed	29.84(7.9)
Srisawat 2018 [51]	Thailand	59	68.8(13.8)	40, 19	severe sepsis/septic shock	Mixed	NA
Suzuki 2002 [52]	Japan	48	64.5(2.04)	35, 13	septic shock	Mixed	25(2.2)
Tani 1998 [53]	Japan	70	58.5(3)	52, 18	sepsis	Mixed	NA
Vincent 2005 [54]	Europe	35	57.6(13.02)	22,13	sepsis/septic shock	abdominal	17.73(6)
Yoshihiko 2017 [55]	Japan	1723	69.7 (13.8)	1019, 704	septic shock	Mixed	25.4(8.9)
Yuan 2017 [56]	China Taiwan	73	68.2(14.4)	41, 32	septic shock	abdominal	21.2(4.2)

APACHE scores between the two groups.

Of the 14 RCTs assessed, 6 and 7 were found to have a low risk of bias in random sequence generation and allocation concealment, respectively. Eight trials explicitly reported outcome blinding assessors, while 7 demonstrated a low risk of bias in incomplete outcome data. Among the 21 non-RCTs evaluated, 12 exhibited a low risk of bias in selection of participants into the study, and the majority demonstrated a low risk of bias in measurement of outcomes and selection of the reported result. A visual representation of the risk of bias assessment for both RCTs and non-RCTs can be found in Fig. 2.

3.2. Primary outcomes

Twenty-nine trials reported all-cause mortality at 28 days. As demonstrated in Fig. 3, using PMX-HP was related to lower 28-day mortality, with a pooled OR of 0.75 (95 % CI 0.65–0.88; p < 0.00001). Because there was significant heterogeneity across the trials (I^2 = 63 %, p < 0.00001); thus, we performed subgroup analysis to identify trials that contributed to the heterogeneity. The patients in mixed infection site group (Fig. 3) or in the <70 years of age group (Fig. 4) may benefit more from PMX-HP, according to subgroup analysis of 30 trials reporting 28-day mortality. There was no significant heterogeneity in abdominal infection site group (I^2 = 22 %, p = 0.26; Fig. 3) and in the APACHE II < 25 group (I^2 = 5 %, p = 0.40, Fig. S1). There was no subgroup interaction effect on 28-day mortality according to trial evaluation of critically sick patients (APACHE II < 25 vs. APACHE II ≥ 25, Fig. S1) or severity of trial participants (sepsis vs. septic shock alone vs. sepsis or septic shock, Fig. S2).

3.3. Secondary outcomes

PMX-HP did not lower 90-day mortality according to the 6 trials included 495 patients (OR, 1.02: 95 % CI 0.70–1.48; Table 2). Treatment with PMX-HP may reduce the ICU length of stay (MD, −1.38: 95 % CI -3.24–0.49; Fig. 5a) and hospital length of stay (MD, −1.39: 95 % CI -3.27–0.50; Fig. 5b). SOFA was reported having changed in 9 studies. The pooled results revealed a statistically significant relationship between PMX-HP and decrease in SOFA score (MD, −2.11; 95 % CI -3.80–0.43; I^2 = 93 %; n = 580; Table 2). PMX-HP may contribute to reduced the dosage of noradrenaline (n = 93, 3 trials, Table 2) and decrease in serum creatinine (n = 728, 6 trials, Table 2).

However, PMX-HP had no effect on PaO_2/FIO_2 (n = 644, 7 trials, Table 2) or MAP (n = 778, 7 trials, Table 2). Pooled data from three studies indicated that there was a risk of platelet reduction following PMX-HP therapy (MD, −2.24; 95 % CI -4.72–0.24; I^2 = 0 %;

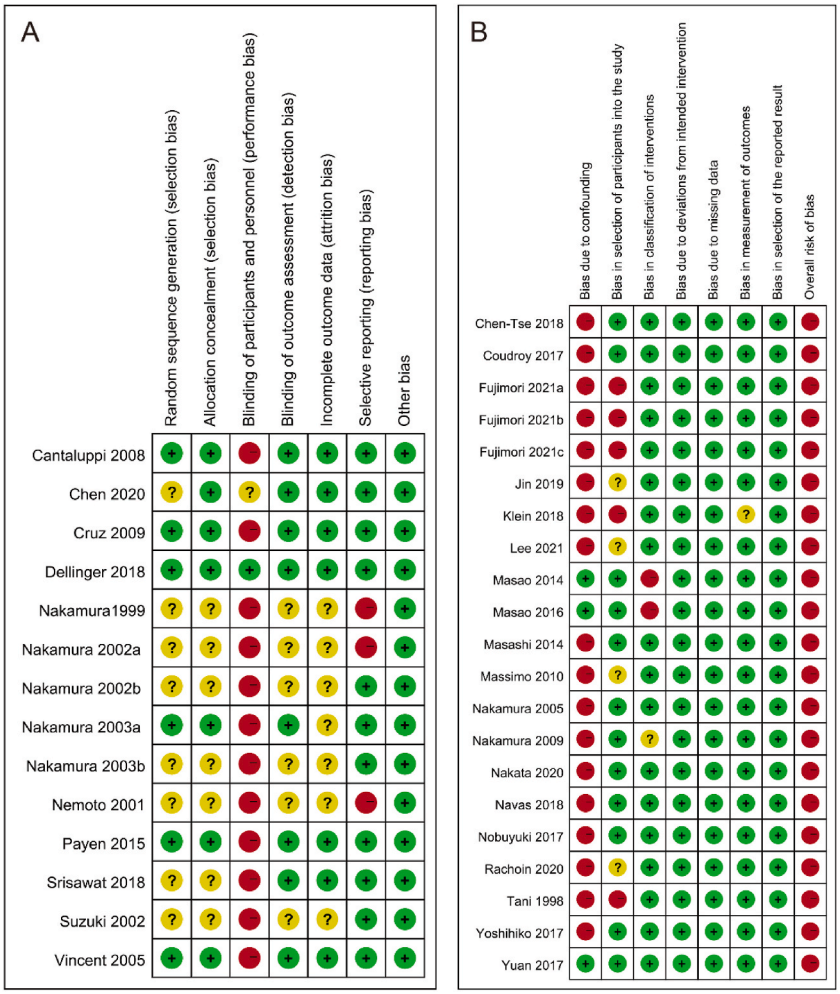

Fig. 2. Risk of bias summary. The authors' judgment of each risk of bias item for each included trial was reviewed. A, Randomized controlled trials. B, Nonrandomized controlled trials.

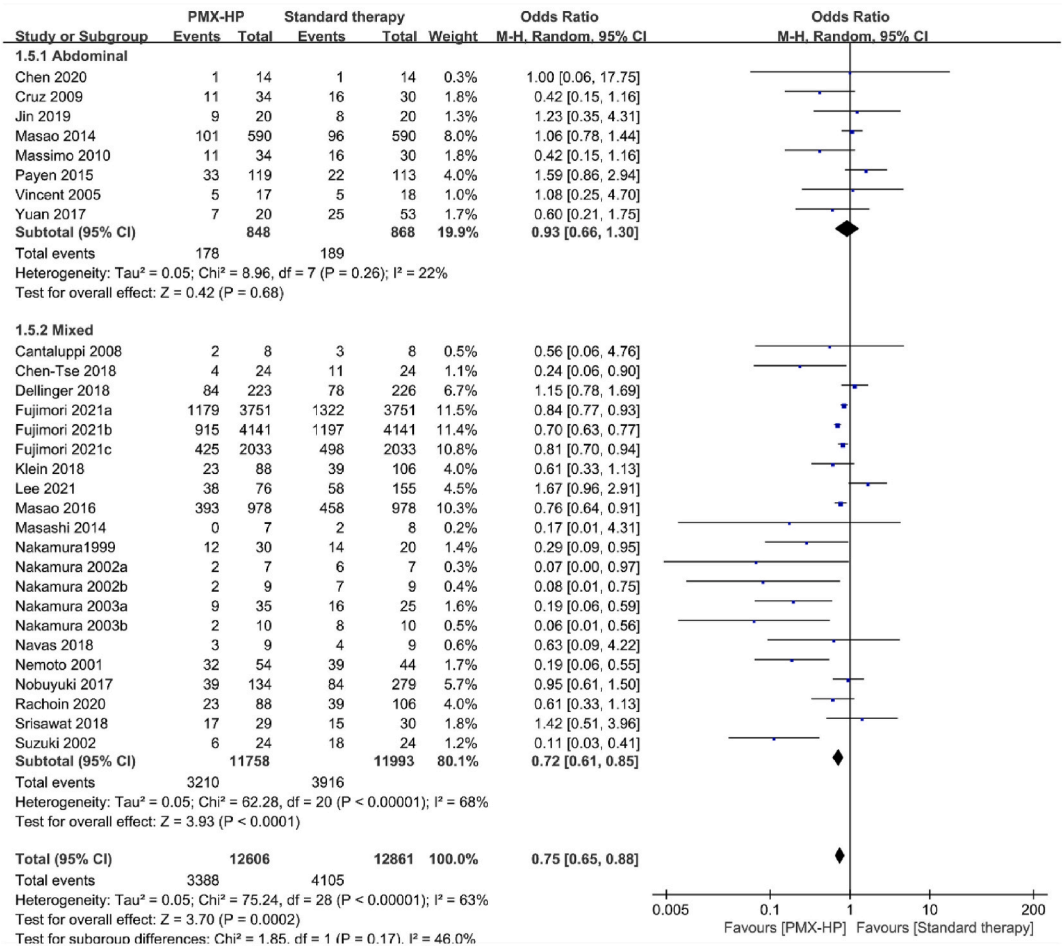

Fig. 3. Odds ratios (ORs) of 28-day mortality by infection site subgroup meta-analysis. PMX-HP = polymyxin B hemoperfusion.

n = 496; Table 2).

Several studies have focused on inflammatory cytokines as well. Serum endotoxin concentrations were compared before and after PMX-HP treatment in 11 studies including 903 participants. The aggregated data indicated that endotoxin concentrations were significantly reduced following PMX-HP therapy (MD, −1.22; 95 % CI, −1.62 to −0.81; I^2 = 98 %; Fig. 6), although this must be regarded with caution due to the considerable heterogeneity. Additionally, it may reduced the levels of IL-6 (MD, −5.3; 95 % CI -0.66–0.40; I^2 = 32 %; n = 313; Table 2), WBC (MD, −3.71; 95 % CI -7.82–0.40; I^2 = 85 %; n = 169; Table 2), and CRP (MD, −10.52; 95 % CI -22.48–1.44; I^2 = 55 %; n = 111; Table 2). There was no changes in IL-1β (n = 279; 3 trials, Table 2), IL-10 (n = 231, 2 trials; Table 2), TNF-α (n = 247, 3 trials; Table 2).

Three trials reported public data on major adverse events related to treatments. PMX-HP was not associated with at least one adverse event (OR 2.26, 95 % CI, 0.99–5.16, p = 0. 05) (Fig. 7). Both Nemoto et al. [13] and Suzuki et al. [52] reported no serious adverse effects are associated with PMX-HP. Vincent reported one case of fever associated with the device. Cruz et al. [27] reported that cartridge clotting in four individuals (6 %), hypotension in one (1.5 %), and tachycardia in two (3 %). Payen et al. [49] documented significant adverse effects in the PMX-HP group, four patients (3.4 %) experienced hemorrhagic episodes.

4. Discussion

In summary, this meta-analysis, along with thirty papers, confirmed that PMX-HP had a sizable advantage (OR, 0.75, 95 % CI, 0.65–0.88) for 28-day mortality patients with sepsis/septic shock. Patients in the mixed infection site group or those aged <70 years may benefit more from PMX-HP, according to subgroup analysis of 30 trials reporting 28-day mortality. PMX-HP may have had a favourable impact of lowering endotoxin levels (MD, −1.22, 95 % CI, −1.62 to - 0.81, p < 0.0001) and imoroved organ system function (MD, −2.11, 95 % CI -3.80 - 0.43, p = 0.01).

The PMX-HP treatment is an extracorporeal device with polymyxin B absorbent column has been used as an adjunct treatment for sepsis since the 1990s [57–59]. Blood purification in sepsis has largely been evaluated used hemofiltration methods in early experiments and clinical trials [60–62]. Clinical trials have shown that patients with AKI and sepsis who receive renal replacement therapy

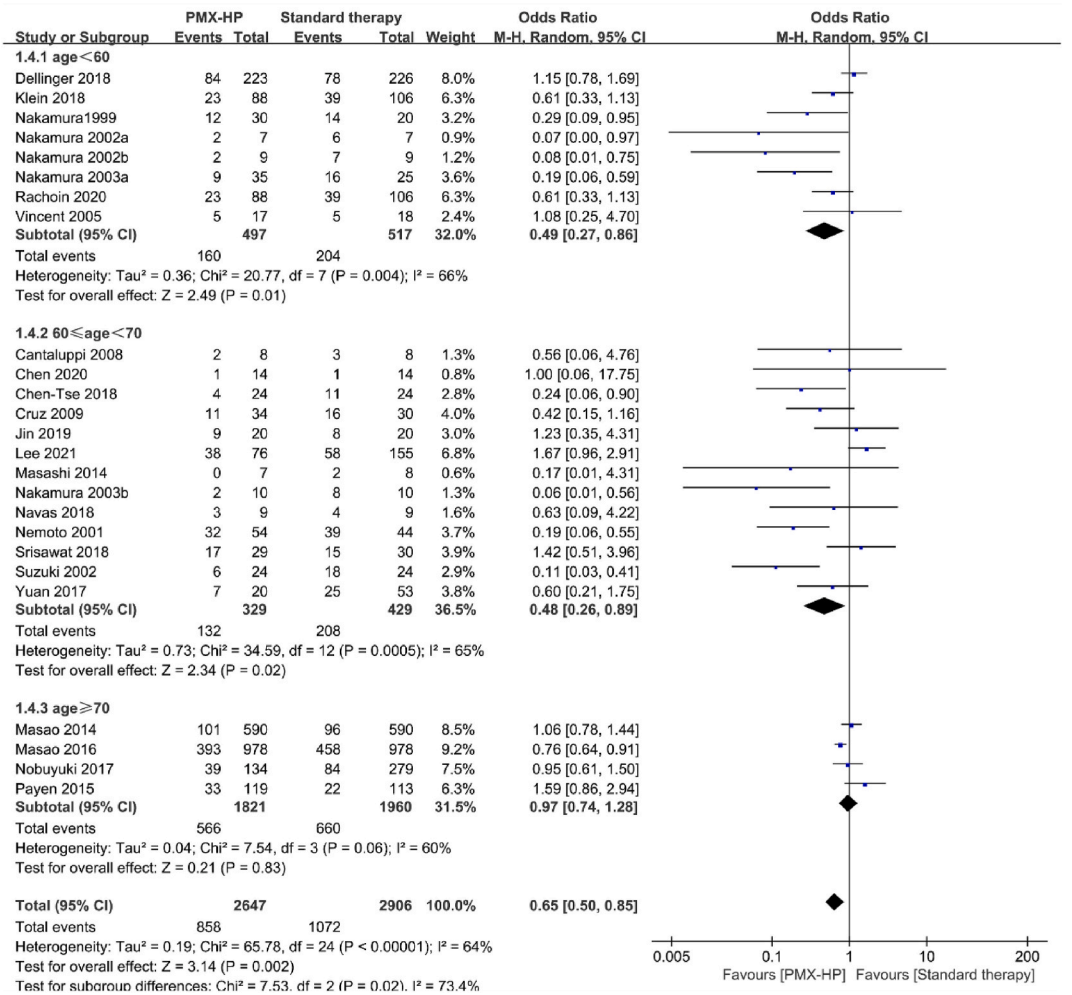

Fig. 4. Odds ratios (ORs) of 28-day mortality by age subgroup meta-analysis. PMX-HP = polymyxin B hemoperfusion.

Table 2
Outcome measures.

	Studies	Total no. of patients	Effect estimate (95 % CI)	*P* value	I^2(%)
90 day mortality	6	495	Pooled OR,1.02(0.70,1.48)	0.91	47
ICU length of stay	7	8109	Pooled OR,-1.38(-3.24,0.49)	0.15	61
Hospital length of stay	6	790	Pooled OR,-1.39(-3.27,0.50)	0.15	0
SOFA	9	580	MD, −2.11(-3.80,-0.43)	0.01	93
Noradrenaline	3	93	MD, −0.09(-0.23,0.06)	0.23	0 %
MAP	7	778	MD, 4.34(2.31,6.37)	< 0.0001	0
PaO_2/FIO_2	7	644	MD, 17.77(-13.18,48.71)	0.26	68
Platelets	3	496	MD, −2.24(-4.72,0.24)	0.08	0
Serum creatinine	6	728	MD, −0.58(-1.50,0.34)	0.06	38
EAA	11	913	MD, −1.22(-1.62,0.81)	< 0.00001	98
CRP	3	111	MD, −10.52(-22.48,1.44)	0.08	55
WBC	4	169	MD,-3.71(-7.82,0.40)	0.08	85
IL-1β	3	279	MD,0.27(-0.20,0.73)	0.26	40
IL-6	4	314	MD,0.53(-0.66,-0.40)	< 0.00001	32
IL-10	2	231	MD,0.05(-0.08,0.18)	0.44	0
TNF-α	3	247	MD, −26.90(-106.25,52.45)	0.51	97

(RRT) beyond conventionally recommended doses are not more likely to improve survival [62–66]. In addition, continuous veno-venous hemofiltration (CVVH) has been implicated in worsening severe sepsis dysfunction [64]. PMX-HP may become an alternative strategy to improve targeting blood purification and improved survival in sepsis patients. The effects of PMX-HP treatment on

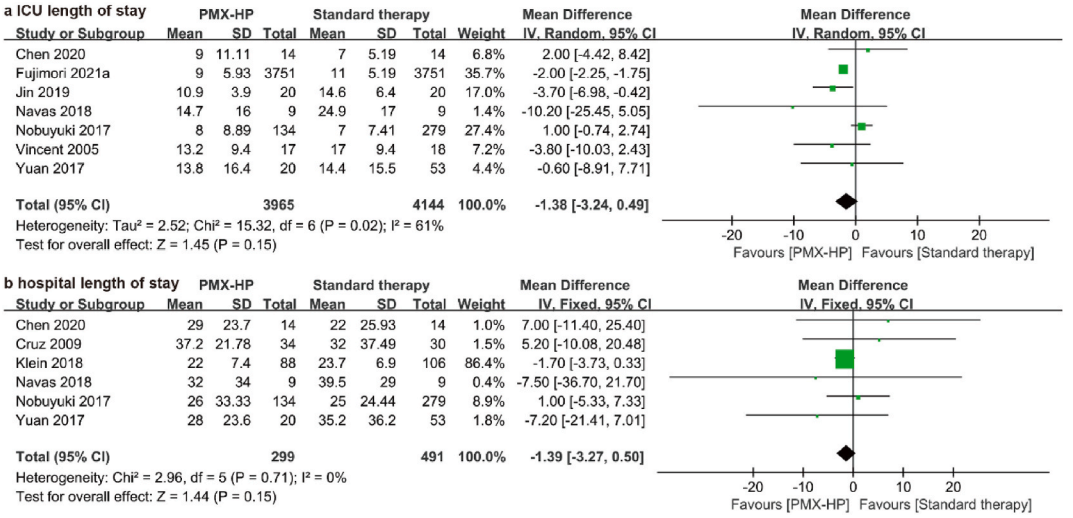

Fig. 5. Forest plot of comparison: PMX-HP versus standard therapy for ICU length of stay and hospital length of stay. PMX-HP = polymyxin B hemoperfusion.

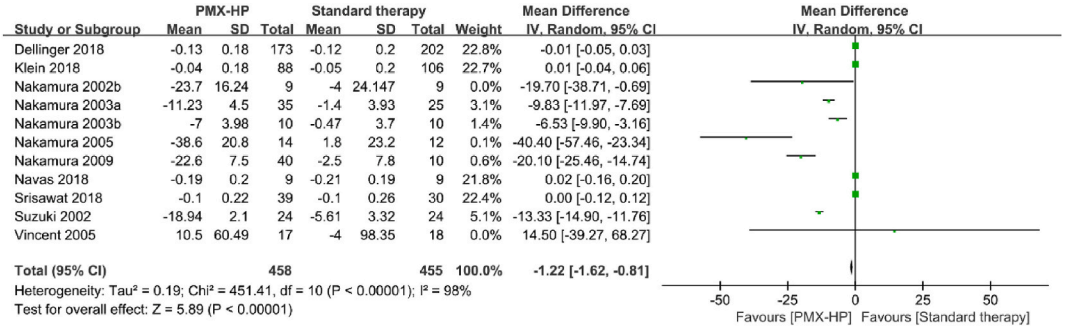

Fig. 6. Forest plot of the comparison of the EAA levels between the PMX-DHP group and the standard therapy. PMX-HP = polymyxin B hemoperfusion.

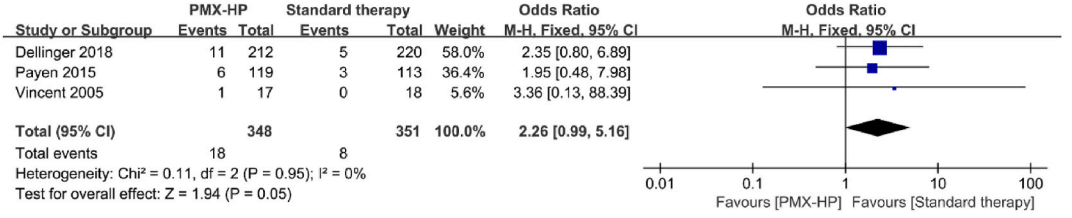

Fig. 7. Forest plot of the comparison of PMX-DHP versus standard therapy for hemoperfusion-related adverse events. PMX-HP = polymyxin B hemoperfusion.

mortality are inconsistent because of several factors. First, it is important to begin PMX-HP treatment as soon as possible. Takeyama et al. [67] reported that treating septic shock patients with PMX-HP within 6 h had a considerably shorter duration of ventilatory support and requires fewer catecholamines. Second, the sepsis cascade induced by endotoxin is amplified by acute kidney injury [68]. Forin et al. [69] reported a flowchart for a rational approach and treatment of endotoxic shock patients based on evidence from the literature in their clinical practice. According their flowchart, it was useful for lowering endotoxin level at least 2-h treatments with PMX-HP at precise times (T6 and T30).

The principal impact of polymyxin B is considered to be endotoxin binding and neutralization, which is quintessential in the pathophysiology of sepsis and septic shock. Furthermore, several instances have been described in which PMX-HP treatment used to be beneficial in patients with gram-positive bacterial septic shock without endotoxemia [70,71]. Thus, although the mechanism has no longer been thoroughly elucidated, it is realistic to speculate that binding neutralization and the discount of different associated

elements such as interleukin-6 [52,72,73], tumor necrosis factor-α [72,74], and neutrophil elastase [75] would be beneficial for enhancing such cases. Additionally, the results showed that PMX-HP treatment decreased endotoxin levels and improved organ system function in our study. However, some studies have failure to demonstrate that PMX-HP reduces the plasma level of endotoxin [76] and reduces the levels of inflammatory markers (such as TNF-α, IL-1β, and IL-6) [26]. Recently, an observational study [69] yielded the same results as our study, and PMX-HP may reduction in endotoxin levels and improvement of hemodynamics. Takuya et al. [77] reported that the use of PMX-HP as a cytokine modulator could be an additional therapeutic strategy to improve septic shock outcomes via the crucial role of IL-6 signaling in endothelial dysfunction. Our results also show that PMX-HP can reduce IL-6 levels (Table 2). According to the principle of PMX-HP and our results, abdominal infection patients with predominant G-bacteria should have the better benefit from PMX-HP. However, the subgroup analysis showed PMX-HP tends to be effective for the treatment of abdominal infections (OR 0.93, 95 % Cl, 0.66 to 1.30), but the difference was not significant ($p = 0.26$). Eight studies focused on abdominal infection in our study, and only 4 RCTs, so more highquality RCTs are needed to explore the clinical role of PMX-HP in endotoxin removal and abdominal infection in adult patients with severe sepsis or septic shock.

PMX-HP not only directly adsorbs circulating endotoxin but also affects hemodynamics, mediators, and pulmonary oxygenation. Specially, PMX-HP reduces $CD16^{+}$-$CD14^{+}$ monocytes and TLR4 expression [78], improving outcomes in septic shock patients. Adsorption of these monocytes may be the mechanism behind PMX-HP's effectiveness. Furthermore, numerous studies have documented the efficacy of PMX-HP in elevating blood pressure among individuals with sepsis [27,52,79–86]. Our study also indicates that the administration of PMX-HP is especially beneficial in enhancing MAP in patients with sepsis and septic shock. This observation may be attributed to the direct adsorption of anandamide and the subsequent reduction of nitric oxide levels in septic individuals [87,88]. Additional, while previous studies have demonstrated an increase in the PaO_2/FIO_2 ratio following PMX-HP treatment [27,80,82,83,85], our study found no significant difference in the change of this ratio between the PMX-HP and standard therapy groups.

There have been seven prior meta-analyses on the effectiveness of PMX-HP against sepsis. The first two reviews by Cruz et al. [14] and Qiu et al. [15] examined the impact of treatment with PMX-HP therapy on mortality, while the third review, by Zhou et al. [16] examined the effectiveness of a number of blood purification methods, including PMX-HP. One of the most significant features that set our analysis apart from those earlier analyses was the article eligible for review. In this evaluation, we included numerous non-RCTs (retrospective studies and prospective clinical studies) and attempted to show that PMX-HP improves survival among adult critically sick patients with sepsis or septic shock can develop by removing inflammatory cytokines. Although eligible studies differ, the magnitude of the effect of treatment with PMX-HP on mortality in our study (OR, 0.77; 95 % CI, 0.66–0.90) was similar to that in a previous meta-analyses: Cruz et al. [14] (RR, 0.50; 95 % CI, 0.37–0.68), Qiu et al. [15] (RR, 0.24, 95 % CI, 0.16–0.38), and Zhou et al. [16] (RR, 0.57, 95 % CI, 0.45–0.72).

In the current study, the incidence of haemoperfusion-related adverse events in the PMX-HP group was the same asthe control group (OR 2.26, 95 % CI, 0.99–5.16). However, because the individual studies included in this study lacking adequate data, well-designed RCTs are needed. Few clinically significant hemodynamic problems (1.5%–3%) were reported among the included papers for which additional material was not analysed by meta-analysis; indicating that PMX-HP treatment is usually well tolerated in clinical settings.

Our extensive search for clinical trials with no language restrictions is a significant asset of this study. By contacting the authors through e-mail, we conducted a thorough analysis of duplicate research populations. Furthermore, to the best of our knowledge, this is the largest sample size meta-analysis of PMX-HP provides a solid outcome in patients with sepsis or septic shock.

Our analysis has several limitations. First, some of the included trials were of suboptimal quality. In 8 of the 14 RCTs, the risk of bias with respect to random sequence generation and assignment concealment were considered unclear. Second, the majority of the trials included were not RCTs. This may increase the possibility of bias in this meta-analysis. Finally, a lack of included studies may resulted in an erroneous assessment of publication bias.

5. Conclusion

As a result, the expected risk of mortality in patients with sepsis/sepsis shock and the balance of benefit and damage. Furthermore, a noteworthy reported that the positive impact of PMX-HP treatment diminished with increasing age. Although there is uncertainty in the clearance of endotoxin and intra-abdominal infection of PMX-HP treatment in patients with sepsis/septic shock, we consider that PMX-HP has the potential to be an adjuvant therapy in critically ill adult patients aged < 70 years or with mixed infection site. However, due to the scarcity of RCTs, further large, rigorous RCTs are needed to validate or disprove these findings before the implications for practice are evident.

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Availability of data and materials

Data included in article/supp. material/referenced in article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because this a meta-analysis study is exempted from review under the Measures for Ethical Review of Life Sciences and Medical Research Involving Humans.

Consent for publication

Does not apply.

CRediT authorship contribution statement

Chao Li: Writing – review & editing, Writing – original draft, Data curation. **Jinlian Zhang:** Formal analysis, Data curation. **Ping Yang:** Methodology, Investigation. **Ranran Wang:** Supervision, Software. **Ting Chen:** Writing – review & editing, Project administration. **Lixia Li:** Writing – review & editing, Data curation.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33735.

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