

Dear reviewers,

**Reviewer's code: 00733674**

• Reviewers' Comments to Author:

*This moderate-size case-control study uses propensity-score to assess the effect of polymixin B (PMX) hemoperfusion (HP) on clinical outcomes in presumed gram-negative sepsis after source control. The results are in accordance with larger randomized studies, which show some effect on hemodynamics and no effect on survival. Therefore, the results are not very novel, but are still interesting. The manuscript itself is well written and english is very good. I have some questions/suggestions:*

<Major issues>

*Q1. Hemodynamic stability was one of the main outcomes and both groups (after matching) were still different regarding the use of vasopressors (it is stated that the use of vasopressors was comparable, but only in yes/no sense, since there was significantly more use of vasopressin in PMX group, which is a stronger vasopressor than dopamine, which was more used in control group). Why did the authors not use VDI (vasopressor dependency index) as one of the propensity matching indexes? Furthermore, VDI values after 72h were similar in both groups (and close to 0), but the PMX group started with much higher VDI values, which probably contributed to the significant between group difference (Table 2). The groups should be matched for VDI! This is much more important than sex, causative microorganism etc.*

**Answer:** Patients with abdominal septic shock after the introduction of PMX-HP treatment showed more aggressive and severe condition compared to patients before the introduction of PMX-HP treatment. This is the reason why we performed the propensity score matching

method for analysis. However, the initial disease status of PMX group was more severe, and it was almost impossible to include VDI as the matching factor mainly due to the limitation of retrospective design of study and the small number of cases. Nevertheless, to ensure maximum homogeneity of the two groups, we included several factors for the propensity matching method to correct confounder factors as many as possible. Besides, we believe that our idea was reasonable to show the efficiency of hemoperfusion treatment for the management of sepsis because disease status was more miserable in the experimental group compared with the control group and PMX. However, as you pointed out, the lack of matching the VDI could be a limitation of this study. Therefore, prospective RCT should be conducted with including VDI as matching factor to confirm current study.

***Q2. How exactly were changes in outcome parameters (VDI, SOFA etc.) compared between the groups, since there are two values in each group (0, 72h)? In the methods it is stated, that paired samples T test was used, but this can only be used for within-group comparison of before/after (i.e. 0-72 h) but not between group. Perhaps ANOVA should be used to simultaneously assess the effect of group and time.***

**Answer:** We agree with your opinion. In fact, treatment responses were compared by paired t-test in the same group and one-way ANOVA was used to simultaneously assess the effect of group and time. We are sorry for missing the above information while writing the manuscript. As you pointed out, we revised our manuscript in the method section.

<Methods>

### **Statistical analysis**

SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA) was used for statistical

analysis. The  $p$  value of less than 0.05 was considered statistically significant. Continuous variables were analyzed using Student's  $t$ -test and expressed as the mean standard deviation. Categorical variables were presented as proportions, and were analyzed via  $\chi^2$  test or Fisher's exact test. The variations in SOFA score were analyzed using Wilcoxon rank sum test. We used propensity-score matching in order to minimize the lead-time bias and selection bias. Propensity-score matching was conducted to adjust for confounding of baseline characteristics and the severity of clinical conditions. To estimate the propensity score, a logistic regression analysis of clinical factors including age, sex, body weight, underlying malignancy, APACHE II score, pre-existing organ dysfunction, initial SOFA score, microorganism responsible for sepsis, and the initial values of lab including the count of WBC, platelet count, hemoglobin and the level of prothrombin time (PT) or international normalized ratio (INR), was performed in patients who underwent PMX-HP treatment. In the propensity score-matched population, we compared the continuous variables using a paired  $t$  test or the Wilcoxon rank test and categorical variables with the McNemar's or Bowker's test. The C-statistics were estimated to evaluate the goodness of fit. We used 1:1 matching and a caliper width equal to 0.01 of the standard deviation of the logit of the propensity score was used.



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***Q3. SOFA score, one of the main significant outcomes, includes serum creatinine, which is lowered by PMX-CRRT therapy. It is stated in the manuscript that the proportion of patients on CRRT was not different between the groups, but I believe this is not enough to exclude the effect of CRRT treatment on SOFA improvement. Perhaps a modified SOFA without renal sub-score could be used, or urine output should be analyzed, which is not affected by CRRT itself, but more directly reflects renal and cardiovascular status. Anyway, this should be also commented in the discussion.***

**Answer:** We totally agree with your opinion. As you point out, it may not be enough to rule out the impact of CRRT treatment on SOFA improvement in that the proportion of performing CRRT between the two groups are not the same. Although modified SOFA without renal sub

score could be used, we could not analyze unfortunately. For next study, we will fully consider this limitation and we will perform additional subgroup analysis on modifies SOFA scores to completely exclude the impact of renal replacement therapy such as CRRT for clinical outcomes. Also, according to your advice, we added the following statement to the limitation section of the text which was discussed as below.

#### <Discussion>

Despite these interesting results of the PMX-HP, our study has some limitations inherent to its retrospective design and small sample size. Since it covers a period of more than six years, the evolution of intensive care may have affected the survival. However, a single intensivist performed the treatment according to the standard protocol, and no major changes in SSC guidelines have occurred. In order to overcome these limitations, we performed a propensity score matching to correct for disease severity and baseline characteristics. Moreover, we believe that the bias might be minimized because the PMX-HP treatment was indicated to only patients with abdominal sepsis who underwent source control for the infectious foci. Additionally, the detection of further statistically significant differences in parameters such as 28-day mortality or ICU mortality was precluded due to the small sample size. A prospective multicenter randomized trial with a large sample size is needed in the near future to confirm our study results.

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*completely exclude the impact of renal replacement therapy such as CRRT for clinical outcomes. In fact, in order to overcome these limitations, we performed a propensity score matching to correct for disease severity and baseline characteristics. Moreover, we believe that the bias might be minimized because the PMX-HP treatment was indicated to only patients with abdominal sepsis who underwent source control for the infectious foci. Additionally, the detection of further statistically significant differences in parameters such as 28-day mortality or ICU mortality was precluded due to the small sample size. A prospective multicenter randomized trial with a large sample size is needed in the near future to confirm our study results.*

***Q4. How do the authors explain, that ICU stay was shorter in PMX group, although days on ventilator were comparable. What was keeping patients in the ICU? Vasopressors (than the days on vasopressors should be presented) or dialysis dependence (than this should be given)? It also seems that somewhat sooner discharge after PMX "moved" the mortality from ICU to the 28-days value (since overall mortality in the end was comparable).***

**Answer:** Thank you for your comment. Staying or discharge from ICU depends on variable factors such as presence of invasive pulmonary support, renal replacement support or hemodynamic supports. Also, considering that patients of this study were a postoperative condition, the stability of surgical wound or intestinal anastomosis should be regarded as to determine to stay or discharge from the ICU. Therefore, in this study, the ventilator day was similar between the two groups, but the difference in the length of ICU stay could be affected by the complex interaction of the various factors mentioned above. Especially, the establishment of hemodynamics through tapering of inotropic agents could have a more significant effect. Additionally, we tried to maximize the comparability between two groups by performing PS matching method in the current study, however, it could not be completely excluded that there is a significant difference in ventilator day due to the small sample size.

Therefore, we believe that it will be possible for a more sophisticated analysis if more sample sizes are obtained to analyze.

***Q5. nafamostat is known to have aggregation inhibitory and dis-aggregatory effects on thrombocytes (see DOI 10.1097/01.mat.0000209224.94089.bc). Do the authors think this could affect thrombocyte count and hemostasis***

**Answer:** Thanks for your comment. Considering the effect of nafamostat on platelet disaggregation, thrombocyte count and hemostasis might be effected by the medication. However, nafamostat is routinely administrated continuously for the anticoagulation for patients with CRRT in our institution, which means that nafamostat was used for patients with CRRT in the control group. In addition, coagulation SOFA score was improved in PMX group despite of routine nafamostat administration for hemoperfusion. Therefore, we believe that nafamostat could not make a significant effect on thrombocyte count and hemostasis by the PMX therapy..

***Q6. SOFA (which depends on thrombocytes) via reduction of aggregation caused by DIC/sepsis? Which anticoagulant was used for CRRT in the control group. please specify in the methods.***

**Answer:** Actually, nafamostat is routinely administrated continuously for the anticoagulation for patients with CRRT in our institution. According to your advice, we revised the sentences in method section as same as below.

**<Methods>**

### **Study protocol; Polymyxin B hemoperfusion group versus. Control group**

The study protocol is summarized in Figure 1. In case of PMX group, the first PMX-HP session was initiated within 12 hours after surgical source control followed by a second PMX-HP session within 24 hours after completion of the first session. A dual-lumen catheter (12Fr Arrow International, Reading, PA, USA) was inserted into the internal jugular vein or femoral vein guided by ultrasound. Subsequently, two sessions of PMX-HP were performed using toraymyxin cartridge (Toraymyxin, Toray industries, Tokyo, Japan) in the continuous renal replacement therapy (CRRT) machine. The blood flow rate varied between 80 to 120 mL/min, and Nafamostat mesylate (Futhan, Torii Pharmaceuticals, Tokyo, Japan) was used as anticoagulant for the circuit at a dose of 20-30mg/h. [3, 19] Based on the study of *Kawazoe et al* [20], each session was conducted for 6 hours except in cases indicated for PMX-HP therapy discontinuation.

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### **<Minor issues>**

***Q1. Given the importance of mortality, I would suggest % mortality for both groups is added to the abstract, although the difference is not significant.***



**Answer:** Thank you for your point out. We revised the abstract according to your recommendation.

<Abstract>

## **RESULTS**

After propensity score matching, 40 patients were analyzed (20 patients in the PMX group and 20 patients in the control group). The scores of total Sequential Organ Failure Assessment (SOFA) score, renal SOFA and coagulation SOFA were significantly improved in the PMX group but not in the control group. (from  $11.2 \pm 5.8$  to  $4.7 \pm 3.5$  in PMX group versus  $10.0 \pm 4.0$  to  $8.7 \pm 7.3$  in control group,  $p=0.047$  from  $2.6 \pm 1.0$  to  $0.7 \pm 1.0$  in PMX group versus  $2.6 \pm 1.5$  to  $2.8 \pm 1.6$  in control group,  $p=0.000$ , from  $1.6 \pm 1.5$  to  $1.3 \pm 1.3$  in PMX group versus  $1.2 \pm 1.2$  to  $2.8 \pm 1.8$  in control group,  $p=0.014$ , respectively). Further, the length of intensive care unit (ICU) stay was significantly shorter in PMX group. However, no statistically significant difference was found in ICU mortality.

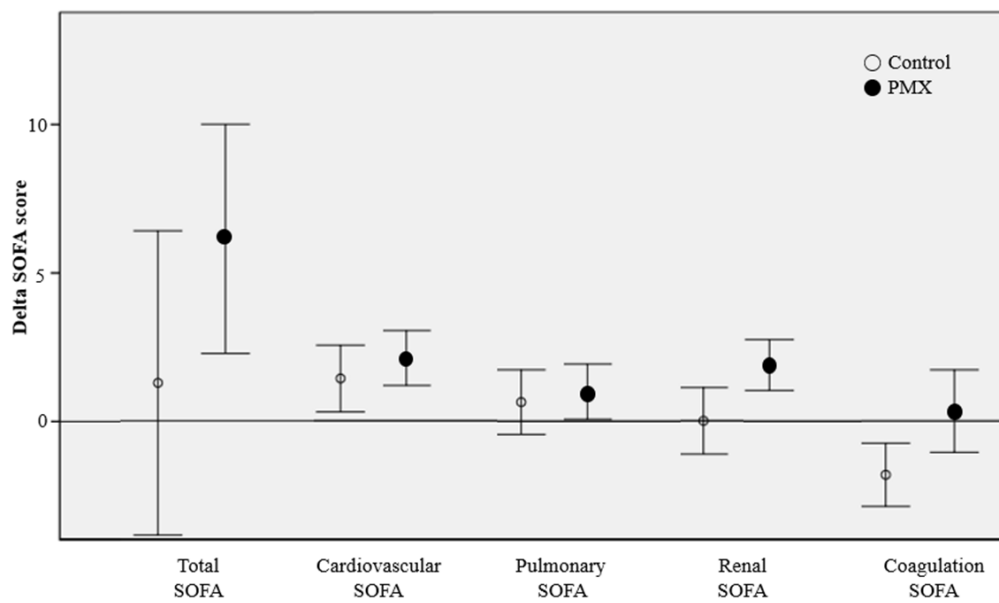
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## **RESULTS**

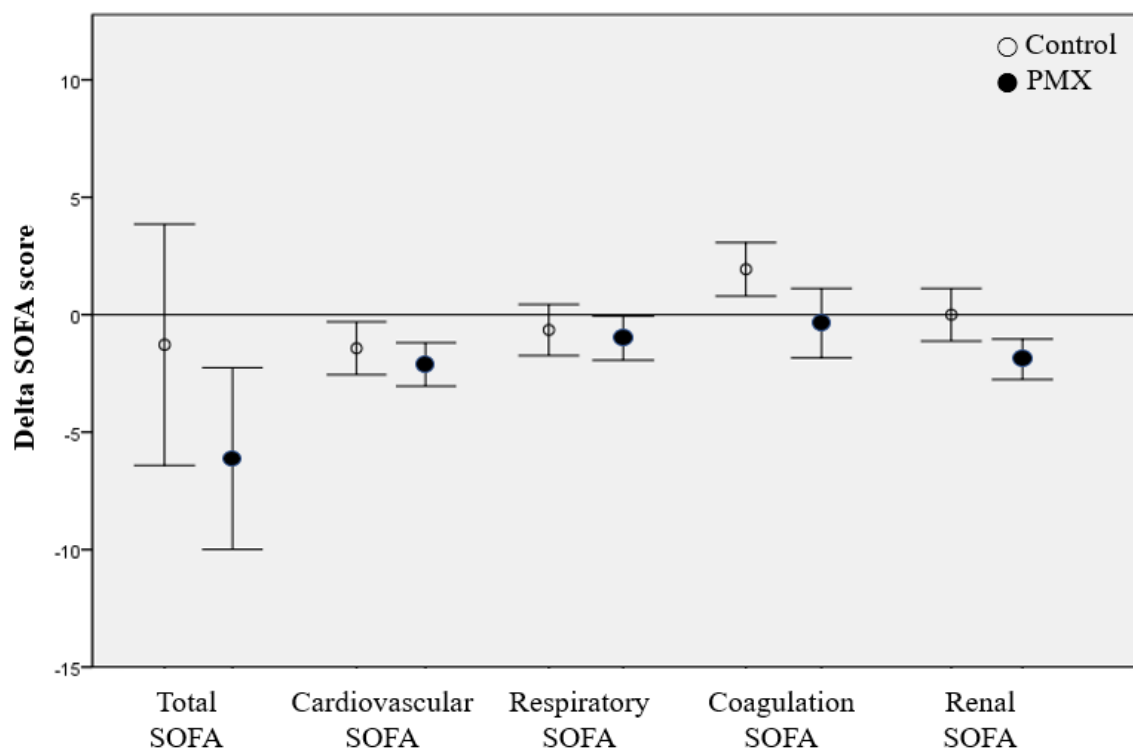
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**Q2. Figure 3: In the footnote it is stated that "Negative values of delta SOFA scores indicate improvement of organ function", but values on the graph are positive. This is probably an error, since patients improved.**

**Answer:** We are really thank you for your review. After reviewing your review, we found an error in the statistical process. We corrected the error and revised the figure.



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**Reviewer's code: 02650654**

• **Reviewers' Comments to Author:**

*It would be interesting to have some notes about the patho-physiology of this treatment.*

***Q1. Did the final outcome of these diseases necessitate of subsequent surgery?***

**Answer:** Thank for your point out. In fact, no cases were required re-operation.

## Reviewer's code: 00068723

### ● Reviewers' Comments to Author:

*The authors investigated the usefulness of hemoperfusion with polymyxin B (PMX-HP) to patients after surgery due to sepsis from abdominal infection. They found out that the PMX-HP was useful. The aim was clear, and the conclusion was useful. But information was limited.*

*Q1. Was PMX-HP commercially available? If so, it was assumed that literatures exist on its clinical application. How did the other clinicians report? Or was this study the first report on application of PMX-HP after surgery? If so, logical flow should be clearly written from what was the problem in the authors' field to how PMX-HP was thought up.*

**Answer:** Thank you for your comment. PMX-HP is currently commercially available. And several multicenter trials have been reported such as EUPHAS trial (*JAMA* 2009;301(23):2445-2452. doi:10.1001/jama.2009.856), EUPHRATES trial (*Intensive Care Med* (2018) 44:2205–2212) which showed the effectiveness of PMX-HP for abdominal septic shock.

*Q2. Figure 3. Where was this figure explained in the text? “Figure 3” should be inserted where the figure explained. Did the data indicate improvement SOFA score? How was the date obtained? Figure 3 seemed the only significant data of this study. This figure should be fully explained, and discussed.*

**Answer:** We are sorry for missing the explanation about “Figure 3” as you pointed out. We are really thank you for your review and corrected the error and added the explanation of “Figure 3” in the text as same as below.

Regarding the clinical effects of PMX-HP, there was a significant improvement in the SOFA score at 72 hours in patients included in the PMX-HP group compared with the control group. (from  $11.2 \pm 5.8$  to  $4.7 \pm 3.5$  in PMX group vs.  $10.0 \pm 4.0$  to  $8.7 \pm 7.3$  in control group,  $p = 0.047$ ) Especially, the renal and coagulation SOFA scores were significantly improved in PMX group.(from  $2.6 \pm 1.0$  to  $0.7 \pm 1.0$  in PMX group versus  $2.6 \pm 1.5$  to  $2.8 \pm 1.6$  in control group,  $p = 0.000$ , from  $1.6 \pm 1.5$  to  $1.3 \pm 1.3$  in PMX group versus  $1.2 \pm 1.2$  to  $2.8 \pm 1.8$  in control group,  $p = 0.014$ , respectively) Furthermore, the inotropic score and VDI were significantly decreased in PMX group.(from  $163.7 \pm 302.1$  to  $8.9 \pm 19.1$  of inotropic score in PMX group versus  $90.8 \pm 181.7$  to  $1.4 \pm 4.2$  in control group,  $p = 0.006$ , and from  $2.4 \pm 3.4$  to  $0.1 \pm 0.3$  of VDI in PMX group versus  $1.0 \pm 2.0$  to  $0.0 \pm 0.1$  in control group,  $p = 0.001$ , respectively) (Table 3) The length of ICU stay was significantly shorter in the PMX group than the control group. ( $10.9 \pm 3.9$  days in PMX group vs.  $14.6 \pm 6.4$  days in control group,  $p = 0.036$ ) The ICU mortality rate was lower in the PMX group (n=4, 20%) than in the control group, (n=8, 40%) without any statistically significant difference. Similarly, there was no significant difference between the two groups in the in-hospital mortality and duration of mechanical ventilation. (Table 4)

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0.000, from  $1.6 \pm 1.5$  to  $1.3 \pm 1.3$  in PMX group versus  $1.2 \pm 1.2$  to  $2.8 \pm 1.8$  in control group,  $p = 0.014$ , respectively) Furthermore, the inotropic score and VDI were significantly decreased in PMX group. (from  $163.7 \pm 302.1$  to  $8.9 \pm 19.1$  of inotropic score in PMX group versus  $90.8 \pm 181.7$  to  $1.4 \pm 4.2$  in control group,  $p = 0.006$ , and from  $2.4 \pm 3.4$  to  $0.1 \pm 0.3$  of VDI in PMX group versus  $1.0 \pm 2.0$  to  $0.0 \pm 0.1$  in control group,  $p = 0.001$ , respectively) (Table 3). *The PMX group showed a greater reduction compared to the control group in terms of renal SOFA (mean delta SOFA score, -1.9 vs. 0,  $p = 0.007$ ) and coagulation SOFA (mean delta SOFA score, -0.36 vs. 1.93,  $p = 0.013$ ) However, the two groups were similar in term of total SOFA (mean delta SOFA score, -6.13 vs. -1.28,  $p = 0.121$ ), cardiovascular SOFA (mean delta SOFA score, -2.12 vs. -1.43,  $p = 0.315$ ) respiratory SOFA (mean delta SOFA score, -1.0 vs. -0.65,  $p = 0.613$ ) (Figure 3) The length of ICU stay was significantly shorter in the PMX group than the control group. ( $10.9 \pm 3.9$  days in PMX group vs.  $14.6 \pm 6.4$  days in control group,  $p = 0.036$ ) The ICU mortality rate was lower in the PMX group ( $n=4$ , 20%) than in the control group, ( $n=8$ , 40%) without any statistically significant difference. Similarly, there was no significant difference between the two groups in the in-hospital mortality and duration of mechanical ventilation. (Table 4)*

**Q3. Discussion was long. Discussion should be focused on the significant of the study.**

**Answer:** Thank you for your recommendation. We revised the discussion part according to your opinion.

## **DISCUSSION**

In the current study, PMX-HP treatment significantly improved the hemodynamic parameters such as inotropic score and VDI, and the degree of organ failure represented by the renal, coagulation or total SOFA score, and the length of ICU stay, for patients whose infection focus were successfully removed by surgical intervention.

In terms of hemodynamic aspects, the inotropic score and VDI decreased

significantly in the PMX group consistent with previous studies that showed a significantly increment in arterial pressure and decreased need for vasopressor after PMX-HP treatment. [4, 14] Polymyxin B is a lipopeptide antibiotics isolated from *Bacillus polymyxa*. It disrupts the outer membrane of gram-negative bacilli and binds to the lipid A portion of LPS selectively. [19] Circulating LPS from gram-negative bacteria usually activates the inflammatory reaction, complement or coagulation system of the hosts. Nakamura et al. [22, 23] reported that circulating monocyte and neutrophils were removed through the PMX cartridge, and PMX-HP reduced the levels of TNF-alpha, IL-6,10, plasminogen activator inhibitor 1, metalloproteinase and anandamide. These mechanisms of PMX-HP improved tissue oxygenation and hemodynamic status against infection, and contributed to the improvement of hemodynamics in critically ill patients with abdominal septic shock.

Moreover, PMX-HP treatment improved the cardiac function via elimination of myocardial depressant mediator such as anandamide of 2-arachidonoylglycerol. Therefore, it reduces the dosage of catecholamine drugs and enhances the hemodynamic outcome. [24] We propose that this mechanism decreases the adverse cardiovascular effects of high-dose catecholamines such as arrhythmia, decreased cardiac output, ischemic change of mesentery caused by potent vasoconstriction. Maynar et al. [14] reported that 28-day mortality rates were significantly decreased in patients who reduced their norepinephrine dose by more than half within 24 hours after PMX-HP. Our study also revealed a significant improvement in the inotropic score and VDI of the PMX group and suggested that PMX-HP treatment in reduced the levels of myocardial depressant mediator in cardiac function.

The role of PMX-HP in septic shock would also affect the pulmonary function by absorbing various inflammatory mediators during septic shock including endotoxins and proinflammatory cytokines. The improvement in hypercytokinemia and inflammation prevented the damage to pulmonary endothelium and reduced the intrapulmonary shunting, consequently. [1, 25, 26] Based on the possibility of pulmonary protective function by PMX-HP, Takeda et al [25] reported that it improved the pulmonary oxygenation in severe cases of acute respiratory distress syndrome

(ARDS). Pulmonary complications are common in septic shock, and rapidly increased due to fluid resuscitation or compromised respiratory function triggered by anesthesia after major surgery, and therefore PMX-HP might improve and protect pulmonary functions in patients after emergency surgery due to abdominal sepsis who has high risk of pulmonary complications such as ARDS. [27] However, we failed to detect a statistically significant improvement in pulmonary function probably due to its small sample size, and a further study with a large sample size should be needed.

In addition, one of the most common complications of septic shock is acute kidney injury (AKI) and it occurs in more than 20 % of patients with sepsis that is related to higher mortality rate. [28] *Ebihara* et al. suggested that PMX-HP restored the angiopoietin-1 levels and diminished the levels of angiopoietin-2 in septic AKI, [29] thereby preventing the apoptosis of renal tubular cells resulting in a protective effect against AKI. [19] Our results demonstrated a dramatic decrease in renal SOFA score, and considering the high mortality of septic AKI, authors expect that the removal of endotoxin or cytokines might protect the renal function in abdominal septic shock.

We also demonstrated an improvement in the ICU mortality rate of patients who underwent PMX-HP therapy compared with the control group although the results showed no statistical significance. However, our study showed a significant reduction in the length of ICU stay and SOFA score at 72 hours indicating improvement in overall organ function. PMX-HP therapy may have improved the prognosis in the early phases of intraabdominal septic shock and promoted organ preservation, ultimately.

Despite these interesting results of the PMX-HP, our study has some limitations inherent to its retrospective design and small sample size. Since it covers a period of more than six years, the evolution of intensive care may have affected the survival. However, a single intensivist performed the treatment according to the standard protocol, and no major changes in SSC guidelines have occurred. In order to overcome these limitations, we performed a propensity score matching to correct for disease severity and baseline characteristics. Moreover, we believe that the bias might be minimized because the PMX-HP treatment was indicated to only patients with



abdominal sepsis who underwent source control for the infectious foci. Additionally, the detection of further statistically significant differences in parameters such as 28-day mortality or ICU mortality was precluded due to the small sample size. A prospective multicenter randomized trial with a large sample size is needed in the near future to confirm our study results.

Actually, there have been studies to identify the effect of PMX-HP in various randomized controlled trials in the meantime. In the EUPHAS I trial of 2009 [4], PMX-HP significantly reduced the 28-day mortality and improved SOFA score in patients with septic shock associated with gram-negative infection. In the EUPHAS 2 trial of 2014, there was a significant decrease in SOFA score in patients with only abdominal sepsis. [13] We agree that PMX-HP is more effective in patients with abdominal sepsis following surgical elimination of infection foci. In case of other gram-negative infections except for intra-abdominal infections, such as infection of the lower respiratory tract, the control of infectious source should be accomplished via eradication of the bacterial pathogens using antibiotics, and this limitation might be implicated in a resistance to antibiotics or drug toxicity. On the other hand, in patients with abdominal sepsis, PMX-HP may be used after complete elimination of infection focus via surgical control, resulting in clearance of the residual circulating endotoxin more effectively compared with other sites of infection. [7] We expect that this study, which involved only patients with abdominal sepsis controlled surgically, would be useful in establishing treatment guidelines for PMX-HP intervention.

In conclusion, PMX-HP would be a feasible treatment modality in ICU patients with peritonitis to restore organ function and improve hemodynamics. It is expected to facilitate clinical outcomes especially in patients with complete elimination of the source of GNB infection via surgical procedures. A further prospective study with large samples is needed to establish the precise guidelines for PMX-HP therapy.

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## ***DISCUSSION***

*In the current study, PMX-HP treatment significantly improved the hemodynamic*

parameters such as inotropic score and VDI, and the degree of organ failure represented by the renal, coagulation or total SOFA score, and the length of ICU stay, for patients whose infection focus were successfully removed by surgical intervention.

In terms of hemodynamic aspects, the inotropic score and VDI decreased significantly in the PMX group consistent with previous studies that showed a significantly increment in arterial pressure and decreased need for vasopressor after PMX-HP treatment. [4, 14] Polymyxin B is a lipopeptide antibiotics isolated from *Bacillus polymyxa*. It disrupts the outer membrane of gram-negative bacilli and binds to the lipid A portion of LPS selectively. [19] *Circulating LPS activates the inflammatory reaction, complement or coagulation system of the hosts.* Nakamura et al. [22, 23] reported that circulating monocyte and neutrophils were removed through the PMX cartridge, and PMX-HP reduced the levels of TNF-alpha, IL-6,10, plasminogen activator inhibitor 1, metalloproteinase and anandamide. *These mechanisms of PMX-HP improved tissue oxygenation and hemodynamic status, and contributed to the improvement of hemodynamics in patients with abdominal septic shock.*

Moreover, PMX-HP treatment improved the cardiac function via elimination of myocardial depressant mediator such as anandamide of 2-arachidonoylglycerol. Therefore, it reduces the dosage of catecholamine drugs and enhances the hemodynamic outcome. [24] We propose that this mechanism decreases the adverse cardiovascular effects of high-dose catecholamines such as arrhythmia, decreased cardiac output, ischemic change of mesentery caused by potent vasoconstriction. Maynar et al. [14] reported that 28-day mortality rates were significantly decreased in patients who reduced their norepinephrine dose by more than half within 24 hours after PMX-HP. Our study also revealed a significant improvement in the inotropic score and VDI of the PMX group and suggested that PMX-HP treatment in reduced the levels of myocardial depressant mediator in cardiac function.

*The role of PMX-HP in septic shock would also affect the pulmonary function by absorbing various inflammatory mediators including endotoxins and proinflammatory cytokines. The improvement in hypercytokinemia and inflammation prevented the damage to pulmonary endothelium consequently. [1, 25, 26] Pulmonary complications are common in septic shock, and rapidly increased due to fluid resuscitation or compromised respiratory function triggered by anesthesia after major surgery, and therefore PMX-HP might improve and protect pulmonary functions in patients after emergency abdominal surgery who has high risk of*

*pulmonary complications such as acute respiratory distress syndrome (ARDS). [27] However, we failed to detect a statistically significant improvement in pulmonary function probably due to its small sample size, and a further study with a large sample size should be needed.*

*In addition, one of the most common complications of septic shock is acute kidney injury (AKI) and it occurs in more than 20 % of patients with sepsis that is related to higher mortality rate. [28] Ebihara et al. suggested that PMX-HP restored the angiopoietin-1 levels and diminished the levels of angiopoietin-2 in septic AKI, [29] thereby preventing the apoptosis of renal tubular cells resulting in a protective effect against AKI. [19] Our results demonstrated a dramatic decrease in renal SOFA score, and considering the high mortality of septic AKI, authors expect that the removal of endotoxin or cytokines might protect the renal function in abdominal septic shock.*

*Our study also showed a significant reduction in the length of ICU stay and SOFA score at 72 hours indicating improvement in overall organ function. PMX-HP therapy may have improved the prognosis in the early phases of intraabdominal septic shock and promoted organ preservation, ultimately.*

*Despite these interesting results of the PMX-HP, our study has some limitations inherent to its retrospective design and small sample size. Since it covers a period of more than six years, the evolution of intensive care may have affected the survival. However, a single intensivist performed the treatment according to the standard protocol, and no major changes in SSC guidelines have occurred. In order to overcome these limitations, we performed a propensity score matching to correct for disease severity and baseline characteristics. Moreover, we believe that the bias might be minimized because the PMX-HP treatment was indicated to only patients with abdominal sepsis who underwent source control for the infectious foci. Additionally, the detection of further statistically significant differences in parameters such as 28-day mortality or ICU mortality was precluded due to the small sample size. A prospective multicenter randomized trial with a large sample size is needed in the near future to confirm our study results.*

*Actually, there have been studies to identify the effect of PMX-HP in various randomized controlled trials in the meantime. In the EUPHAS I trial of 2009 [4], PMX-HP significantly reduced the 28-day mortality and improved SOFA score in patients with septic shock associated with gram-negative infection. In the EUPHAS 2 trial of 2014, there was a*

significant decrease in SOFA score in patients with only abdominal sepsis. [13] We agree that PMX-HP is more effective in patients with abdominal sepsis following surgical elimination of infection foci. *In case of other gram-negative infections, such as infection of the lower respiratory tract, the control of infectious source should be accomplished via using antibiotics, and this limitation might be implicated in a resistance to antibiotics or drug toxicity. On the other hand, in patients with abdominal sepsis, PMX-HP may be used after complete elimination of infection focus via surgical control, resulting in clearance of the residual circulating endotoxin more effectively compared with other sites of infection.* [7] We expect that this study, which involved only patients with abdominal sepsis controlled surgically, would be useful in establishing treatment guidelines for PMX-HP intervention.

*In conclusion, PMX-HP would be a feasible treatment modality in ICU patients with peritonitis to restore organ function and improve hemodynamics. It is expected to facilitate clinical outcomes especially in patients with complete elimination of the source of GNB infection via surgical procedures. A further prospective study with large samples is needed to establish the precise guidelines for PMX-HP therapy.*