Renal Replacement Therapy

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Blood purification therapy for severe sepsis: a multicenter, observational cohort study in northern Japan

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Abstract

Background: Sepsis is associated with life-threatening organ dysfunction caused by a dysregulated host response to infection. However, no specific therapy has been shown to improve mortality in patients with sepsis. We conducted a study to clarify the utilization status of various BPTs and the clinical characteristics of patients who received BPTs in northern Japan. In addition, the association of various BPTs with clinical outcomes was examined.

Methods: This is a sub-analysis of the Tohoku Sepsis Registry, a multicenter, prospective, observational cohort study. To determine whether BPT was independently associated with in-hospital mortality in patients with severe sepsis, the following analyses were performed. Differences between survivors and non-survivors were assessed using Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables. Univariate logistic regression analysis was used to evaluate the factors associated with in-hospital mortality. In the multivariate logistic regression analysis, adjustments were made for the variables that were significant in the univariate logistic regression analysis. Clinical factors associated with mortality were analyzed.

Results: We enrolled 616 consecutive patients (≥ 18 years) with median Sequential Organ Failure Assessment scores of 8.0. During median of 22 days hospitalization, 139 patients died (mortality 22.6%). 20.7% of patients with severe sepsis received any type of BPT (mortality 38.6%). BPT consisted of 65.1% continuous renal replacement therapy (CRRT) with renal indication (mortality 48.8%), 26.0% CRRT with non-renal indication (mortality 21.2%), 22.2% intermittent renal replacement therapy (mortality 32.1%), and 33.1% polymyxin B-immobilized fiber column-direct hemoperfusion (mortality 42.9%). Meanwhile, no BPT group (mortality 18.5%) showed a significantly lower mortality than any BPT group. Besides, in multivariate analyses, all BPT modes were not independently associated with all-cause mortality.

Conclusions: This study suggested the clinical status of BPTs for severe sepsis patients in northern Japan. Among all types of BPT, continuous renal replacement therapy (CRRT) for renal indication was most frequently selected. Severe sepsis patients received BPT had a higher mortality and severity; however, the BPT implementation may not be associated with mortality.

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Trial registration UMIN-CTR, UMIN000010297, Registered on 22 March 2013, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000012055).

Keywords: Blood purification, Hospital mortality, Multivariate analysis, Sepsis, Acute kidney injury

Background

Sepsis is associated with life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In the USA, mortality rates have been reported to be > 15% [2]. Radical treatments include the administration of antimicrobial agents and surgical source control. However, no specific therapy has been shown to improve mortality in patients with sepsis.

Acute kidney injury (AKI) is strongly associated with poor prognosis in patients with sepsis [3]. Renal replacement therapy is recommended for sepsis patients with AKI [4]. However, it is unclear whether renal replacement therapy improves survival or renal recovery after sepsis-induced AKI [5]. Along with renal replacement therapy, blood purification therapy (BPT) has been proposed as a treatment for modulating the inflammatory response in sepsis, even in patients without renal dysfunction [4, 5]. The in-hospital mortality rate in sepsis patients undergoing BPT is reported to be high, ranging from 41 to 79% in patients with renal and non-renal indications [6–9]. However, mortality rates are highly variable, and the number of reports is limited. There is little detailed information on the use of BPT modes in septic patients and mortality rates for each BPT mode.

Several studies have shown the potential of BPT in modulating the immune response. Two meta-analyses [10, 11] of small, randomized controlled trials evaluating the effects of hemoperfusion, plasma exchange, and hemofiltration with hemoperfusion demonstrated favorable results. However, the quality of these studies was not adequate. Even is the focus if only on renal replacement, the optimal timing and implementation remain unclear [12]. Thus, the benefits of BPT in terms of sepsis outcomes remain unclear. Mortality-related factors, such as age [13] and hepatic disease [14], have been reported in sepsis patients. However, there is no literature examining whether BPT is an independent clinical factor associated with survival.

We conducted a study based on prospective and continuously collected database to clarify the utilization status of various BPTs and the clinical characteristics of patients who received BPTs in northern Japan. In addition, the association of various BPTs with clinical outcomes was examined.

Methods

Study design

This is a sub-analysis of the Tohoku Sepsis Registry, a multicenter, prospective, observational cohort study conducted across 10 sites in the Tohoku district of northern Japan, including 3 university hospitals and 7 large community hospitals with > 300 beds. The protocol of the Tohoku Sepsis Registry has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000010297). It is described in detail elsewhere [15]. The study design was approved by the Institutional Review Board of each institution and conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). The need for informed consent was waived due to the observational nature of the study.

Study setting and participants

The Tohoku Sepsis Registry included consecutive patients admitted to intensive care units (ICUs) with severe sepsis or those presenting with severe sepsis after admission to ICUs or general wards in the 10 included hospitals between January and December 2015.

Participants were eligible if they were diagnosed with severe sepsis according to the 2012 International Sepsis Guidelines: sepsis-induced tissue hypoperfusion or organ dysfunction, including sepsis-induced hypotension, elevated serum lactate levels, low urine output despite adequate fluid resuscitation (< 0.5 mL/kg/h for > 2 h), acute lung injury with a ratio of arterial oxygen pressure to fractional inspired oxygen (PaO_2:FiO_2) of < 250.0 in the absence of pneumonia as the source of infection or a PaO_2:FiO_2 ratio of < 200.0 in the presence of pneumonia as the source of infection, elevated serum creatinine levels (> 2.0 mg/dL), elevated serum total bilirubin levels (> 2.0 mg/dL), low platelet counts ($< 10.0 \times 10^4/mm^3$), and coagulopathy with an international normalized ratio of > 1.5 [16]. Patients aged < 18 years were excluded.

Data collection

The registered information includes that on age, sex, pre-existing comorbidities, and medications before admission, in addition to the unit where sepsis was diagnosed, the presence or absence of septic shock, severity as assessed using the Acute Physiologic Assessment and

Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, and primary site of infection. Other information includes physiological data, testing results, and treatment details, including drugs, source control interventions, and BPTs. The lengths of ICU and hospital stay and outcomes at 28 days post-diagnosis and at discharge were documented.

AKI was diagnosed according to the AKI Network criteria [17], which are used for classifying the different stages of AKI (stages 0–3) based on serum creatinine levels and urine output. AKI stage 1 is defined as an elevated serum creatinine level of ≥ 0.3 mg/dL or an increase of 150.0–200.0% from the baseline serum creatinine level or a reduction in urine output of < 0.5 mL/kg/h for > 6 h. AKI stage 2 is defined as an increase of 200.0%–300.0% from the baseline serum creatinine level or a reduction in urine output of < 0.5 mL/kg/h for > 12 h. AKI stage 3 is defined as an elevated serum creatinine level of ≥ 4.0 mg/dL with an acute increase of ≥ 0.5 mg/dL or $> 300.0\%$ from the baseline serum creatinine level or a reduction in urine output of < 0.3 mL/kg/h for 24 h or anuria for 12 h.

BPT

In this study, BPT consisted of continuous renal replacement therapy (CRRT), including CRRT with renal and non-renal indications, intermittent renal replacement therapy (IRRT), and polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP). The indications for BPT were based on the clinical judgment of the attending physicians at each institution. The equipment used and operational settings were determined by the clinician based on resources available at the institution. No uniform protocol was followed.

Participants were divided into the no BPT and different BPT groups. Patients were included in the BPT group regardless of the frequency or duration of BPT. If multiple BPTs were administered, patients were classified into more than one BPT group.

Outcomes

The primary outcome of this study was in-hospital mortality. Secondary outcomes included 28-day mortality, ICU-free days, length of ICU stay, and length of hospital stay. In-hospital mortality and 28-day mortality were defined as all-cause mortality at discharge or 28 days after the diagnosis of sepsis, respectively. ICU-free days represented the number of days on which ICU admission was not required within a 28-day period following the diagnosis of severe sepsis. The number of ICU-free days for patients who died within the 28-day period was 0.

Statistical analysis

Baseline patient characteristics (age, sex, preexisting comorbidities, worst physiological data on day 1 of diagnosis, and treatment modalities) were compared between the two groups of BPT (BPT vs. no PBT) by using Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables. Continuous variables were tested for normality with the Shapiro–Wilk test, with all continuous variables showing the skewed distribution ($p < 0.05$), thus summarized by median and interquartile range.

To determine whether BPT was independently associated with in-hospital mortality in patients with severe sepsis, the following analyses were performed. Differences between survivors and non-survivors were assessed using Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables. Univariate logistic regression analysis was used to evaluate the factors associated with in-hospital mortality at a significance level of 5%. Odds ratios and 95% confidence intervals were calculated. The results of univariate logistic regression analysis were used to select variables for multivariate logistic regression analysis. In the multivariate logistic regression analysis, adjustments were made for the type of BPT, as well as variables that were significant in the univariate logistic regression analysis. Since SOFA and APACHE II scores were correlated (Spearman's rank correlation coefficient, $r = 0.687$; $p < 0.001$), only SOFA score was included in multivariable logistic regression analysis. SOFA score includes the Glasgow Coma Scale, mean arterial pressure, PaO_2:FiO_2 ratio, and platelet counts, which were also excluded from the multivariate logistic regression analysis. Eventually, type of BPT, SOFA score, lactate level, AKI stage, primary site of infection, mechanical ventilation use within 24 h, inotropes or vasopressors use were included in the multivariate logistic regression analysis. There were six BPT types included in multivariate logistic regression analysis: BPT, CRRT with renal indications, CRRT with non-renal indications, IRRT, and PMX-DHP. We performed six multivariate logistic regression models for each of the BPT types, and clinical factors associated with mortality were analyzed. The goodness of fit was assessed using the Hosmer–Lemeshow test. All statistical analyses were conducted using Stata® software, version 15.1 (StataCorp, College Station, Texas, USA). Significance was defined as a two-sided p value of < 0.05.

Results

Patient characteristics

In total, 616 patients in the Tohoku Sepsis Registry were enrolled. The median (interquartile range [IQR]) age was 75.0 (65.0–83.0) years. The proportion of male patients was 61.5%. The median (IQR) APACHE II and SOFA scores were 20.0 (15.0–26.0) and 8.0 (5.0–11.0), respectively. Patient characteristics are shown in Table 1.

Table 1 Characteristics of the patients

Variables	All ($N=616$)	No BPT ($N=489$)	Any BPT ($N=127$)	*p* value
Age (year)	75 (65–83)	76 (66–84)	71 (63–81)	*0.016*
Male sex	379/616 (61.5)	297/489 (60.7)	82/127 (64.6)	*0.429*
Severity				
APACHE II score (0–71)	20 (15–26)	19 (14–25)	25 (20–31)	*< 0.001*
SOFA score (0–24)	8 (5–11)	7 (5–10)	11 (8–14)	*< 0.001*
Comorbidity				
Chronic kidney disease	61/616 (9.9)	29/489 (5.9)	32/127 (25.2)	*< 0.001*
Malignancy	71/616 (11.5)	49/489 (10.0)	22/127 (17.3)	*0.022*
Diabetes mellitus	176/616 (28.6)	137/489 (28.0)	39/127 (30.7)	*0.550*
Hepatic disease	22/616 (3.6)	15/489 (3.1)	7/127 (5.5)	*0.186*
Others	229/616 (37.2)	193/489 (39.5)	36/127 (28.3)	*0.021*
Physiological variable (Day 1)				
Worst GCS score	14 (9–15)	14 (10–15)	13 (8–15)	*0.034*
Worst heart rate (beats/min)	113 (95–128)	112 (96–127)	114 (92–130)	*0.965*
Worst mean arterial pressure (mmHg)	65.7 (53.7–82.5)	67.3 (56.0–84.7)	58.3 (46.0–72.7)	*< 0.001*
Lactate level (mg/dL)	25.2 (18.0–40.2)	24.3 (18.0–36.9)	34.2 (17.1–55.8)	*0.009*
PaO2:FiO2	232.5 (133.3–328.1)	236.8 (137.5–326.7)	206.1 (127.8–328.1)	*0.390*
Worst creatinine level (mg/dL)	1.2 (0.8–2.2)	1.1 (0.8–1.7)	2.9 (1.5–4.9)	*< 0.001*
Bilirubin level (mg/dL)	0.9 (0.6–1.5)	0.9 (0.6–1.5)	0.9 (0.5–1.5)	*0.908*
Platelet count (cells × 10^4/mm^3)	15.9 (10.2–23.1)	16.8 (11.2–23.5)	12.3 (7.3–19.0)	*< 0.001*
AKI-related variables (Day 1–3)				
AKI	258/616 (41.9)	152/489 (31.1)	106/127 (83.5)	*< 0.001*
AKI stage				*< 0.001*
0	358/616 (58.1)	337/489 (69.0)	21/127 (16.5)	–
1	63/616 (20.4)	56/489 (11.5)	7/127 (5.5)	–
2	57/616 (9.3)	53/489 (10.8)	4/127 (3.2)	–
3	138/616 (22.4)	43/489 (8.8)	95/127 (74.8)	–
Primary site of infection				*0.006*
Lung	217/616 (35.2)	184/489 (37.6)	33/127 (26.0)	–
Urinary tract	99/616 (16.0)	82/489 (16.8)	17/127 (13.4)	–
Abdomen	184/616 (29.8)	143/489 (29.2)	41/127 (32.3)	–
Others	116/616 (18.8)	80/489 (16.4)	36/127 (28.4)	–
Blood purification therapy				
Any BPT	127/614 (20.7)	–	127/127 (100.0)	–
Any CRRT	107/614 (17.4)	–	107/127 (84.3)	–
CRRT for renal indications	82/613 (13.4)	–	82/126 (65.1)	–
Within 24 h	68/613 (11.1)	–	68/126 (54.0)	–
Within 24 and 48 h	7/613 (1.1)	–	7/126 (5.6)	–
After 48 h	7/613 (1.1)	–	7/126 (5.6)	–
CRRT for non-renal indications	33/612 (5.4)	–	33/127 (26.0)	–
Within 24 h	32/612 (5.2)	–	32/127 (25.2)	–
Within 24 and 48 h	0/612 (0.0)	–	0/127 (0.0)	–
After 48 h	1/612 (0.2)	–	1/127 (0.8)	–
IRRT	28/611 (4.6)	–	28/126 (22.2)	–
Within 24 h	8/611 (1.3)	–	8/126 (6.4)	–
Within 24 and 48 h	4/611 (0.7)	–	4/126 (3.2)	–
After 48 h	16/611 (2.6)	–	16/126 (12.7)	–
PMX-DHP	42/611 (6.9)	–	42/127 (33.1)	–
Within 24 h	37/611 (6.1)	–	37/127 (29.1)	–
Within 24 and 48 h	4/611 (0.7)	–	4/127 (3.2)	–
After 48 h	1/611 (0.2)	–	1/127 (0.8)	–
Other therapies				

Table 1 (continued)

Variables	All ($N=616$)	No BPT ($N=489$)	Any BPT ($N=127$)	*p* value
Mechanical ventilation within 24 h	281/612 (54.1)	190/485 (39.2)	91/127 (71.7)	*< 0.001*
Inotropes or vasopressors	312/610 (51.1)	220/484 (45.5)	92/126 (73.0)	*< 0.001*
Antimicrobial therapy	590/596 (99.0)	471/473 (99.6)	119/123 (96.8)	*0.005*
Drainage or operation	221/612 (36.1)	168/486 (34.6)	53/126 (42.1)	*0.119*

Data are expressed as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables

Missing data were not included

The Wilcoxon rank sum test was used for the continuous variables, and the Chi-square test was used for categorical variables

APACHE II acute physiology and chronic health evaluation II, *SOFA* sequential organ failure assessment, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury, *BPT* blood purification therapy, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *PMX-DHP* polymyxin B immobilized fiber column-direct hemoperfusion

Detailed patient characteristics are provided in Table 5, according to the type of BPT. The proportions of patients treated with any BPT, any CRRT, IRRT, and PMX-DHP were 20.7%, 17.4%, 4.6%, and 6.9%, respectively.

Comparison of variables between the no BPT and any BPT groups showed the following results: the BPT group was a younger (median 76 [IQR 66–84] *vs.* 71 [63–81], $p=0.016$) and a more severe disease group with higher APACHE II score (19 [14–25] *vs.* 25 [20–30], $p<0.001$) and SOFA score (7 [5–10] *vs.* 11 [8–14], $p<0.001$). Chronic kidney disease (5.9% *vs.* 25.2%, $p<0.001$) and malignant disease (10.0 *vs.* 17.3%, $p=0.022$) are more frequent comorbidities with BPT, and AKI (31.1% *vs.* 83.5%, $p<0.001$) is more frequent as its complication. The proportion of patients receiving mechanical ventilation within 24 h (39.2% *vs.* 71.7%, $p<0.001$), proportion of patients receiving inotropes or vasopressors (45.5% *vs.* 73.0%, $p<0.001$) was higher in BPT group comparing with no BPT group.

Clinical outcomes according to the type of BPT

Table 2 reports the clinical outcomes according to the type of BPT. During a median hospitalization period of 22 days, a total of 139 patients died (mortality rate, 22.6%). The in-hospital mortality rates in patients treated with no BPT, any BPT, any CRRT, CRRT for renal indications, CRRT for non-renal indications, IRRT, and PMX-DHP were 18.5%, 38.6%, 41.1%, 48.8%, 21.2%, 32.1%, and 42.9%, respectively. Significant differences in in-hospital mortality rates were observed between patients treated with any BPT ($p<0.001$), any CRRT ($p<0.001$), CRRT for renal indications ($p<0.001$), or PMX-DHP ($p<0.001$) and those treated with no BPT. The number of ICU-free days differed significantly between the no BPT and any BPT groups (22.0 *vs.* 12.0 days). According to the type of BPT, only the IRRT group exhibited no significant difference in the number of ICU-free days. Patients in the other BPT groups had significantly fewer ICU-free days than those in the no BPT group. The number of ICU days was significantly higher in BPT groups other than the PMX-DHP group than in the no BPT group. The number of hospital days was also significantly higher in the any BPT, CRRT for non-renal indications, and IRRT groups than in the no BPT group.

Factors associated with in-hospital mortality

Significant differences in the following variables were observed between survivors and non-survivors: APACHE II ($p<0.001$), SOFA ($p<0.001$), and Glasgow Coma Scale ($p<0.001$) scores, heart rate ($p=0.030$), mean arterial pressure ($p<0.001$), serum lactate levels ($p<0.001$), PaO_2:FiO_2 ratio ($p<0.001$), serum creatinine levels ($p<0.001$), platelet counts ($p=0.020$), AKI ($p<0.001$), AKI stage ($p<0.001$), and primary site of infection ($p<0.001$), mechanical ventilation use (within 24 h of diagnosis) ($p<0.001$), use of inotropes or vasopressors ($p<0.001$), any BPT ($p<0.001$), any CRRT ($p<0.001$), CRRT for renal indications ($p<0.001$), and PMX-DHP ($p=0.005$). In the univariate logistic regression analysis, the same variables were significantly associated with mortality at discharge, except for serum creatinine levels (Table 3).

Effects of BPT type on mortality

In the multivariate logistic regression analysis of BPT type, all BPT types were not associated with in-hospital mortality. Instead, SOFA score, serum lactate levels, and AKI stage 3 were significantly associated with in-hospital mortality (Table 4).

Discussion

Based on the prospective and continuously collected database of severe sepsis patients recruited from the Tohoku Sepsis Registry in northern Japan, 20.7% of patients with severe sepsis received any type of BPT. The in-hospital mortality rate for patients who received any BPT was

Table 2 Differences in clinical outcomes between those treated with BPT and without BPT

	Mortality at discharge		Mortality at 28 days		28-day ICU-free days		ICU days		Hospital days	
	N	***p*-value**	***N***	***p*-value**	**Median**	***p*-value**	**Median**	***p*-value**	**Median**	***p*-value**
All (*N* = 616)	139/616 (22.6)	–	110/499 (22.0)	–	20.5 (5.0–25.0)	–	6.0 (3.0–11.5)	–	22.0 (12.0–51.0)	–
No BPT (*N* = 489)	90/487 (18.5)	*REF*	69/378 (22.0)	*REF*	22.0 (11.0–22.0)	*REF*	5.0 (3.0–11.0)	*REF*	21.0 (12.0–46.0)	*REF*
Any BPT (*N* = 127)	49/127 (38.6)	*< 0.001*	41/119 (34.5)	*< 0.001*	12.0 (0.0–21.0)	*< 0.001*	8.0 (4.0–16.0)	*< 0.001*	28.0 (13.0–69.0)	*0.037*
Any CRRT (*N* = 107)	44/107 (41.1)	*< 0.001*	37/99 (37.4)	*< 0.001*	9.0 (0.0–20.0)	*< 0.001*	8.0 (4.0–17.0)	*< 0.001*	27.0 (12.0–69.0)	*0.090*
CRRT for renal indications (*N* = 82)	40/82 (48.8)	*< 0.001*	33/78 (42.3)	*< 0.001*	3.0 (0.0–19.0)	*0.003*	8.0 (4.0–18.0)	*0.001*	26.5 (9.0–72.0)	*0.416*
CRRT for non-renal indications (*N* = 33)	7/33 (21.2)	*0.833*	6/29 (20.7)	*0.744*	17.0 (1.0–21.0)	*< 0.001*	9.0 (6.0–15.0)	*0.003*	34.0 (22.0–69.0)	*0.011*
IRRT (*N* = 28)	9/28 (32.1)	*0.074*	5/27 (18.5)	*0.973*	19.0 (7.5–23.0)	*0.061*	8.0 (4.5–14.0)	*0.031*	45.5 (26.0–70.5)	*0.004*
PMX-DHP (*N* = 42)	18/42 (42.9)	*< 0.001*	16/40 (40.0)	*0.001*	10.0 (0.0–21.0)	*< 0.001*	7.5 (3.0–17.0)	*0.117*	33.0 (14.0–64.0)	*0.089*

Data are expressed as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables

Missing data were not included. The Wilcoxon rank sum test was used for the continuous variables, and the Chi-square test was used for categorical variables

BPT blood purification therapy, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *PMX-DHP* polymyxin B immobilized fiber column-direct hemoperfusion, *ICU* intensive care unit, *REF* reference

Table 3 The differences between survivors and non-survivors

Variables	Survivors ($N=477$)	Non-survivors ($N=139$)	*p*	Unadjusted OR (95% CI)
Age (year)	76 (65–83)	75 (65–84)	*0.808*	1.001 (0.988–1.014)
Male sex	285/477 (67.6)	94/139 (59.7)	*0.093*	0.711 (0.477–1.060)
Severity				
APACHE II score (0–71)	19 (14–24)	26 (22–33)	*< 0.001*	1.112 (1.082–1.142)
SOFA score (0–24)	7 (5–10)	10 (7–13)	*< 0.001*	1.215 (1.152–1.282)
Comorbidity				
Chronic kidney disease	42/477 (8.8)	19/139 (13.7)	*0.091*	1.640 (0.920–2.924)
Malignancy	50/477 (10.5)	21/139 (15.1)	*0.133*	1.520 (0.877–2.631)
Diabetes mellitus	143/477 (30.0)	33/139 (23.7)	*0.152*	0.727 (0.467–1.126)
Hepatic disease	17/477 (3.6)	5/139 (3.6)	*0.985*	0.985 (0.366- 2.787)
Others	180/477 (37.7)	49/139 (35.3)	*0.594*	0.903 (0.612–1.333)
Physiological variables (day 1)				
Worst GCS score	14 (10–15)	11 (6–14)	*< 0.001*	0.863 (0.824–0.905)
Worst heart rate (beats/min)	111 (95–126)	119 (102–131)	*0.030*	1.006 (0.998–1.014)
Worst mean arterial pressure (mmHg)	66.7 (56.0–86.0)	59.3 (46.7–73.7)	*< 0.001*	0.979 (0.969–0.989)
Lactate level (mg/dL)	24.3 (17.1–37.8)	30.6 (18.8–62.3)	*< 0.001*	1.015 (1.009–1.021)
PaO2:FiO2	243.5 (148.4–333.3)	180.6 (94.6–312.5)	*< 0.001*	0.997 (0.996–0.999)
Worst creatinine level (mg/dL)	1.2 (0.8–2.0)	1.6 (1.0–2.9)	*< 0.001*	1.083 (0.983–1.194)
Bilirubin level (mg/dL)	0.9 (0.6–1.5)	1.0 (0.6–1.5)	*0.379*	1.055 (0.983–1.194)
Platelet count (cells $\times 10^4/mm^3$)	16.4 (10.8–23.4)	14.2 (7.9–22.4)	*0.020*	0.981 (0.962–1.000)
AKI-related variables (day 1–3)				
AKI	167/477 (35.0)	91/139 (65.5)	*< 0.001*	3.519 (2.366–5.235)
AKI stage				
0	310/477 (65.0)	48/139 (34.5)	*< 0.001*	1.000
1	48/477 (10.1)	15/139 (10.8)		2.018 (1.049–3.884)
2	41/477 (8.6)	16/139 (11.5)		2.520 (1.312–4.842)
3	78/477 (16.4)	60/139 (43.2)		4.968 (3.157–7.819)
Primary site of infection			*< 0.001*	
Lung	147/477 (30.8)	70/139 (50.4)		1.000
Urinary tract	155/477 (32.5)	29/139 (20.9)		0.210 (0.100–0.441)
Abdomen	90/477 (18.9)	9/139 (6.5)		0.393 (0.241–0.640)
Others	84/477 (17.8)	31/139 (22.3)		0.766 (0.464–1.263)
Blood purification therapy				
Any BPT	72/475 (15.2)	38/139 (34.5)	*< 0.001*	2.952 (1.920–4.540)
Any CRRT	63/475 (13.3)	44/139 (31.7)	*< 0.001*	3.029 (1.941–4.727)
CRRT for renal indications	42/474 (8.9)	40/139 (28.8)	*< 0.001*	4.156 (2.559–6.750)
CRRT for non-renal indications	26/473 (5.5)	7/139 (5.0)	*0.833*	0.912 (0.387–2.148)
IRRT	19/474 (4.0)	9/137 (6.6)	*0.207*	1.684 (0.744–3.812)
PMX-DHP	24/473 (5.1)	18/138 (13.0)	*0.005*	2.806 (1.475–5.340)
Other therapies				
Mechanical ventilation within 24 h	190/474 (40.1)	91/138 (65.9)	*< 0.001*	2.894 (1.946–4.305)
Inotropes or vasopressors	218/472 (46.2)	94/138 (68.1)	*< 0.001*	2.489 (1.667–3.718)
Antimicrobial therapy	458/462 (99.1)	132/134 (98.5)	*0.522*	0.576 (0.104–3.182)
Drainage or operation	178/474 (29.1)	43/138 (31.2)	*0.169*	1.329 (0.886–1.993)

Data are expressed as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables

The Wilcoxon rank sum test was used for the continuous variables, and the Chi-square test was used for categorical variables

Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were analyzed using a univariable logistic regression model

APACHE II Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury, *BPT* blood purification therapy, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *PMX-DHP* polymyxin B immobilized fiber column-direct hemoperfusion

Table 4 Factors influencing in-hospital mortality in multivariable logistic regression analysis

	Any BPT (*N* = 127)		Any CRRT (*N* = 107)		CRRT for renal indications (*N* = 82)		CRRT for non-renal indications (*N* = 33)		IRRT (*N* = 28)		PMX-DHP (*N* = 42)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Odds ratio	1.161	(0.613–2.200)	1.259	(0.642–2.465)	1.579	(0.711–3.506)	0.787	(0.299–2.072)	0.806	(0.551–1.179)	1.491	(0.794–2.798)
SOFA score	1.137	(1.051–1.230)	1.137	(1.051–1.230)	1.139	(1.052–1.232)	1.135	(1.049–1.229)	1.126	(1.040–1.219)	1.134	(1.048–1.227)
Lactate level	1.010	(1.003–1.018)	1.010	(1.003–1.018)	1.011	(1.003–1.018)	1.011	(1.003–1.018)	1.011	(1.003–1.018)	1.009	(1.002–1.017)
AKI stage(Day 1–3)												
0	1.000	–	1.000	–	1.000	–	1.000	–	1.000	–	1.000	–
1	0.902	(0.404–2.011)	0.898	(0.402–2.006)	0.905	(0.406–2.019)	0.895	(0.401–1.200)	0.881	(0.394–1.966)	0.925	(0.414–2.066)
2	1.679	(0.783–3.598)	1.690	(0.789–3.620)	1.664	(0.777–3.563)	1.631	(0.759–3.502)	1.671	(0.778–3.587)	1.736	(0.808–3.730)
3	2.427	(1.260–4.674)	2.337	(1.211–4.507)	1.997	(0.956–4.169)	2.650	(1.517–4.632)	2.799	(1.562–5.011)	2.575	(1.469–4.513)
Primary site of infection												
Lung	1.000	–	1.000	–	1.000	–	1.000	–	1.000	–	1.000	–
Urinary tract	0.181	(0.075–0.439)	0.184	(0.076–0.442)	0.187	(0.078–0.450)	0.186	(0.077–0.450)	0.173	(0.069–0.430)	0.175	(0.072–0.424)
Abdomen	0.384	(0.209–0.705)	0.379	(0.205–0.698)	0.376	(0.204–0.694)	0.399	(0.218–0.731)	0.366	(0.199–0.674)	0.364	(0.197–0.673)
Others	0.674	(0.372–1.222)	0.668	(0.368–1.212)	0.662	(0.365–1.201)	0.682	(0.378–1.231)	0.693	(0.384–1.249)	0.660	(0.365–1.195)
Mechanical ventilation within 24 h	0.974	(0.559–1.699)	0.975	(0.368–1.212)	0.988	(0.567–1.722)	1.015	(0.581–1.771)	1.024	(0.586–1.789)	0.972	(0.558–1.693)
Inotropes or vasopressors	1.360	(0.746–2.479)	1.343	(0.737–2.449)	1.298	(0.709–2.378)	1.388	(0.760–2.536)	1.441	(0.786–2.640)	1.367	(0.749–2.494)

ORs (95% CI) were estimated using multivariate analysis adjusted for significant covariates in the univariable analysis

Due to collinearity with the APACHE II score, the SOFA score was used for all analyses

Variables used for calculating the SOFA score, i.e., GCS score, MAP, PaO_2:FiO_2 ratio, and platelet count, were not included in the multivariable model

For all multivariable logistic regression models, the *p*-values for the Hosmer–Lemeshow test were between 0.165 and 0.254

BPT blood purification therapy, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *PMX-DHP* polymyxin B immobilized fiber column-direct hemoperfusion, *OR* odds ratio, *CI* confidence interval, *AKI* acute kidney injury

38.6%. Among all types of BPT, CRRT for renal indication was most frequently selected. BPT consisted of 65.1% CRRT with renal indication (mortality 48.8%), 26.0% CRRT with non-renal indication (mortality 21.2%), 22.2% IRRT (mortality 32.1%), and 33.1% PMX-DHP (mortality 42.9%). Meanwhile, no BPT group (mortality 18.5%) showed a significantly lower mortality than any BPT group. According to BPT type, the CRRT for non-renal indications group and IRRT group exhibited relatively low mortality rates. Besides, any BPT was not independently associated with all-cause in-hospital mortality. To our knowledge, this is the first study based on prospective cohort focusing on the effectiveness of BPTs for severe sepsis.

Compared to previous Japanese study [18] that aggregated BPT patients in critical care, our PMX-DHP utilization rate is comparatively lower (33.1% *vs.* 43.4%) and our CRRT utilization rate is apparently higher (84.3% *vs.* 46.3%). While that previous study did its patient collection in 2013, ours in 2015. At international society of intensive care and emergency medicine conference in 2014, a randomized controlled trial reported did not confirm mortality benefit of PMX-DHP in patients with septic shock due to peritonitis [19], which was published early in 2015 [20]. This turn of the tide against PMX-DHP may have affected the results. The cohort in the previous Japanese study was sepsis patients, but severe sepsis was selected in this study; thus, CRRT may be selected more frequently for unstable hemodynamics.

In previous studies, the 28-day and in-hospital mortality rates of sepsis patients treated with BPTs ranged from 21 to 67% [6, 8, 9, 20–27] and 41% to 79% [6–9], respectively, and the lengths of ICU and hospital stay ranged from 7 to 26 days [6, 9, 20, 24, 26, 27] and 23 days to 59 days [6, 9, 21, 24], respectively. In this study, the 28-day and in-hospital mortality rates were 34.5% and 38.6%, respectively. This 28-day mortality rate is comparable to those in previous studies [6, 8, 9, 20–27]. The in-hospital mortality rate is lower than those in previous studies [6–9], although the severity of illness in the patients in this study receiving BPT was not particularly low in terms of APACHE II and SOFA scores. The lengths of ICU and hospital stay were shorter in our study but were broadly comparable to those reported elsewhere [6, 9, 20, 21, 24, 26, 27].

The mortality rates at 28 days and at discharge were significantly higher in the any BPT group than in the no BPT group (34.5% *vs.* 18.3% and 38.6% *vs.* 18.5%, respectively). We consider that this result may have been influenced by the high severity of illness in patients requiring BPT. On analysis according to BPT type, similarly high mortality rates were observed in the CRRT for renal indications and PMX-DHP groups. In contrast, the CRRT for non-renal indications group may have exhibited relatively low mortality rates and differed from other modalities in terms of other characteristics (e.g., low APACHE II scores and less renal impairment). The IRRT group also did not exhibit a significantly higher mortality rate. The IRRT group was also the only group to not exhibit significant differences in the number of ICU-free days. From this group, 50.0% of patients were also included in the CRRT for renal indications group, and in 57.1% of patients, treatment commenced >48 h after diagnosis. It is possible that IRRT may have been administered to a patient population with stable circulatory hemodynamics. This may have been responsible for the lack of significance in mortality rates and the number of ICU-free days in the IRRT group compared with those in the no BPT group.

Our findings also suggested that none of the BPTs was independently associated with all-cause in-hospital mortality. Although the BPT groups tended to have higher mortality rates, there was no evidence to suggest that BPTs contributed to adverse effects on the outcomes of this study. There is no clear evidence that a particular BPT (CRRT for renal indications [6, 7, 23, 24, 26], CRRT for non-renal indications [8], or PMX-DHP [21]) is associated with better clinical outcomes, and our data support this. It may be difficult to expect significant improvements in prognosis with current BPTs. The establishment of a new method of BPT is eagerly awaited. Novel methods, including methods using the AN69 surface-treated hemofilter (sepXiris®) [28], modified AN69 surface-treated hemofilter (oXiris®) [29, 30], and extracorporeal cytokine adsorption device (CytoSorb®) [31], are currently being investigated. Further, large-scale studies are needed to evaluate the prognosis associated with the use of these methods.

This study has several limitations. First, the protocols of the various types of BPTs were based on the clinical judgment of the attending physicians at each institution and were not standardized. Thus, there was potential for variability in the application of BPT (e.g., indication, blood flow rate, dialysate flow rate, replacement flow rate, ultrafiltration rate, type of anticoagulation, and type of membrane). To address this, we included the institution as a variable in the multivariate logistic regression analysis. Second, this study did not have an adequately large sample size and may not be well adjusted for confounding variables. These limitations may affect the external validity of this study. Therefore, these findings should be interpreted with caution.

Conclusions

Our study showed that 20.7% of patients with severe sepsis received any BPT, and the mortality rate of patients who received any BPT was 38.6%. Among all types of BPT, CRRT for renal indication was most frequently selected. Patients who received BPT showed higher

severity of illness, and the mortality of any BPT group was significantly higher than that of no BPT group. According to BPT type, the CRRT for non-renal indications group and IRRT group may have exhibited relatively low mortality rates. BPT may not be independently associated with all-cause in-hospital mortality, although patients with severe sepsis who were treated with BPTs exhibited higher mortality rates. More detailed analyses adjusting for potential confounding variables are needed in additional cohorts in the future.

Appendix

See Table 5.

Table 5 Detailed baseline characteristics of the patients

Variables	All (*N* = 616)	No BPT (*N* = 489)	Any BPT (*N* = 127)	Any CRRT (*N* = 107)	CRRT for renal indications (*N* = 82)	CRRT for non-renal indication (*N* = 33)	IRRT (*N* = 28)	PMX-DHP (*N* = 42)
Age (year)	75.0 (65.0–83.0)	76.0 (66.0–84.0)	71.0 (63.0–81.0)	71.0 (61.0–82.0)	71.0 (61.0–80.0)	73.0 (60.0–84.0)	71.0 (60.0–78.5)	72.5 (62.0–79.0)
Male sex	379/616 (61.5)	297/489 (60.7)	82/127 (64.6)	69/107 (64.5)	54/82 (65.9)	12/33 (36.4)	24/28 (85.7)	25/42 (59.5)
Severity								
APACHE II score (0–71)	20.0 (15.0–26.0)	19.0 (14.0–25.0)	25.0 (20.0–31.0)	25.0 (19.0–32.0)	25.0 (20.0–32.5)	21.0 (17.0–29.0)	26.0 (22.0–29.0)	26.0 (21.0–29.0)
SOFA score (0–24)	8.0 (5.0–11.0)	7.0 (5.0–10.0)	11.0 (8.0–14.0)	11.0 (8.0–14.0)	11.0 (8.0–14.0)	10.0 (9.0–11.0)	9.0 (8.0–12.0)	11.0 (9.0–14.0)
Comorbidity								
Chronic kidney disease	61/616 (9.9)	29/489 (5.9)	32/127 (25.2)	25/107 (23.4)	23/82 (28.1)	3/33 (9.1)	16/28 (57.1)	4/42 (9.5)
Malignancy	71/616 (11.5)	49/489 (10.0)	22/127 (17.3)	19/107 (17.8)	16/82 (19.5)	3/33 (9.1)	2/28 (7.1)	11/42 (26.2)
Diabetes mellitus	176/616 (28.6)	137/489 (28.0)	39/127 (30.7)	33/107 (30.8)	25/82 (30.5)	10/33 (30.3)	12/28 (42.9)	7/42 (16.7)
Hepatic disease	22/616 (3.6)	15/489 (3.1)	7/127 (5.5)	6/107 (5.6)	5/82 (6.1)	1/33 (3.0)	1/28 (3.6)	2/42 (4.8)
Stroke	89/616 (14.5)	82/489 (16.8)	7/127 (5.5)	7/107 (6.5)	6/82 (7.3)	2/33 (6.1)	1/28 (3.6)	2/42 (4.8)
Heart failure (acute and/or chronic)	64/616 (10.4)	44/489 (9.0)	20/127 (15.8)	18/107 (16.8)	14/82 (17.1)	4/33 (12.1)	6/28 (21.4)	4/42 (9.5)
Collagen disease	32/616 (5.2)	26/489 (5.3)	6/127 (4.7)	5/107 (4.7)	4/82 (4.9)	2/33 (6.1)	0/28 (0.0)	1/42 (2.4)
Myocardial infarction (acute and/or old)	27/616 (4.4)	21/489 (4.3)	6/127 (4.7)	6/107 (5.6)	4/82 (4.9)	3/33 (9.1)	0/28 (0.0)	1/42 (2.4)
Gastroduodenal ulcer	27/616 (4.4)	22/489 (4.5)	5/127 (3.9)	0/107 (0.0)	2/82 (2.4)	2/33 (6.1)	3/28 (10.7)	1/42 (2.4)
Arterial disease	25/616 (4.1)	22/489 (4.5)	3/127 (2.4)	2/107 (1.9)	2/82 (2.4)	0/33 (0.0)	0/28 (0.0)	1/42 (2.4)
Chronic Obstructive Pulmonary Disease	22/616 (3.6)	21/489 (4.3)	1/127 (0.8)	1/107 (0.9)	1/82 (1.2)	1/33 (3.0)	1/28 (3.6)	1/42 (2.4)
Physiological variable (Day 1)								
Worst GCS score	14.0 (9.0–15.0)	14.0 (10.0–15.0)	13.0 (8.0–15.0)	13.5 (8.0–15.0)	13.5 (8.0–15.0)	14.0 (6.0–14.0)	14.0 (10.0–15.0)	13.0 (8.0–14.0)
Worst heart rate (beats/min)	113.0 (95.0–128.0)	112.0 (96.0–127.0)	114.0 (92.0–130.0)	114.0 (92.0–130.0)	115.0 (95.0–135.0)	113.0 (89.0–120.0)	109.0 (79.5–130.0)	123.5 (98.0–141.0)
Worst mean arterial pressure (mmHg)	65.7 (53.7–82.5)	67.3 (56.0–84.7)	58.3 (46.0–72.7)	58.0 (45.0–68.7)	57.3 (43.0–68.3)	62.0 (49.3–73.3)	61.5 (51.3–77.5)	52.8 (41.3–64.0)

Table 5 (continued)

Variables	All (*N* = 616)	No BPT (*N* = 489)	Any BPT (*N* = 127)	Any CRRT (*N* = 107)	CRRT for renal indications (*N* = 82)	CRRT for non-renal indication (*N* = 33)	IRRT (*N* = 28)	PMX-DHP (*N* = 42)
Lactate level (mg/dL)	25.2 (18.0–40.2)	24.3 (18.0–36.9)	34.2 (17.1–55.8)	34.2 (18.9–55.9)	34.2 (18.0–54.6)	38.0 (29.7–71.1)	36.0 (49.1–78.6)	38.0 (27.0–64.0)
PaO2:FiO2	232.5 (133.3–328.1)	236.8 (137.5–326.7)	206.1 (127.8–328.1)	230 (127.8–332.9)	198.5 (113.8–313.0)	262.4 (137.5–373.5)	112.4 (96.3–309.5)	186.8 (117.5–308.2)
Worst creatinine level (mg/dL)	1.2 (0.8–2.2)	1.1 (0.8–1.7)	2.9 (1.5–4.9)	2.7 (1.5–4.4)	3.1 (1.7–4.9)	1.7 (1.0–2.5)	2.3 (1.4–3.2)	2.2 (1.4–3.6)
Bilirubin level (mg/dL)	0.9 (0.6–1.5)	0.9 (0.6–1.5)	0.9 (0.5–1.5)	0.9 (0.5–1.5)	0.9 (0.5–1.5)	0.8 (0.6–1.3)	2.3 (2.0–2.6)	1.3 (1.4–3.6)
Platelet count (cells × 10^4/mm^3)	15.9 (10.2–23.1)	16.8 (11.2–23.5)	12.3 (7.3–19.0)	12.3 (7.2–19.0)	11.3 (6.8–18.2)	13.5 (9.6–27.7)	15.4 (9.1–21.5)	9.3 (5.5–18.2)
AKI-related variables (Day 1–3)								
AKI	258/616 (41.9)	152/489 (31.1)	106/127 (83.5)	93/107 (86.9)	82/82 (100.0)	19/33 (57.6)	25/28 (89.3)	31/42 (73.8)
AKI stage								
0	358/616 (58.1)	337/489 (69.0)	21/127 (16.5)	14/107 (13.1)	0/82 (0.0)	14/33 (42.4)	3/28 (10.7)	11/42 (26.2)
1	63/616 (20.4)	56/489 (11.5)	7/127 (5.5)	6/107 (5.6)	0/82 (0.0)	6/33 (18.2)	0/28 (0.0)	3/42 (7.1)
2	57/616 (9.3)	53/489 (10.8)	4/127 (3.2)	2/107 (1.9)	0/82 (0.0)	2/33 (6.1)	1/28 (3.6)	2/42 (4.8)
3	138/616 (22.4)	43/489 (8.8)	95/127 (74.8)	85/107 (79.4)	82/82 (100.0)	11/33 (33.3)	24/28 (85.7)	26/42 (61.9)
Primary site of infection								
Lung	217/616 (35.2)	184/489 (37.6)	33/127 (26.0)	26/107 (24.3)	21/82 (25.6)	6/33 (18.2)	10/28 (35.7)	6/42 (14.3)
Urinary tract	99/616 (16.0)	82/489 (16.8)	17/127 (13.4)	12/107 (11.2)	8/82 (9.8)	5/33 (15.2)	4/28 (14.3)	8/42 (19.1)
Abdomen	184/616 (29.8)	143/489 (29.2)	41/127 (32.3)	37/107 (34.6)	26/82 (31.7)	16/33 (48.5)	6/28 (21.4)	19/42 (45.2)
Central nerve system	8/616 (1.3)	7/489 (1.4)	1/127 (0.8)	1/107 (0.9)	1/82 (1.2)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)
Soft tissue	44/616 (7.1)	30/489 (6.1)	14/127 (11.0)	11/107 (10.3)	8/82 (9.8)	3/33 (9.1)	6/28 (21.4)	4/42 (9.5)
Skeletal system	5/616 (0.8)	5/489 (1.0)	0/127 (0.0)	0/107 (0.0)	0/82 (0.0)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)
Wound	5/616 (0.8)	5/489 (1.0)	0/127 (0.0)	0/107 (0.0)	0/82 (0.0)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)
Intravascular catheter	11/616 (0.8)	5/489 (1.0)	6/127 (4.7)	5/107 (4.7)	4/82 (4.9)	1/33 (3.0)	0/28 (0.0)	2/42 (4.8)
Endocardium	3/616 (0.5)	2/489 (0.4)	1/127 (0.8)	1/107 (0.9)	1/82 (1.2)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)
Medical device	2/616 (0.3)	2/489 (0.4)	0/127 (0.0)	0/107 (0.0)	0/82 (0.0)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)
Others	15/616 (2.4)	8/489 (1.6)	7/127 (5.5)	7/107 (6.5)	7/82 (8.5)	1/33 (3.0)	1/28 (3.6)	1/42 (3.4)
Unknown	23/616 (3.7)	16/489 (3.3)	7/127 (5.5)	7/107 (6.5)	6/82 (7.3)	1/33 (3.0)	1/28 (3.6)	2/42 (4.8)
Blood purification therapy								
Any BPT	127/614 (20.7)	–	127/127 (100.0)	107/107 (100.0)	82/82 (100.0)	32/32 (100.0)	28/28 (100.0)	42/42 (100.0)
Any CRRT	107/614 (17.4)	–	107/127 (84.3)	107/107 (100.0)	82/82 (100.0)	32/32 (100.0)	15/28 (53.6)	32/42 (76.2)
CRRT for renal indications	82/613 (13.4)	–	82/126 (65.1)	82/106 (77.4)	82/82 (100.0)	8/32 (25.0)	14/28 (50.0)	25/41 (58.5)
Within 24 h	68/613 (11.1)	–	68/126 (54.0)	68/106 (64.2)	68/82 (82.9)	5/32 (15.6)	12/28 (42.9)	19/41 (46.3)
Within 24 and 48 h	7/613 (1.1)	–	7/126 (5.6)	7/106 (6.6)	7/82 (8.5)	1/32 (3.1)	2/28 (7.1)	4/41 (9.8)
After 48 h	7/613 (1.1)	–	7/126 (5.6)	7/106 (6.6)	7/82 (8.5)	2/32 (6.3)	0/28 (0.0)	1/41 (2.4)
CRRT for non-renal indications	33/612 (5.4)	–	33/127 (26.0)	33/107 (30.8)	8/82 (9.8)	33/33 (100.0)	4/28 (14.3)	11/42 (26.2)
Within 24 h	32/612 (5.2)	–	32/127 (25.2)	32/107 (29.9)	8/82 (9.8)	32/33 (97.0)	4/28 (14.3)	11/42 (26.2)
Within 24 and 48 h	0/612 (0.0)	–	0/127 (0.0)	0/107 (0.0)	0/82 (0.0)	0/33 (0.0)	0/28 (0.0)	0/42 (0.0)

Table 5 (continued)

Variables	All ($N=616$)	No BPT ($N=489$)	Any BPT ($N=127$)	Any CRRT ($N=107$)	CRRT for renal indications ($N=82$)	CRRT for non-renal indication ($N=33$)	IRRT ($N=28$)	PMX-DHP ($N=42$)
After 48 h	1/612 (0.2)	–	1/127 (0.8)	1/107 (0.9)	0/82 (0.0)	1/33 (3.0)	0/28 (0.0)	0/42 (0.0)
IRRT	28/611 (4.6)	–	28/126 (22.2)	15/106 (14.2)	14/81 (17.3)	4/33 (12.1)	28/28 (100.0)	6/41 (14.6)
Within 24 h	8/611 (1.3)	–	8/126 (6.4)	2/106 (1.9)	1/81 (1.2)	1/33 (3.0)	8/28 (28.6)	3/41 (7.3)
Within 24 and 48 h	4/611 (0.7)	–	4/126 (3.2)	1/106 (0.9)	1/81 (1.2)	1/33 (3.0)	4/28 (14.3)	1/44 (2.4)
After 48 h	16/611 (2.6)	–	16/126 (12.7)	12/106 (11.3)	12/81 (14.8)	2/33 (6.1)	16/28 (57.1)	2/41 (4.9)
PMX-DHP	42/611 (6.9)	–	42/127 (33.1)	32/107 (29.9)	24/82 (29.3)	11/33 (33.3)	6/28 (21.4)	42/42 (100.0)
Within 24 h	37/611 (6.1)	–	37/127 (29.1)	29/107 (27.1)	21/82 (25.6)	11/33 (33.3)	6/28 (21.4)	37/42 (88.1)
Within 24 and 48 h	4/611 (0.7)	–	4/127 (3.2)	2/107 (1.9)	2/82 (2.4)	0/33 (0.0)	0/28 (0.0)	4/42 (9.5)
After 48 h	1/611 (0.2)	–	1/127 (0.8)	1/107 (0.9)	1/82 (1.2)	0/33 (0.0)	0/28 (0.0)	1/42 (2.4)
Other therapies								
Mechanical ventilation within 24 h	281/612 (54.1)	190/485 (39.2)	91/127 (71.7)	79/107 (73.8)	59/82 (72.0)	28/33 (84.9)	19/28 (67.9)	31/42 (73.8)
Inotropes or vasopressors	312/610 (51.1)	220/484 (45.5)	92/126 (73.0)	81/106 (76.4)	63/81 (77.8)	26/33 (78.8)	17/28 (60.7)	31/41 (75.6)
Antimicrobial therapy	590/596 (99.0)	471/473 (99.6)	119/123 (96.8)	100/104 (96.2)	76/80 (95.0)	31/32 (96.9)	27/27 (100.0)	41/41 (100.0)
Drainage or operation	221/612 (36.1)	168/486 (34.6)	53/126 (42.1)	47/106 (44.3)	32/81 (39.5)	21/33 (63.6)	10/28 (35.7)	22/42 (52.4)

Data are expressed as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables. Missing data were not included

APACHE II Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury, *BPT* blood purification therapy, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *PMX-DHP* polymyxin B immobilized fiber column-direct hemoperfusion

Abbreviations

AKI: Acute kidney injury; BPT: Blood purification therapy; ICU: Intensive care unit; PaO2FiO2: Ratio of arterial oxygen pressure to fractional inspired oxygen; APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; CRRT: Continuous renal replacement therapy; IRRT: Intermittent renal replacement therapy; PMX-DHP: Polymyxin B-immobilized fiber column direct hemoperfusion; IQR: Interquartile range.

Acknowledgements

The other Tohoku Sepsis Registry investigators also contributed to the collection and analysis of data at each institution: Tohoku University Hospital, Hachinohe City Hospital, Ohta Nishinouchi Hospital, Osaki Citizen Hospital, Niigata University Medical and Dental Hospital, Sendai City Hospital, South Miyagi Medical Center, Sendai Medical Center, Yamagata Prefectural Central Hospital, and Akita University Hospital. We would like to thank S. Osaki for data management and administrative support.

Authors' contributions

KS designed the study and wrote the initial draft of the manuscript. KN contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. HN contributed to the conception of the study and critically revised the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The data that support the findings of this study are available from the principal investigator of the Tohoku Sepsis Registry, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the principal investigator of the Tohoku Sepsis Registry.

Declarations

Ethics approval and consent to participate

All data were retrieved from a database named Tohoku Sepsis Registry (University Hospital Medical Information Network Clinical Trials Registry No. UMIN000010297). The Institutional Review Board of each institution approved the study. All Institutional Review Boards waived the need for informed consent due to the observational study design requiring no treatments beyond the daily clinical practice, according to the Japanese guideline (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare, Japan; Ethical Guidelines for Medical and Health Research Involving Human Subjects. March 2015).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 30 November 2020 Accepted: 29 August 2021
Published online: 08 September 2021

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