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ORIGINAL ARTICLE

Analysis of the efficacy of direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) according to the prognostic factors in patients with colorectal perforation

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Abstract
Purpose Direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) has been reported to improve the outcomes in patients with colorectal perforation. We retrospectively identified prognostic factors in patients with colorectal perforation and considered the efficacy of PMX-DHP based on these prognostic factors.
Methods One hundred and fifty-six patients who underwent surgery for colorectal perforation in our department between November 1995 and March 2011 were enrolled in this study. The clinicopathological factors were compared between the survivor and non-survivor groups.
Results There were 28 patients (17.9 %) who died within 28 days after surgery. According to the multivariate analysis, an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 17 or more was a significant independent prognostic factor ($P = 0.002$, odds ratio = 5.39). There was a significant difference in the survival rates between the patients with APACHE II scores of 16 or less and those with scores of 17 or more who had received the PMX-DHP (+) ($P < 0.0001$).
Conclusion The APACHE II score is useful as a prognostic factor in patients with colorectal perforation, and the survival rate was 50 % or lower among the patients with APACHE II scores of 17 or higher. Therefore, PMX-DHP appears to have limited efficacy in serious cases.

Keywords Direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) · Colorectal perforation · Prognostic factor · APACHE II score · Sepsis

Introduction

Colorectal perforation is a life-threatening condition that is associated with high mortality because it causes septic shock and multiple organ failure [1–3]. However, in recent years, some reports have indicated that direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP), in addition to advances in perioperative management, improves the outcomes in patients with colorectal perforation [4–8]. We retrospectively identified prognostic factors in patients with colorectal perforation and considered the efficacy of PMX-DHP based on these prognostic factors.

Methods

Patient selection

One hundred and fifty-six patients who underwent surgery for colorectal perforation in our department between November 1995, when PMX-DHP was introduced, and March 2011 (i.e., the past 15 years) were enrolled in this study. Cases with iatrogenic perforation were excluded from this study.

Clinicopathological factors

We retrospectively investigated the prognostic factors in patients undergoing surgery for colorectal perforation. The

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patients who died within 28 days after surgery were classified into the non-survivor group. The clinicopathological factors, such as the patient background, preoperative status, surgical factors, postoperative status and severity scores, were analyzed. For the patient background, their age, gender, and preoperative comorbidities were investigated. Regarding the preoperative status, the presence of free air in computed tomography (CT) scans, white blood cell (WBC) depression, shock, systemic inflammatory response syndrome (SIRS) and the number of SIRS criteria were investigated. In terms of the surgical factors, the time from the perforation to surgery, perforation site, cancer-associated perforation and construction of an artificial anus were investigated. For the postoperative status, the use of PMX-DHP was investigated. With respect to the severity scores, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated. In addition, the severity scores were calculated based on preoperative vital signs and clinical laboratory test values.

PMX-DHP

The blood access route was the femoral or the subclavian vein. The endotoxin adsorption column used was a PMX-20R (Toray Industries, Tokyo, Japan), and the blood flow volume was 80–120 mL/min. PMX-DHP was carried out for 120 min per session. Therapy was discontinued when adverse events appeared or it was judged that it would be difficult to continue PMX-DHP. When a patient failed to recover from the shock state after one course of therapy, another course was repeated 24 h later.

Therapeutic strategy for colorectal perforation

In our therapeutic strategy for colorectal perforation, emergency surgery should be performed immediately, while anti-shock therapy is preferably provided for the patients with concomitant septic shock prior to the surgery. Since the clinical course of patients with septic shock depends on the bacteria responsible, blood cultures should be performed to identify the bacteria after surgery. In addition, a mainly crystalloid fluid solution is administered to maintain the circulatory blood volume so that the uterine blood flow can be maintained optimally at 0.5–1.0 mL/kg/h. When a patient shows a low output state, in which the blood pressure cannot be appropriately maintained even with infusion of a crystalloid solution, noradrenaline and other vasopressors are administered continuously. For the cases with postoperative respiratory failure, mechanical ventilation should be performed with intratracheal intubation, and when the respiratory failure persists, tracheotomy should be performed. In addition, among the recent therapeutic strategies for patients who develop disseminated intravascular coagulation (DIC) after surgery, it has been determined that heparin, gabexate mesylate, and nafamostat mesylate should be administered, and the administration of antithrombin is performed for patients with decreased antithrombin activity, although this therapeutic strategy has changed with time. We used the standard therapeutic strategies for the time period throughout this study.

Statistical analysis

Discrete variables were compared using Fisher's exact probability test, and continuous variables were compared using the Mann–Whitney U test. Clinicopathological factors, for which there was a significant difference in the univariate analysis, were used as co-variables for the multivariate analysis. For the multivariate analysis, the logistic regression model was used with the odds ratio to measure the association by applying a stepwise procedure. Differences were considered to be statistically significant at $P < 0.05$. When cut-off values for the number of SIRS criteria and the severity scores were analyzed, Akaike's Information Criterion (AIC) [9] was used. Values were fixed as the cut-off values when the AIC value was the lowest. Values were expressed as medians (min–max).

Results

Patient characteristics

The patient characteristics are shown in Table 1. The median age was 72.5 years (27–97 years). There were 71 males and 85 females. The perforation sites were the cecum in 10 patients, ascending colon in 16 patients, transverse colon in five patients, descending colon in 10 patients, sigmoid colon in 101 patients, rectum in 12 patients and multiple in two patients. The most frequently encountered cause of perforation was a diverticulum in 69 patients (44.2 %). There were 46 patients (29.5 %) with a perforation due to colorectal cancer.

Comparisons of clinicopathological factors between the survivor and non-survivor groups

There were 28 patients (17.9 %) in the non-survivor group (Table 2). In a univariate analysis comparing the non-survivor and survivor groups, there were significantly more patients with multiple SIRS criteria ($P = 0.03$), PMX-DHP ($P = 0.03$), high APACHE II scores ($P < 0.0001$) and high SOFA scores ($P < 0.0001$) who were non-survivors. With respect to the other clinicopathological factors, there were no significant differences between the two groups.

Table 1 Patient characteristics

	No. of patients (%)
Total	156
Age[a]	72.5 years (27–97)
Sex	
Male	71 (45.5 %)
Female	85 (54.4 %)
Perforation site	
Cecum	10 (6.4 %)
Ascending colon	16 (10.3 %)
Transverse colon	5 (3.2 %)
Descending colon	10 (6.4 %)
Sigmoid colon	101 (64.7 %)
Rectum	12 (7.7 %)
Multiple	2 (1.3 %)
Cause of perforation	
Diverticulum	69 (44.2 %)
Colorectal cancer	46 (29.5 %)
Idiopathic	21 (13.5 %)
Trauma	8 (5.1 %)
Others	12 (7.7 %)

[a] Median (min–max)

Cut-off values for the scores

In order to fix the cut-off values for the number of SIRS criteria and the APACHE II and SOFA scores for comparisons between the survivor and non-survivor groups, each AIC value for these scores was calculated. As a result, the AIC value was the lowest when patients had three or four SIRS, when the APACHE II scores were between 16 and 17, and when the SOFA scores were between four and five. Therefore, the number of SIRS criteria and the APACHE II and SOFA scores of four, 17 and five, respectively, were fixed as the cut-off values (Tables 3, 4, 5).

Prognostic factors for non-survival

In the univariate analysis using the number of SIRS criteria, the APACHE II score and the SOFA score cut-off values described above, there were significantly more patients with more than four SIRS criteria ($P = 0.04$), an APACHE II score of 17 or more ($P < 0.0001$) or a SOFA score of five or more ($P = 0.0004$) in the non-survivor group than in the survivor group (Table 6). According to the multivariate analysis using these scores, an APACHE II score of 17 or more was a significant and independent prognostic factor ($P = 0.002$, odds ratio = 5.39) (Table 7).

Table 2 Comparisons of the clinicopathological factors between the survivor and non-survivor groups

	Survivor group ($n = 128$)	Non-survivor group ($n = 28$)	P value
Patient background			
Age (≥75/≤74)	77/51	13/15	0.21
Gender (male/female)	60/68	11/17	0.53
Preoperative comorbidity (+/−)	99/29	22/6	1.00
Preoperative status			
Free air (+/−)	63/65	29/9	0.09
WBC (<4000/mm^3/≥4000 mm^3)	31/97	11/17	0.16
Shock (+/−)	17/111	5/23	0.55
SIRS (+/−)	78/50	22/6	0.09
No. of SIRS criteria[a]	2 (0–4)	2 (0–4)	0.03
Surgical factors			
Time from perforation to surgery (>12 h/≤12 h)	74/54	19/9	0.40
Perforation site (C–T/D–RS)	26/102	5/23	1.00
Cancer-associated perforation (+/−)	38/90	9/19	0.82
Construction of artificial anus (+/−)	99/29	25/3	0.20
Postoperative status			
PMX-DHP (+/−)	93/35	26/2	0.03
Severity scores			
APACHE II score[a]	10 (1–27)	16.5 (5–27)	<0.0001
SOFA score[a]	2 (0–7)	3 (1–7)	<0.0001

In a univariate analysis of the non-survivor and survivor groups, there were significantly more patients with multiple SIRS criteria ($P = 0.03$), PMX-DHP ($P = 0.03$), high APACHE II scores ($P < 0.0001$) and high SOFA scores ($P < 0.0001$) in the non-survivors

[a] Median (min–max)

Table 3 Cut-off values according to Akaike's Information Criterion (AIC) and the number of SIRS criteria

No. of SIRS criteria	AIC value
≥0/1	150.3
≤1/≥2	147.5
≤2/≥3	147.7
≤3/4	146.3

The AIC value was lowest when patients met three or four SIRS criteria

Table 4 Cut-off values according to Akaike's Information Criterion (AIC) and the APACHE II score

APACHE II score	AIC value
≤13/≥14	132.6
≤14/≥15	133.3
≤15/≥16	131.5
≤16/≥17	130.0
≤17/≥18	134.0
≤18/≥19	132.6

[a] Median (min–max)

The AIC value was lowest when the APACHE II scores were between 16 and 17

Table 5 Cut-off values according to Akaike's Information Criterion (AIC) and the SOFA score

SOFA score	AIC value
≤1/≥2	139.4
≤2/≥3	138.8
≤3/≥4	140.9
≤4/≥5	138.0
≤5/≥6	142.4
≤6/≥7	149.8

The AIC value was lowest when the SOFA scores were between four and five

Table 6 Comparisons of scores between the survivor and non-survivor groups

	Survivor group ($n = 128$)	Non-survivor group ($n = 28$)	P value
No. of SIRS criteria (4/≤3)	4/124	4/24	0.04
APACHE II score (≤17/≤16)	13/115	14/14	<0.0001
SOFA score (≤5/≤4)	10/118	10/18	0.0004

There were significantly more patients who met four SIRS criteria ($P = 0.04$), had APACHE II scores of 17 or more ($P < 0.0001$), had SOFA scores of five or more ($P = 0.0004$) in the non-survivor group compared with the survivor group

Comparison of the clinicopathological factors between the patients with and without PMX-DHP

One hundred and nineteen patients (76.3 %) underwent PMX-DHP. In a univariate analysis of the patients treated with PMX-DHP (PMX-DHP (+) group) compared to those without PMX-DHP (PMX-DHP (−) group), there were significantly more patients with free air detected by CT ($P < 0.001$), WBC depression ($P < 0.001$), construction of an artificial anus ($P = 0.0001$), high APACHE II scores ($P < 0.0001$), and high SOFA scores ($P < 0.0001$) (Table 8). With respect to the other clinicopathological factors, there were no significant differences between the two groups.

Table 7 Prognostic factors for non-survivors

	P value	Odds ratio	95 % confidence interval
No. of SIRS criteria ≥4	0.45	1.94	0.35–10.7
APACHE II score ≥17	0.002	5.39	1.81–16.0
SOFA score ≥5	0.07	2.93	0.93–9.26

According to the multivariate analysis performed using these scores, an APACHE II score of 17 or more was a significant and independent prognostic factor ($P = 0.002$, odds ratio = 5.39)

Table 8 Comparison of the clinicopathological factors between the patients with and without PMX-DHP

	PMX-DHP (+) group ($n = 119$)	PMX-DHP (−) group ($n = 37$)	P value
Patient background			
Age (≥75/≤74)	54/65	12/25	0.19
Gender (male/female)	51/68	20/17	0.26
Preoperative comorbidity (+/−)	94/25	27/10	0.50
Preoperative status			
Free air (+/−)	70/49	12/25	<0.01
WBC (<4000/mm^3/ ≥4000 mm^3)	40/79	2/35	<0.001
Shock (+/−)	19/100	3/34	0.29
SIRS (+/−)	85/34	15/22	<0.001
No. of SIRS criteria[a]	2 (0–4)	1 (0–3)	<0.0001
Surgical factors			
Time from perforation to surgery (>12 h/≤12 h)	49/70	14/23	0.85
Perforation site (C–T/D–RS)	21/98	10/27	0.24
Cancer-associated perforation (+/−)	38/81	9/28	0.42
Construction of artificial anus (+/−)	103/16	20/17	0.0001
Severity scores			
APACHE II score[a]	12 (3–27)	8 (1–19)	<0.0001
SOFA score[a]	2 (0–7)	1 (0–5)	0.004

In the univariate analysis of the patients treated with PMX-DHP (PMX-DHP (+) group) compared to those without PMX-DHP (PMX-DHP (−) group), there were significantly more patients with free air detected by CT ($P < 0.001$), white blood cell depression ($P < 0.001$), construction of an artificial anus ($P = 0.0001$), high APACHE II scores ($P < 0.0001$), and high SOFA scores ($P < 0.0001$) in the PMX-DHP (+) patients

[a] Median (min–max)

Comparison of the clinicopathological factors between the survivor and non-survivor groups among the patients with PMX-DHP

Twenty-six patients (21.8 %) died within 28 days after surgery in the PMX-DHP (+) group. In a univariate analysis of the non-survivor and survivor groups, there were significantly more patients with high APACHE II ($P < 0.0001$) and SOFA scores ($P = 0.0001$) in the non-survivors (Table 9). With respect to the other clinicopathological factors, there were no significant differences between the two groups.

The efficacy of PMX-DHP according to the APACHE II score

The survival rates in the PMX-DHP (+) and (−) groups according to the APACHE II scores are shown in Table 10, which were 78.2 % (93/119) and 94.6 % (35/37), respectively. Therefore, the survival rate in the PMX-DHP (+) group was lower than that in the PMX-DHP (−) group. According to the APACHE II score, in the PMX-DHP (−) group, the survival rates were 66.7 % (2/3) and 50.0 % (1/2) among the patients with APACHE II scores of 8 and 12, respectively, and 100 % among the patients with other APACHE II scores. With respect to the details of the two patients who died in the PMX-DHP (−) group, one patient was an 89-year-old female who underwent surgery because of a perforation due to carcinoma of the ascending colon, and died suddenly of cardiac arrest on the 22nd postoperative day. The other patient, a 39-year-old female who underwent surgery because of traumatic perforation of the sigmoid colon died of hemorrhagic shock on the day after the operation. On the other hand, in the PMX-DHP (+) group, the survival rate was 60.0 % or higher among the patients with APACHE II scores of 16 or less. Except for the two patients with APACHE II scores of 18 and 22, survival rates of 50.0 % or less were recognized among the patients with APACHE II scores of 17 or more. In the PMX-DHP (−) group, there were no significant differences in the survival rates between the patients with APACHE II scores of 16 or less and those with scores of 17 or more. On the other hand, there was a significant difference in the survival rate between the two sub-groups among the PMX-DHP (+) patients ($P < 0.0001$) (Fig. 1). Regarding the cause of death within 28 days after surgery in 26 patients in the PMX-DHP (+) group, it was estimated that all of these patients might have developed multiple organ failure after sepsis shock. Sixteen out of the 26 patients (61.5 %) failed to be weaned from mechanical ventilation due to the development of postoperative respiratory failure. In addition, 10 patients (38.5 %) developed DIC, and required anti-DIC therapy.

Table 9 Comparison of the clinicopathological factors between the survivor and non-survivor groups among the patients with PMX-DHP

	Survivor group ($n = 93$)	Non-survivor group ($n = 26$)	P value
Patient background			
Age (≥75/≤74)	52/41	13/13	0.66
Gender (male/female)	40/53	11/15	1.00
Preoperative comorbidity (+/−)	73/20	21/5	1.00
Preoperative status			
Free air (+/−)	52/41	18/8	0.26
WBC (<4000/mm^3/≥4000 mm^3)	29/64	11/15	0.35
Shock (+/−)	15/78	4/22	1.00
SIRS (+/−)	64/29	21/5	0.33
No. of SIRS criteria[a]	2 (0–4)	2 (0–4)	0.14
Surgical factors			
Time from perforation to surgery (>12 h/≤12 h)	52/41	18/8	0.26
Perforation site (C–T/D–RS)	17/76	4/22	1.00
Cancer-associated perforation (+/−)	30/63	8/18	1.00
Construction of artificial anus (+/−)	80/13	24/2	0.52
Severity scores			
APACHE II score[a]	11 (3–27)	17 (5–27)	<0.0001
SOFA score[a]	2 (0–7)	4 (1–7)	0.0001

In a univariate analysis of the non-survivor and survivor groups, there were significantly more patients with high APACHE II ($P < 0.0001$) and SOFA scores ($P = 0.0001$) in the non-survivor group

[a] Median (min–max)

Discussion

As a colorectal perforation frequently causes septic shock and multiple organ failure, it is a life-threatening condition associated with a mortality rate of 13.8–35.0 % [1–3, 10]. Gram-negative bacteria, such as *Escherichia coli*, easily cause bacteremia, and endotoxin, which is present on the outer membrane of gram-negative bacteria, interacts with the host during gram-negative sepsis. Furthermore, endotoxin causes the release of cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, which lead to septic shock and multiple organ failure [4, 6]. Consequently, perioperative management approaches based on prognostic factors are needed to improve the outcome in patients with colorectal perforation.

We attempted to identify prognostic factors in patients who underwent surgery in our department. Some previous studies have reported prognostic factors for colorectal

Table 10 The efficacy of PMX-DHP according to the APACHE II score

APACHE II score	PMX-DHP (+) group			PMX-DHP (−) group		
	No. of patients	Survivors	Survival rate (%)	No. of patients	Survivors	Survival rate (%)
1	0	–	–	1	1	100
2	0	–	–	4	4	100
3	1	1	100	0	–	–
4	1	1	100	5	5	100
5	5	4	80.0	3	3	100
6	4	4	100	1	1	100
7	6	5	83.3	4	4	100
8	10	10	100	3	2	66.7
9	8	6	75.0	2	2	100
10	13	13	100	3	3	100
11	9	8	88.9	3	3	100
12	12	9	75.0	2	1	50.0
13	9	9	100	1	1	100
14	6	4	66.7	2	2	100
15	5	4	80.0	1	1	100
16	5	4	80.0	0	–	–
17	6	3	50.0	1	1	100
18	1	1	100	0	–	–
19	6	4	66.7	1	1	100
20	3	1	33.3	0	–	–
22	1	1	100	0	–	–
24	3	0	0	0	–	–
25	1	0	0	0	–	–
26	1	0	0	0	–	–
27	3	1	33.3	0	–	–
Total	119	93	78.2	37	35	94.6

The survival rates of the PMX-DHP (+) and (−) groups were 78.2 % (93/119) and 94.6 % (35/37), respectively

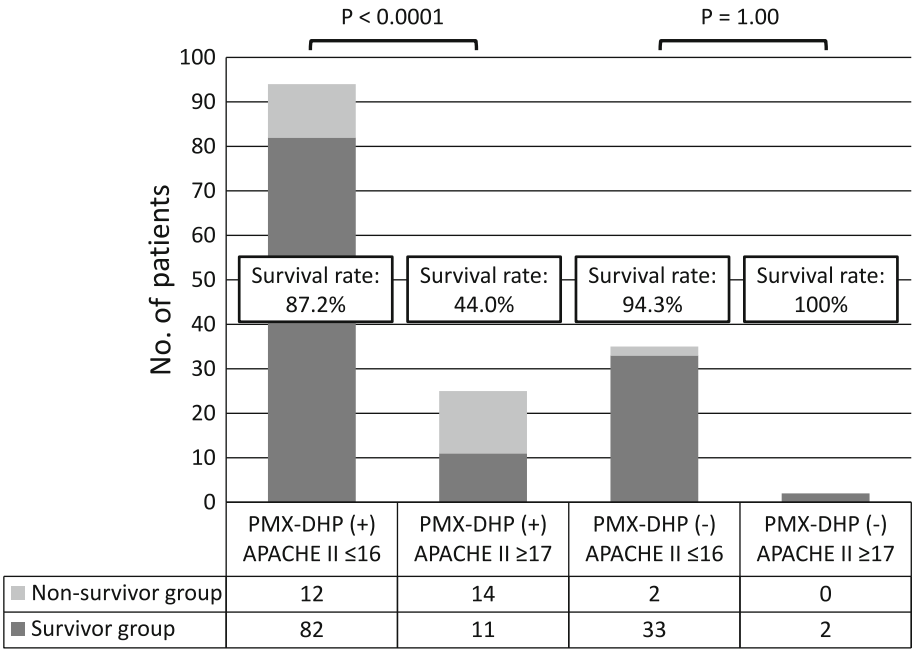

Fig. 1 Survival rate according to the APACHE II score. In the PMX-DHP (−) group, there were no significant differences in the survival rates between the patients with APACHE II scores of 16 or less and those with scores of 17 or more. On the other hand, there was a significant difference in the survival rate between the two sub-groups in the PMX-DHP (+) group ($P < 0.0001$)

perforation [4, 6]. However, few reports have enrolled as many patients as the current investigation. We also analyzed the efficacy of PMX-DHP on the basis of the prognostic factors in our patients.

In the analysis of the prognostic factors, significant differences were recognized in the number of SIRS criteria, use of PMX-DHP, APACHE II score, and the SOFA score. SIRS is defined by the American College of Chest Physicians and the Society of Critical Care Medicine as a condition that includes two or more of the following: body temperature >38 or <36 °C; heart rate >90 beats/min; respiratory rate >20 breaths/min; $PaCO_2$ <32 Torr; WBC >12000 or <4000/mm^3; or with >10 % immature cells [11]. For these reasons, SIRS indicates the presence of septic shock, and is a condition associated with high mortality [12, 13]. Moreover, SIRS has also been reported to reflect the prognosis in surgical patients [14, 15]. In this study, the number of SIRS criteria was closely associated with the patient prognosis. Sun et al. [16] also reported that an increase in mortality was observed as more SIRS criteria were fulfilled. The extent of SIRS can be estimated by both vital signs and blood examinations, and has been proven to be a simple prognostic factor for patients with colorectal perforation.

In the same manner, the APACHE II and SOFA scores were found to be useful as prognostic factors in patients with colorectal perforation. The APACHE II score is a reliable and useful means of classifying the severity of disease and estimating the prognosis in ICU patients [17]. Some other authors have previously reported that the assessment of severity using the APACHE II score was useful for estimating the prognosis in patients with colorectal perforation [2, 18, 19]. The APACHE II scores were significantly higher in the non-survivor group, and were also useful for predicting the severity of the patient condition in this study. Some authors have reported that the mortality rate was significantly higher in patients with APACHE II scores of 15 or more [2], 19 or more [18], or 20 or more [19].

Some authors have reported that assessment of the severity using the SOFA score was also useful [18, 20, 21]. In their analyses of the severity using the SOFA scores, the patients with SOFA scores of seven [20] or eight or more [18, 21] had significantly higher mortality rates. In order to select the optimal cut-off values for the APACHE II and SOFA scores in the present study, the AIC values associated with each severity score was calculated. As a result, APACHE II and SOFA scores of 17 and five, respectively, were used as the cut-off values. In this study, the proportion of patients with APACHE II scores of 17 or more was 10.2 % (13/128) in the survivor group and 50.0 % (14/28) in the non-survivor group, and there were significantly more patients with APACHE II scores of 17 or more in the non-survivors. In the same manner, the proportion of patients with SOFA scores of five or more was 7.8 % (10/128) in the survivor group and 35.7 % (10/28) in the non-survivor group, respectively, and there were significantly more patients with SOFA scores of five or more in the non-survivors. As the multivariate analysis revealed that an APACHE II score of 17 or more was a significant independent prognostic factor, it is necessary to keep in mind that the patients with APACHE II scores of 17 or more are at a higher risk of mortality.

In this study, the efficacy of PMX-DHP was also examined according to the prognostic factors. PMX-DHP was developed as a method to absorb endotoxin in the blood [22]. Recent studies have shown that its use improves the survival [22, 23] and hemodynamic status [4, 24] in patients with sepsis. However, some authors have reported that the improvement of survival and the alterations in plasma endotoxin levels following PMX-DHP treatment remained equivocal in clinical studies [8, 25]. Therefore, we attempted to analyze the efficacy of PMX-DHP using the APACHE II scores. When we compared the clinicopathological factors between the PMX-DHP (+) and (−) groups, there were more patients found in the PMX-DHP (+) group. In our department, PMX-DHP is intended for serious cases, such as those with preoperative shock or WBC depression, and our data indicated that PMX-DHP was actually performed for more serious cases. Moreover, when we compared the clinicopathological factors between the survivor and non-survivor groups among the patients with PMX-DHP in a univariate analysis, there were significantly more patients with high APACHE II and SOFA scores who received PMX-DHP. In fact, except for the two patients with APACHE II scores of 18 and 22, survival rates of 50.0 % or less were recognized among the patients with APACHE II scores of 17 or more. Therefore, our findings suggest that the efficacy of PMX-DHP is limited in serious cases. In this study, the number of severe cases with respiratory failure and DIC caused by sepsis was high among the non-survivors in the PMX-DHP (+) group, and the survival rate of these patients was predicted supposed to be low. Nemoto et al. [23] reported that PMX-DHP did not improve the survival rate in patients with APACHE II scores greater than 30. On the other hand, there were two patients with APACHE II scores of 17 or more in the PMX-DHP (−) group, and both patients survived. Because only these two patients among all of the patients with APACHE II scores of 17 or more in the PMX-DHP (−) group, it is necessary to accumulate more patients with the same severity in order to make a proper comparison with the PMX-DHP (+) group. There have been some previous randomized clinical trials comparing the PMX-DHP (+) and (−) groups. However, there was no significant difference in the 28-day mortality between these groups [4, 26].

Moreover, it was pointed out that the early termination of one trial caused an overestimation of the improvement of survival [27]. Therefore, further investigations are needed to confirm the true impact of PMX-DHP. Two prospective randomized control trials, the primary end points of which are the 28-day mortality, are currently underway in Europe and USA [8]. It is expected that new knowledge concerning the improvement of survival by PMX-DHP will be obtained from those studies.

Conflict of interest Kiichi Sugimoto and co-authors have no conflicts of interest to declare.

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