Validity of Low-Intensity Continuous Renal Replacement Therapy*

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Objective: To study the hospital mortality of patients with severe acute kidney injury treated with low-intensity continuous renal replacement therapy.

Design: Multicenter retrospective observational study (Japanese Society for Physicians and Trainees in Intensive Care), combined with previously conducted multinational prospective observational study (Beginning and Ending Supportive Therapy).

Setting: Fourteen Japanese ICUs in 12 tertiary hospitals (Japanese Society for Physicians and Trainees in Intensive Care) and 54 ICUs in 23 countries (Beginning and Ending Supportive Therapy).

Patients: Consecutive adult patients with severe acute kidney injury requiring continuous renal replacement therapy admitted to the participating ICUs in 2010 (Japanese Society for Physicians and Trainees in Intensive Care, $n = 343$) and 2001 (Beginning and Ending Supportive Therapy Beginning and Ending Supportive Therapy, $n = 1,006$).

Interventions: None.

Measurements and Main Results: Patient characteristics, variables at continuous renal replacement therapy initiation, continuous renal replacement therapy settings, and outcomes (ICU and hospital mortality and renal replacement therapy requirement at hospital discharge) were collected. Continuous renal replacement therapy intensity was arbitrarily classified into seven subclasses: less than 10, 10–15, 15–20, 20–25, 25–30, 30–35, and more than 35 mL/kg/hr. Multivariable logistic regression analysis was conducted to investigate risk factors for hospital mortality. The continuous renal replacement therapy dose in the Japanese Society for Physicians and Trainees in Intensive Care database was less than half of the Beginning and Ending Supportive Therapy database (800 mL/hr vs 2,000 mL/hr, $p < 0.001$). Even after adjusting for the body weight and dilution factor, continuous renal replacement therapy intensity was statistically different (14.3 mL/kg/hr vs 20.4 mL/kg/hr, $p < 0.001$). Patients in the Japanese Society for Physicians and Trainees in Intensive Care database had a lower ICU mortality (46.1% vs 55.3%, $p = 0.003$) and hospital mortality (58.6% vs 64.2%, $p = 0.070$) compared with patients in the Beginning and Ending Supportive Therapy database. In multivariable regression analysis after combining the two databases, no continuous renal replacement therapy intensity subclasses were found to be statistically different from the reference intensity (20–25 mL/kg/hr). Several sensitivity analyses (patients with sepsis, patients from Western countries in the Beginning and Ending Supportive Therapy database) confirmed no intensity-outcome relationship.

Conclusions: Continuous renal replacement therapy at a mean intensity of 14.3 mL/kg/hr did not have worse outcome compared with 20–25 mL/kg/hr of continuous renal replacement therapy, currently considered the standard intensity. However, our study is insufficient to support the use of low-intensity continuous renal replacement therapy, and more studies are needed to confirm our findings. (*Crit Care Med* 2013; 41:2584–2591)

***See also p. 2655.**

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Continuous renal replacement therapy (CRRT) has become a common treatment for critically ill patients with severe acute kidney injury (AKI) in the last two decades (1, 2). However, mortality of patients requiring CRRT remains high (3, 4). Although multiple clinical studies including several randomized controlled trials (RCTs) have been conducted to improve the quality of management of patients with severe AKI (5–7), many issues regarding CRRT are still unresolved. One of such issues is the optimal dose/intensity of CRRT. Initially, one single-center RCT found that patients treated with 35 mL/kg/hr of CRRT had better outcome than those treated with 20 mL/kg/hr (8). However, more recently, two large RCTs have found that increasing CRRT intensity to 35 or 40 mL/kg/hr did not improve the outcome of patients with severe AKI (9, 10). Based on these findings, current AKI guidelines recommend delivering an effluent volume of 20–25 mL/kg/hr for CRRT in AKI (11). However, the lower limit of the CRRT intensity, currently defined as 20 mL/kg/hr, has been poorly studied (12, 13).

The Japanese Society for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group has conducted a multicenter retrospective study for CRRT, aiming for studying multiple unresolved issues regarding CRRT. As CRRT in Japan is often performed with an intensity of lower than 20 mL/kg/hr, in this study, we have compared our database with the previously conducted multicenter study (1) and assessed the impact of low-intensity CRRT on patient outcome. We have also combined the two databases and assessed the impact of different CRRT intensity.

MATERIALS AND METHODS

This is a multicenter retrospective study conducted in 14 ICUs in 12 centers in Japan. The study protocol was reviewed by the ethics committee or investigational review board of each participating center. Because of the anonymous and retrospective fashion of this study, ethical committees in all centers waived the need for informed consent.

Study Population

All patients who were admitted to one of the participating centers between January 2010 and December 2010 were retrospectively screened. Consecutive patients who were equal to or older than 18 years and were treated with CRRT for AKI according to the Risk, Injury, Failure, Loss, End-stage kidney disease criteria (14) were included in the study. Patients with any renal replacement therapy (RRT) before admission to the ICU or patients with end-stage renal failure on chronic dialysis were excluded. If a patient was admitted to the ICU and treated with CRRT for more than once during the same hospital admission, only the first ICU admission was included.

Data Collection

A case report form was developed for the purpose of the study, and the following information was obtained: gender, date of birth, body weight (measured or estimated at ICU admission), date of hospital admission, premorbid creatinine, date of ICU admission, the Simplified Acute Physiology Score (SAPS) II on the day of ICU admission (15), and primary diagnosis. The contributing factors to AKI were identified from a list of possible choices (septic shock, cardiogenic shock, drug induced, hypovolemia, major surgery, and other) according to the judgment of the treating clinician. More than one contributing factor could be selected in each case. At the initiation of CRRT, following information was collected: use of vasopressors and mechanical ventilation, mean arterial pressure (MAP), Pa_{O_2}/F_{IO_2} ratio, lactate, Glasgow Coma Scale (GCS), platelet count, bilirubin, diuretics use, urine output, creatinine, and urea. Information regarding CRRT was also collected: date and time of CRRT initiation and discontinuation, mode of CRRT (continuous venovenous hemofiltration [CVVH], continuous venovenous hemodialysis, continuous venovenous hemodiafiltration [CVVHDF]), blood flow, dialysate, and replacement flow rate. The CRRT dose was defined as the sum of the dialysate and replacement flow rate (mL/hr), as all CVVH and CVVHDF were conducted with postdilution. Intensity of CRRT was defined as the CRRT dose divided by body weight (mL/kg/hr). ICU and hospital mortality and RRT requirement at hospital discharge were also collected.

The Beginning and Ending Supportive Therapy for the Kidney Study

The Beginning and Ending Supportive Therapy (BEST) for the kidney study is a multicenter prospective study for severe acute renal failure, conducted in 54 centers in 23 countries (16). Data were collected mainly in 2001. Among included patients, 1,006 patients were treated with CRRT, and their characteristics, treatment modality, and outcomes were previously published (1). As the current JSEPTIC study was conducted based on the BEST kidney study, collected variables were quite similar between the two studies, which allowed us to compare and combine the two databases. In the BEST kidney database, both premorbid renal function (normal, chronic renal dysfunction, or unknown) and premorbid creatinine were collected. On the other hand, in the JSEPTIC database, only premorbid creatinine was collected. Therefore, in this study, chronic kidney disease was defined as the estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 (17), and unknown premorbid renal function was defined as premorbid creatinine unavailable. As approximately half patients receiving CVVH or CVVHDF were treated with predilution in the BEST database, treatment intensity was corrected using a dilution factor, as previously reported (1).

Statistical Analysis

Data are presented as medians and interquartile ranges (25th–75th percentiles) or percentages. The Fisher exact test or chi-square test was used for nominal variables, and the Mann-Whitney test was used for numerical variables, to compare the JSEPTIC and BEST databases. A p value of less than 0.05 was considered statistically significant. To study the impact of different CRRT intensity on hospital mortality, intensity was

arbitrarily divided into seven subclasses: less than 10, 10–15, 15–20, 20–25, 25–30, 30–35, and more than 35 mL/kg/hr. Multivariable logistic regression analysis was conducted to investigate risk factors for hospital mortality. The following variables were investigated as independent risk factors using a backward elimination approach: age, gender, premorbid renal function (normal as a reference), duration between hospital and ICU admission, SAPS II, postoperative admission, diagnostic grouping (cardiovascular as a reference), contributing factors to AKI, vasopressor use, MAP, mechanical ventilation use, Pao_2/Fio_2 ratio, lactate, GCS, platelet count, bilirubin, diuretics use, urine output, creatinine, urea, duration between ICU admission and CRRT initiation, mode of CRRT (CVVH as a reference), CRRT intensity subclasses (20–25 mL/kg/hr as a reference), and name of databases (BEST as a reference). Name of databases and intensity subclasses were forced to remain in the analysis. The other variables were allowed to stay if the multivariable *p* value was of less than 0.05. Forty-two patients (38 from BEST and four from JSEPTIC) were excluded from this analysis due to lack of information for CRRT intensity.

TABLE 1. Demographics of Study Patients

	Beginning and Ending Supportive Therapy	Japanese Society for Physicians and Trainees in Intensive Care	*p*
Age, yr	66 (51–74)	69 (59–77)	< 0.001
Gender, male, %	65.8	65.9	> 0.99
Weight, kg	75 (65–85)	59 (50–68)	< 0.001
Premorbid renal function, %			
Normal	44.4	44.6	0.12
Chronic kidney disease	33.7	28.9	
Unknown	21.9	26.5	
Premorbid creatinine, μmol/L	96 (77–143)	90 (66–159)	0.057
Hospital to ICU,[a] d	1 (0–7)	1 (0–7)	0.062
Simplified Acute Physiology Score II	48 (39–62)	53 (40–68)	< 0.001
Postoperative admission, %	45.3	30.9	< 0.001
Diagnostic grouping			
Cardiovascular	36.7	40.5	0.24
Gastrointestinal	22.8	23.3	
Sepsis	13.7	11.4	
Respiratory	12.1	14.3	
Hematologic	5.0	2.3	
Neurologic	1.8	1.5	
Trauma	2.0	0.9	
Others	6.0	5.8	
Contributing factors to acute kidney injury, %			
Septic shock	50.2	48.7	0.66
Major surgery	37.6	22.7	< 0.001
Cardiogenic shock	26.1	26.8	0.78
Hypovolemia	20.0	23.3	0.19
Drugs	17.5	5.5	< 0.001
Hepatorenal syndrome	7.3	2.0	< 0.001
Urinary obstruction	2.0	0.3	0.023
Others	11.4	13.1	0.38

[a]Duration between hospital admission and ICU admission.

TABLE 2. Variables at Continuous Renal Replacement Therapy Initiation and Outcomes

	Beginning and Ending Supportive Therapy	Japanese Society for Physicians and Trainees in Intensive Care	*p*
Vasopressor, %	78.8	73.2	0.036
Mean arterial pressure, mm Hg	74 (65–84)	72 (63–80)	0.002
Mechanical ventilation, %	84.1	82.5	0.50
Pao_2/Fio_2 ratio, Torr	210 (142–302)	205 (132–301)	0.68
Lactate, mmol/L	2.3 (1.2–5.2)	2.8 (1.5–6.2)	0.008
Glasgow Coma Scale	14 (10–15)	14 (9–15)	0.40
Platelet count, $10^3/\mu L$	119 (63–196)	87 (54–152)	< 0.001
Bilirubin, mmol/L	20 (12–49)	19 (10–41)	0.017
Diuretics use, %	69.1	42.9	< 0.001
Urine output, mL/hr	17 (4–47)	19 (8–43)	0.15
Creatinine, μmol/L	292 (192–427)	240 (164–334)	< 0.001
Urea, mmol/L	23 (15–34)	17 (12–26)	< 0.001
ICU to start,[a] d	1.2 (0.4–4.1)	0.8 (0.2–1.9)	< 0.001
Mode of CRRT, %			
Continuous arteriovenous hemodialysis	0.1	0.0	< 0.001
Continuous venovenous hemofiltration	52.8	5.2	
Continuous venovenous hemodialysis	13.1	23.6	
Continuous venovenous hemodiafiltration	34.0	71.1	
Blood flow, mL/min	150 (120–180)	100 (80–100)	< 0.001
CRRT dose, mL/hr	2,000 (1,200–2,100)	800 (700–1,000)	< 0.001
Intensity, mL/kg/hr	20.4 (15.3–27.7)	14.3 (11.1–17.8)	< 0.001
CRRT duration, d	3.9 (1.5–10.1)	2.8 (1.4–6.0)	< 0.001
ICU mortality, %	55.3	46.1	0.003
Hospital mortality, %	64.2	58.6	0.070
Renal replacement therapy at hospital discharge among survivors, %	14.5	11.3	0.39

CRRT = continuous renal replacement therapy.
[a]Duration between ICU admission to CRRT initiation.

Several sensitivity analyses were also conducted to confirm the initial findings. First, because high intensity might be more effective in patients with sepsis than in patients without sepsis (18, 19), multivariable regression analysis was repeated for only patients with sepsis (all patients with sepsis). Second, as some of participating centers in the BEST kidney study were from low-income countries, which could have negatively affected patient outcome, only patients from Western countries (Europe, North America, and Australia) in the BEST database were combined with the JSEPTIC database (BEST-W and JSEPTIC). Third, only patients with sepsis from the Western countries in the BEST database and JSEPTIC database were analyzed (BEST-W and JSEPTIC with sepsis). Finally, as including the origin of databases could underestimate the effect of treatment intensity, multivariable regression analysis was also performed without the origin of databases. For all statistical analyses, a commercially available statistical package was used (SPSS 19.0; IBM, Tokyo, Japan).

RESULTS

Three hundred forty-three patients were included in the JSEPTIC database. **Table 1** shows the demographics of study patients. Compared with the BEST database, patients in the JSEPTIC database were older (69 yr vs 66 yr, $p < 0.001$), their body weight was lighter (59 kg vs 75 kg, $p < 0.001$), and they had a higher SAPS II score (53 vs 48, $p < 0.001$). Postoperative ICU admission was less common in the JSEPTIC database compared with the BEST database (30.9% vs 45.3%, $p < 0.001$), but the diagnostic groupings were similar between the two databases

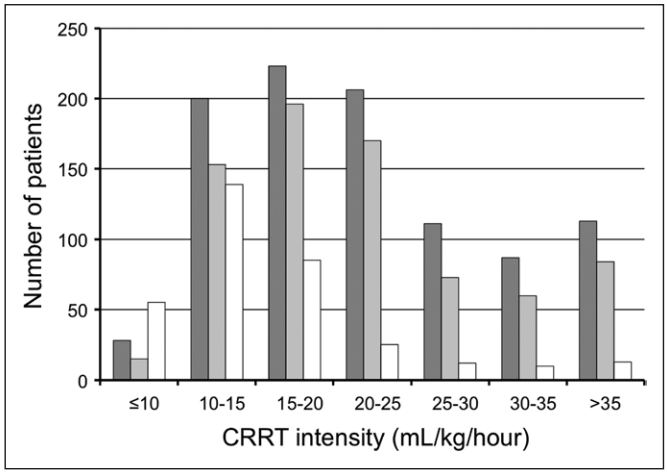

Figure 1. Number of patients with different intensity of continuous renal replacement therapy (CRRT) in the two multicenter databases. BEST = Beginning and Ending Supportive Therapy for the kidney (*dark gray bar*), BEST-W = Patients from Western countries (Europe, North America, and Australia) in the BEST database (*light gray bar*), JSEPTIC = Japanese Society for Physicians and Trainees in Intensive Care (*white bar*).

($p = 0.24$). The most common contributing factor for AKI was septic shock in the both databases (48.7% and 50.1%, $p = 0.66$).

Variables at CRRT initiation and outcomes are shown in **Table 2**. There were several significant differences between the two databases. For example, vasopressor requirement was less frequent (73.2% vs 78.8%, $p = 0.036$) and MAP was lower (72 mm Hg vs 74 mm Hg, $p = 0.002$) in the JSEPTIC database compared with the BEST database. Also, lactate was higher (2.8 mmol/L vs 2.3 mmol/L, $p = 0.008$), platelet count was lower ($87 \times 10^3/\mu L$ vs $119 \times 10^3/\mu L$, $p < 0.001$), and both creatinine and urea were lower ($p < 0.001$) in the JSEPTIC database compared with the BEST database. Mechanical ventilation requirement, oxygenation, GCS, and urine output were similar between the two databases.

CRRT was started statistically, but nonclinically, earlier in the JSEPTIC database (0.8 d vs 1.2 d after ICU admission, $p < 0.001$). In the BEST database, CVVH was the most common mode of CRRT. On the other hand, more than 70% of patients were treated with CVVHDF in the JSEPTIC database. The blood flow rate was lower in the JSEPTIC database compared with the BEST database (100 mL/min vs 150 mL/min, $p < 0.001$). The CRRT dose in the JSEPTIC database was less than half of the BEST database (800 mL/hr vs 2,000 mL/hr, $p < 0.001$). Even after adjusting for the body weight and dilution factor, CRRT intensity was statistically different (14.3 mL/kg/hr vs 20.4 mL/kg/hr, $p < 0.001$). Although patients in the JSEPTIC database tended to be sicker (older age, higher SAPS II, less postoperative admission, higher lactate, lower platelet count) and were treated with lower CRRT intensity, both ICU and hospital mortality were lower compared with the BEST database.

The distribution of CRRT intensity in the two databases is shown in **Figure 1**. Figure 1 also includes data for patients from the Western countries (Europe, North America, and Australia) in the BEST database (BEST-W).

Multivariable logistic regression analysis was conducted to see the impact of database difference and CRRT intensity on hospital mortality (**Table 3**). After removing confounding factors including the name of databases, no CRRT intensity subclasses were found to be statistically different from the reference intensity (20–25 mL/kg/hr).

The results of the four sensitivity analyses (all patients with sepsis, BEST-W and JSEPTIC, BEST-W and JSEPTIC with sepsis, origin of database not included) are shown in **Table 4** and **Figure 2**. Although multivariable regression analysis for hospital mortality was repeated in those four subgroups, none of them found intensity-outcome relationship.

DISCUSSION

In this study, we have compared the two multicenter CRRT databases and found that patients with severe AKI treated with low-intensity CRRT (14.3 mL/kg/hr) did not have worse hospital outcome compared with patients treated with currently considered the standard intensity (20.4 mL/kg/hr). We have also combined the two databases and conducted several multivariable regression analyses, which showed no intensity-outcome relationship. As information for low-intensity CRRT is quite limited in the medical literature, our findings need careful discussion.

To our knowledge, there have been only two studies for low-intensity RRT published in the medical literature (12, 13). One is a single-center prospective study comparing continuous arteriovenous hemofiltration (CAVH, $n = 48$, 7.0 L/d) and pump-driven CVVH ($n = 68$, 15.7 L/d) (12). Although there was no difference in patient background between the two groups, mortality was significantly higher in CAVH (87.5%) compared with CVVH (70.6%, $p < 0.05$). The other study was an open-label single-center RCT comparing CVVH and peritoneal dialysis in 70 adult patients with severe falciparum malaria ($n = 48$) or sepsis ($n = 22$) (13). The mortality rate was 47% in the group assigned to peritoneal dialysis, as compared with 15% in the group assigned to CVVH ($p = 0.005$). In a multivariable analysis, the odds ratio (OR) for death was 5.1 in the group assigned to peritoneal dialysis. Obviously, these two studies did not directly compare different intensity of CRRT but different modes of RRT. Therefore, although lower intensity RRT (CAVH and peritoneal dialysis) could have been related to poor outcome, the confounding factors seen in these studies make an independent assessment of lower intensity CRRT quite complex.

When no direct comparative studies exist, analysis for different intensity levels as reported in multicenter observational studies is another means. In the Dose Response Multicentre International Collaborative Initiative study, a prospective multicenter observational study for RRT conducted in 30 ICUs in eight countries, 18% patients (61 patients) were treated with CRRT of less than 20 mL/kg/hr (20). The adjusted OR for ICU mortality in patients treated with 20–35 mL/kg/hr was 0.79 ($p = 0.492$) and that in patients treated with more than 35 mL/kg/hr was 1.00 ($p = 0.995$), compared with patients treated with less than 20 mL/kg/hr. These data suggest a lack of clear intensity-outcome relationship. The BEST kidney study also reported similar findings: the adjusted OR for hospital

TABLE 3. Multivariable Logistic Regression Analysis for Hospital Mortality

	Odds Ratio (95% CI)	*p*
Age, yr	1.023 (1.013–1.034)	< 0.001
Hospital to ICU,[a] d	1.027 (1.012–1.042)	< 0.001
Simplified Acute Physiology Score II, point	1.025 (1.015–1.034)	< 0.001
Diagnostic grouping		
Cardiovascular	1.000 (reference)	–
Respiratory	2.334 (1.434–3.800)	0.001
Cardiogenic shock	1.417 (1.002–2.003)	0.049
Mean arterial pressure, mm Hg	0.987 (0.977–0.997)	0.014
Mechanical ventilation	1.594 (1.062–2.393)	0.024
Lactate, mmol/L	1.147 (1.094–1.202)	< 0.001
Platelet count, $10^3/\mu L$	0.998 (0.997–0.999)	0.009
Bilirubin, mmol/L	1.003 (1.001–1.004)	0.005
Creatinine, μmol/L	0.999 (0.998–0.999)	0.008
Urea, mmol/L	1.018 (1.003–1.032)	0.015
ICU to start,[b] d	1.046 (1.015–1.079)	0.004
Database		
Beginning and Ending Supportive Therapy	1.000 (reference)	–
Japanese Society for Physicians and Trainees in Intensive Care	0.518 (0.363–0.739)	< 0.001
Intensity, mL/kg/hr		
≤ 10	1.483 (0.740–2.972)	0.27
10–15	1.173 (0.740–1.860)	0.50
15–20	1.061 (0.668–1.686)	0.80
20–25	1.000 (reference)	–
25–30	1.415 (0.741–2.701)	0.29
30–35	1.283 (0.648–2.539)	0.47
> 35	1.166 (0.619–2.197)	0.63

Dashes indicate no *p* values.

[a]Duration between hospital admission and ICU admission.

[b]Duration between ICU admission to continuous renal replacement therapy initiation.

$R^2 = 0.298$.

mortality in patients treated with 20–35 mL/kg/hr was 1.129 ($p = 0.48$) and that in patients treated with more than 35 mL/kg/hr was 1.014 ($p = 0.96$), compared with patients treated with less than 20 mL/kg/hr. Although Nurmohamed et al (21) found that a delivered dose less than 19.7 mL/kg/hr was associated with the lower survival rate ($p = 0.006$), this is a retrospective single-center study and its generalizability is uncertain.

In Japan, it is common to conduct CRRT with low intensity. Indeed, in our database, approximately 80% of included patients were treated with less than 20 mL/kg/hr of CRRT, and the median intensity was 14.3 mL/kg/hr, which was significantly lower than that of the BEST database conducted in 54 centers in 23 countries. However, although Japanese patients were older and had a higher SAPS II score, both ICU mortality (46.1% vs 55.3%, $p = 0.003$) and hospital mortality (58.6% vs 64.2%, $p = 0.07$) were lower than in the BEST kidney database. As patients in our database were admitted to the ICU more recently (study year of the BEST: 2001 and that of the JSEPTIC: 2010), better outcome in our study was possibly due to improved general management of ICU patients. Furthermore, some of participating centers in the BEST kidney study were from low-income countries, which could have further negatively affected patient outcome. Therefore, we have combined the two databases and conducted a multivariable regression analysis to study the impact of different CRRT intensity on hospital mortality, including the name of databases as an independent variable. This analysis, which should have eliminated the bias toward better outcome for low intensity from

TABLE 4. Sensitivity Analysis for Hospital Mortality

	All Patients With Sepsis ($n = 652$)		BEST-W and JSEPTIC ($n = 1,093$)		BEST-W and JSEPTIC With Sepsis ($n = 534$)	
	Odds Ratio (95% CI)	*p*	Odds Ratio (95% CI)	*p*	Odds Ratio (95% CI)	*p*
Database						
BEST	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–
JSEPTIC	0.409 (0.245–0.683)	0.001	0.571 (0.393–0.831)	0.0033	0.669 (0.374–1.196)	0.17
Intensity, mL/kg/hr						
≤ 10	1.039 (0.353–3.058)	0.94	1.144 (0.703–1.863)	0.59	1.630 (0.799–3.327)	0.18
10–15	1.274 (0.654–2.513)	0.49	1.556 (0.762–3.176)	0.22	1.352 (0.442–4.137)	0.60
15–20	0.857 (0.440–1.670)	0.65	1.019 (0.630–1.647)	0.94	1.274 (0.655–2.481)	0.48
20–25	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–
25–30	1.387 (0.566–3.403)	0.47	1.147 (0.584–2.252)	0.69	1.627 (0.620–4.266)	0.32
30–35	1.314 (0.525–3.289)	0.56	1.187 (0.561–2.508)	0.65	1.745 (0.670–4.550)	0.25
> 35	0.786 (0.321–1.925)	0.60	1.316 (0.673–2.573)	0.42	1.305 (0.492–3.467)	0.59

BEST = Beginning and Ending Supportive Therapy, BEST-W = Patients in Western countries in the BEST database, JSEPTIC = Japanese Society for Physicians and Trainees in Intensive Care. Dashes indicate no *p* values.

$R^2 = 0.296$ for all patients with sepsis, 0.276 for BEST-W and JSEPTIC, and 0.291 for BEST-W and JSEPTIC with sepsis.

the JSEPTIC database, found no intensity-outcome relationship. We have also conducted several sensitivity analyses for sepsis and patients from the Western countries and confirmed that low intensity did not result in poor outcome in these subgroups of patients.

If a patient is persistently anuric due to severe AKI but is not treated with CRRT (intensity of zero), he or she eventually will die due to severe solute or volume derangements (e.g., pulmonary edema, hyperkalemia, uremic complications). Therefore, theoretically, there must be a lower limit of intensity between zero and 20 mL/kg/hr, below which patient outcome is likely to be dose-dependent and compromised (**Fig. 3**). Although it has been assumed that this lower limit is 20 mL/kg/hr (22), such assumption is not based on strong evidence. If CRRT is simply to treat or prevent life-threatening complications, the lower limit of intensity can be defined as that where small solute control (uremia, hyperkalemia, metabolic acidosis) can be achieved. Such intensity may be much lower than 20 mL/kg/hr for most patients. As unnecessarily high-intensity CRRT could lead to electrolyte abnormalities, frequent machine troubles, and high cost, seeking for the lower limit of CRRT intensity seems clinically important.

This study contains several limitations. First, as mentioned above, the two cohorts (BEST and JSEPTIC) are not comparable. The data collection is 9-year different (e.g., volume control might have been more meticulously controlled in the JSEPTIC database), the countries are different, JSEPTIC involved only tertiary hospitals, and there were several differences in the patient characteristics between the two cohort. The difference in mortality over the two cohorts could have been related to

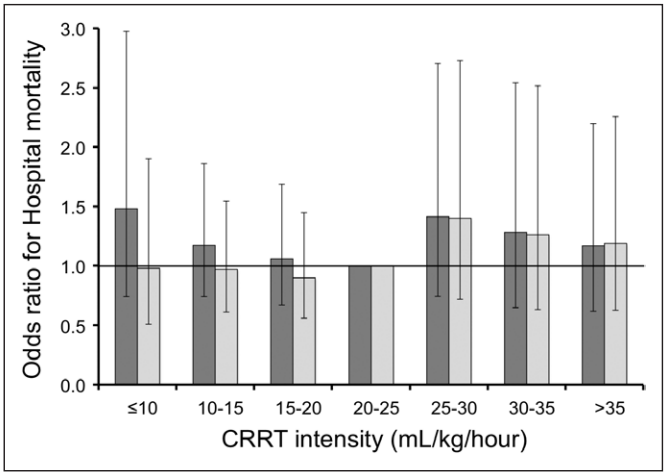

Figure 2. Odds ratios for hospital morality in different intensity of continuous renal replacement therapy (CRRT) in the two multicenter databases, with and without the origin of databases in multivariable regression analysis. *Dark gray bar* = database included, *light gray bar* = database not included.

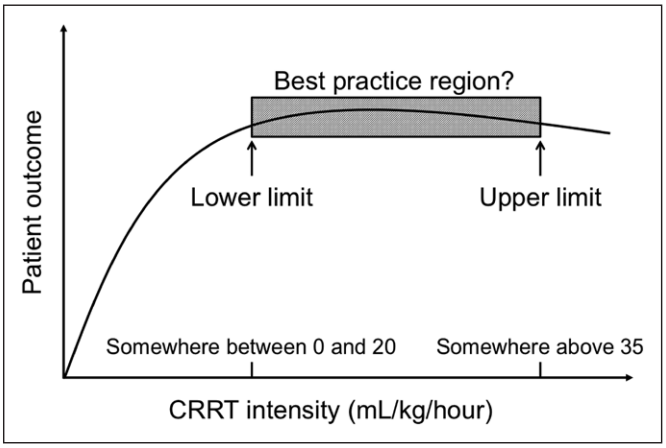

Figure 3. Schematic relationship between the continuous renal replacement therapy (CRRT) intensity and patient outcome.

improvement in standard of care. For example, positive fluid balance has been shown to be related to poor outcome (23). Indeed, an observational study from Finland reported that 1,686 patients treated with RRT between 2007 and 2008 had hospital mortality of only 35% (24). However, this study included all RRT patients and the prevalence of CRRT requirement was not reported. The two large RCTs for RRT intensity also reported low mortality: The Acute Renal Failure Trial Network study reported 48.0% of hospital mortality for less intensive strategy (9), and the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy study reported 44.7% of 90-day mortality for both higher and lower intensity CRRT (10). However, these studies had many exclusion criteria (e.g., moribund state), which might have decreased mortality compared with observational studies (25). Second, this is a retrospective observational study, which is potentially prone to bias. However, the sample size in the multivariable analysis (n = 1,349) is one of the largest for CRRT studies in general and the largest for low-intensity CRRT studies. Third, CRRT intensity was calculated according to the prescribed dialysate and replacement flow rate at the initiation of CRRT. Some patients initially treated with low intensity might have had solute control worsened and had their CRRT intensity increased later. However, although not based on data, our experience suggests that such increase in intensity is uncommon.

CONCLUSIONS

In summary, we have analyzed the impact of low-intensity CRRT on hospital mortality using the two multicenter CRRT databases combined. We have found that CRRT at a mean intensity of 14.3 mL/kg/hr did not have worse outcome compared with CRRT of 20.4 mL/kg/hr intensity, currently considered the lower limit of standard intensity (11). However, our study is insufficient to support the use of low-intensity CRRT, and more studies (especially RCTs) are needed to confirm our findings, although designing of such studies (e.g., population, modality) would be challenging.

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