Artificial Organs

Artificial Organs
35(2):E11–E17, Wiley Periodicals, Inc.

Norepinephrine and Hospital Mortality in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

*Che-Yi Chou, *Hung-Chieh Yeh, †Wei Chen, *Jiung-Hsiun Liu, *Hsin-Hung Lin, *Yao-Lung Liu, *Ya-Fei Yang, *Shu-Ming Wang, and *Chiu-Ching Huang

**Kidney Institute and Division of Nephrology, and †Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, China Medical University Hospital, Taichung, Taiwan*

Abstract: High-dose vasopressor use is associated with increasing mortality in patients with septic shock. We conducted this study to determine if the high-dose of vasopressor used before the initiation of continuous renal replacement therapy (CRRT) is associated with increasing mortality in critically ill patients. We retrospectively reviewed all patients who underwent CRRT in the medical intensive care unit of China Medical University Hospital between 2003 and 2007. The association between mortality and highest vasopressors (dopamine and norepinephrine [NE]) dose used were analyzed using Kaplan–Meier analysis and multivariate Cox regression. A total of 279 patients (170 men and 109 women) treated with CRRT in medical intensive care were reviewed and 237 (84.9%) died. In Kaplan–Meier analysis with log-rank test, dopamine dose of ≥20 μg/kg/min and NE dose of ≥0.3 μg/kg/min were significantly linked to mortality ($P = 0.007$ and <0.001). In multivariate Cox proportional hazards regression, NE dose of ≥0.3 μg/kg/min, Acute Physiology and Chronic Health Evaluation II score, and low platelet count were independently linked to mortality. The hazard ratios and 95% confidence interval (CI) were 1.771 (95% CI: 1.247–2.516, $P = 0.001$), 1.035 (95% CI: 1.012–1.058, $P = 0.003$), and 0.997 (95% CI: 0.996–0.999, $P = 0.003$), respectively. Critically ill patients treated with very high dose of NE before the initiation of CRRT have a very high mortality rate regardless of the acute kidney injury stage.
Key Words: Catecholamines—Mortality—Vasopressor—Dopamine—Norepinephrine—Intensive care unit—Continuous renal replacement therapy—Hemofiltration—Hemodiafiltration—Acute kidney injury.

Dopamine and norepinephrine (NE) are common vasopressors used in patients with shock and are suggested in the international guidelines for management of severe sepsis as well as septic shock (1). The administration of high NE doses is effective and may improve survival in high-risk patients (2–4). Early use of NE may improve mesenteric blood flow, lower lactate levels, and require less infused volume in animal models (3).

However, a mean arterial pressure (MAP) of less than 70 mm Hg after dopamine treatment is associated with increasing mortality (5) and high-dose NE treatment is associated with increasing mortality in septic shock patients (6). Sepsis is one of the most common causes of acute kidney injury that requires continuous renal replacement therapy (CRRT) (7–9), and some patients may benefit from the removal of sepsis-related cytokines during CRRT (10). In clinical practice, we found that acute kidney injury patients treated with a very high dose of vasopressor to maintain blood pressure rarely respond to treatment with CRRT. We hypothesize that patients who need very high dopamine or NE doses before the initiation of CRRT are associated with increasing mortality. We conducted this study to determine if the peak vasopressor dose used before starting CRRT was associated with mortality in critically ill patients.

doi:10.1111/j.1525-1594.2010.01115.x

Received December 2009; revised April 2010.
Address correspondence and reprint requests to Dr. Shu-Ming Wang, Division of Nephrology, Department of Internal Medicine, China Medical University Hospital, No.2, Yude Road North District, Taichung City 40461, Taiwan. E-mail: cychou.chou@gmail.com

PATIENTS AND METHODS

We retrospectively reviewed all patients treated with continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHDF) in the medical intensive care unit (ICU) at China Medical University Hospital between 2003 and 2007. All CVVH and CVVHDF were performed using 15–20 mL/kg/h of bicarbonate-buffered replacement fluid between 2003 and 2004, increasing to 30–40 mL/kg/h of replacement fluid after 2005. The filters in use are AN 69 M100 (Gambro, Lund, Sweden) with predilution, blood flow rates of 100 mL/min, dialysate flow rates of 16.7 mL/min for CVVHDF, and heparin anticoagulation if needed. The treatment is initiated by a nephrologist and then carried out by ICU nurses.

The following data were collected: age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II (11), Sequential Organ Failure Assessment (SOFA) score (12), Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) classification (13), and AKIN (acute kidney injury network) classification modified from the RIFLE criteria (14) of acute kidney injury on the initiation of CRRT. The highest dose of vasopressor including dopamine and NE used before starting CRRT were recorded and biomarkers on admission to ICU were also recorded for analysis. Sepsis was defined as systemic inflammatory response syndrome with an infection (15). Patient survival was recorded from the initiation of CRRT until death or 60 days.

Statistical analysis

The clinical and demographic data were reported as mean ± standard deviation or percent frequency, as appropriate. Statistical significance testing was conducted using *t*-test, chi-square test, and Mann–Whitney *U*-test, as appropriate. Receiver operating characteristic (ROC) curve and area under curve (AUC) were created to identify the dopamine and NE dose in association with mortality. Patients' survival was analyzed using Kaplan–Meier estimate with log-rank test according to the highest dopamine dose ≥20 or <20 μg/kg/min and NE dose ≥0.3 or <0.3 μg/kg/min. Possible prognostic factors including dopamine dose, NE dose, APACHE II, SOFA score, septic shock, mechanical ventilation, MAP, serum potassium, creatinine, urine output, platelet counts, RIFLE, and AKIN classification were analyzed using univariate Cox regression. Prognostic factors that were significant in univariate Cox regression were included in the multivariate Cox proportional hazards regression. A P value of less than 0.05 was considered statistically significant. All calculations were carried out using a standard statistical package (SPSS for Windows, version 12, SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 279 patients (170 men and 109 women) with a mean age of 63.9 ± 16.1 years, treated with CRRT in medical ICU, were reviewed and 237 (84.9%) patients died. The demographic characteristics of the entire study group are shown in Table 1, and 24-h urine output was 0.2 ± 0.4 L and serum creatinine was 4.6 ± 3.8 mg/dL. The nonsurvivors had significantly lower platelet counts and lower MAPs than survivors ($P = 0.001$ and $P = 0.047$). The SOFA score was 16.1 ± 3.8 for patients who died, significantly higher than the SOFA score (13.6 ± 3.5) of survivors ($P < 0.001$). However, the APACHE II score ($P = 0.119$) and the percentage of RIFLE-R, -I and -F classification were not significantly different between survivors and nonsurvivors ($P = 0.067$). The highest dopamine and NE doses used were 19.2 ± 11.2 and 0.65 ± 0.59 μg/kg/min in nonsurvivors, significantly higher than that (12.1 ± 6.5 and 0.27 ± 0.19 μg/kg/min) of survivors ($P < 0.001$ and <0.001). The duration of the admission of ICU to the time of highest NE dose used ranged from 0 to 31 h (median: 1 h) in survivors and ranged from 0 to 51 h (median: 1 h) in nonsurvivors ($P = 0.573$, Mann–Whitney *U*-test). The duration of the time of highest NE used to the initiation of CRRT was from 0 to 87 h (median: 5 h) among survivors and from 0 to 79 h (median: 7 h) among nonsurvivors ($P = 0.09$, Mann–Whitney *U*-test). The ROC curve of APACHE II, RIFLE, AKIN classification, and the highest dopamine and NE doses in association with mortality are shown in Fig. 1. The AUC for dopamine and NE were 0.699 and 0.765, respectively, suggesting the peak dose of NE may be a better predictor than dopamine and APACHE II. The sensitivity, specificity, positive predictive value, and negative predictive value for NE dose of ≥0.3 μg/kg/min were 68.4, 77.1, 93.5, and 33.6%. As shown in Figs. 2 and 3, the peak dopamine dose of ≥20 μg/kg/min and NE dose of ≥0.3 μg/kg/min were significantly associated with mortality ($P = 0.0074$ and $P < 0.001$, log rank test). Of 169 (60.6%) patients treated with a peak NE of ≥0.3 μg/kg/min, 158 (93.5%) patients died in the 60 days since the initiation of CRRT. The percentage was significantly higher than that (73/110, 66.4%) of patients treated with a peak NE of <0.3 μg/kg/min ($P < 0.001$).

The clinical characteristics based on the highest NE dose used are shown in Table 2; the APACHE II

TABLE 1. *Clinical and demographic characteristics of entire study population*

	All patients ($n = 279$)	Survivors ($n = 48$)	Nonsurvivors ($n = 231$)	P
Age (years)	63.9 ± 16.1	62.5 ± 16.2	64.2 ± 16.0	0.512
Male sex	170 (60.9)	25 (52.1)	145 (62.8)	0.167
APACHE II	23.9 ± 8.1	22.2 ± 7.8	24.2 ± 8.2	0.119
SOFA score	15.7 ± 3.9	13.6 ± 3.5	16.1 ± 3.8	<0.001
Sepsis	120 (43)	12 (25)	108 (46.8)	0.006
Septic shock	85 (30.5)	28 (58.3)	57 (24.7)	<0.001
Mechanical ventilation	55 (19.7)	16 (33.3)	39 (16.9)	0.009
MAP	53 ± 10	56 ± 12	52 ± 9	0.047
pH	7.32 ± 0.14	7.32 ± 0.14	7.32 ± 0.14	0.936
Potassium (mEq/L)	4.5 ± 1.3	4.9 ± 1.5	4.4 ± 1.2	0.019
BUN (mg/dL)	70 ± 49	70 ± 55	70 ± 48	0.974
Creatinine (mg/dL)	4.6 ± 3.8	5.6 ± 5.9	4.4 ± 3.1	0.162
Urine output (L/24 h)	0.2 ± 0.4	0.3 ± 0.3	0.2 ± 0.4	0.515
Platelets ($\times 10^3$/mL)	157 ± 113	207 ± 133	147 ± 106	0.001
Dopamine (μg/kg/min)	18 ± 10.8	12.1 ± 6.5	19.2 ± 11.2	<0.001
NE (μg/kg/min)	0.6 ± 0.57	0.27 ± 0.19	0.65 ± 0.59	<0.001
RIFLE classification				
Nonclassified	16 (5.7)	6 (12.5)	10 (4.3)	0.123
Risk	20 (7.2)	4 (8.3)	16 (7.4)	
Injury	21 (7.5)	4 (8.3)	17 (7.4)	
Failure	173 (62)	24 (50)	149 (79.7)	
Loss	20 (7.2)	6 (12.5)	14 (6.1)	
ESKD	29 (10.4)	4 (8.3)	25 (10.8)	
AKIN				
1	29 (10.4)	8 (16.7)	21 (9.1)	0.069
2	21 (7.5)	5 (10.4)	16 (6.9)	
3	214 (76.7)	30 (62.5)	184 (79.7)	

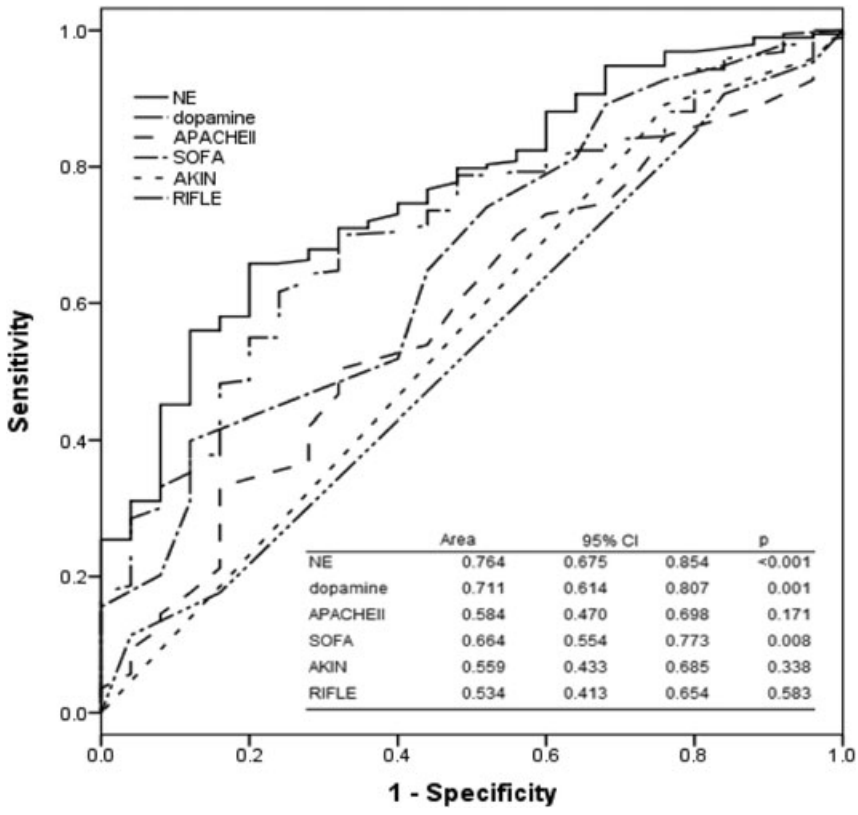
Data are presented as mean ± standard deviation or as number (%). P values are for Student's t-test or chi-square test.

BUN, blood urea nitrogen; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; NE, norepinephrine; RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease; ESKD, end-stage kidney disease; AKIN, Acute Kidney Injury Network.

scores were not significantly different between patients with a NE dose of ≥0.3 μg/kg/min and those with a NE dose of <0.3 μg/kg/min ($P = 0.196$). The SOFA score (16.2 ± 3.7 vs. 14.9 ± 4.1, $P = 0.01$) and MAPs (50.8 ± 8.9 vs. 55.6 ± 10.7 mm Hg, $P < 0.001$) were significantly higher in patients treated with a NE dose of ≥0.3 μg/kg/min. The variables with a $P < 0.05$ in Tables 1 and 2 were analyzed using univariate Cox regression and the variables with a $P < 0.05$ including NE, dopamine, APACHE II score, SOFA score, platelet, MAP, and septic shock were included in multivariate Cox proportional hazard regression. Urine output ($P = 0.109$), RIFLE ($P = 0.315$), and AKIN classification ($P = 0.37$) are specific prognostic factors in patients with acute kidney injury, and were also considered in multivariate Cox proportional hazard regression. As shown in Table 3, the peak NE dose of ≥0.3 μg/kg/min, APACHE II, and low platelet counts were independently associated with 60 days mortality. The hazard ratios were 1.771 (95% confidence interval [CI]: 1.247–2.516, $P < 0.001$) for NE, 1.035 (95% CI: 1.012–1.058, $P = 0.003$) and 1.026 (95% CI: 1.007–1.046, $P = 0.008$) for every one-point increase of APACHE II score, and 0.997 (95% CI: 0.996–0.999, $P = 0.003$) for every 10^3/mL increased platelet counts.

DISCUSSION

In this study, we showed a strong association between the highest vasopressor used before CRRT and patients' mortality in critical patients with acute kidney injury. Patients treated with a NE dose of ≥0.3 μg/kg/min were associated with a 77% increase of mortality and only 6.5% of patients survived on the 60th day. Our finding supports an important clinical issue in the practice of intensive care: critically ill patients treated with a very high dose of vasopressor have a very high mortality rate and CRRT may not improve patients' outcome in our cohort. The association between the highest NE dose and morality can be explained by the poor cardiovascular response to catecholamine (5,16). Similar to our finding, previous studies (6,17–19) have also shown a high mortality rate in septic shock patients treated with a very high NE dose. More prospective interventional studies are needed to determine if CRRT before very high vasopressor use in critically ill patients improves patient survival.



	Area	95% CI		p
NE	0.764	0.675	0.854	<0.001
dopamine	0.711	0.614	0.807	0.001
APACHEII	0.584	0.470	0.698	0.171
SOFA	0.664	0.554	0.773	0.008
AKIN	0.559	0.433	0.685	0.338
RIFLE	0.534	0.413	0.654	0.583

FIG. 1. ROC curve and the area under ROC curve of norepinephrine, dopamine, and disease severity scores in association with 60-day mortality. Peak NE and dopamine dose used before the initiation of continous renal replacement therapy.

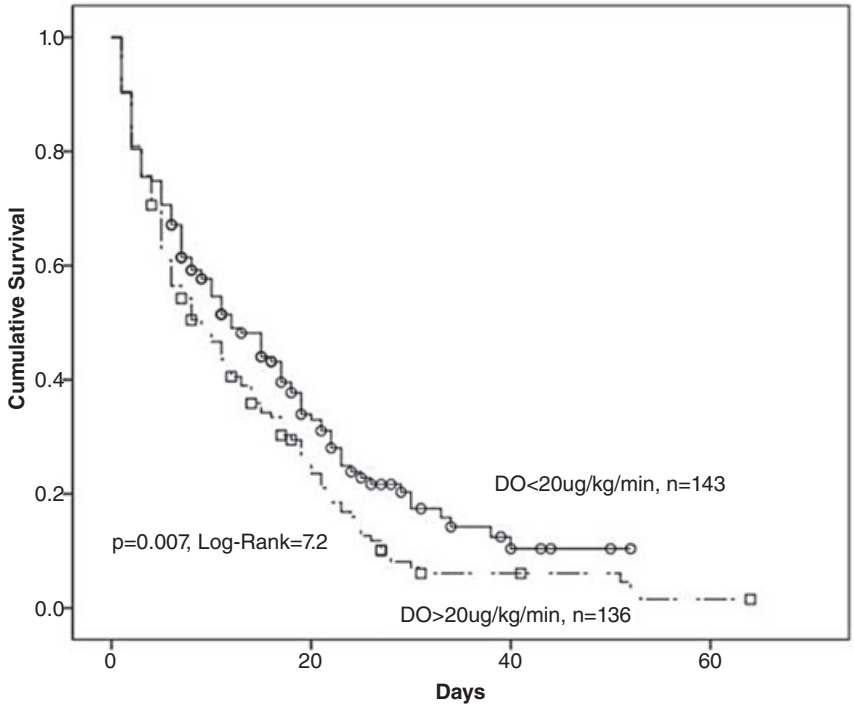


FIG. 2. Kaplan–Meier survival curve for patients with dopamine dose ≥20 or <20 μg/kg/min.

TABLE 2. *Comparison between patients who were treated with peak NE doses ≥ or <0.3 μg/kg/min*

Characteristics	NE<0.3 μg/kg/min ($n = 110$)	NE≥0.3 μg/kg/min ($n = 169$)	P
Age (years)	64.0 ± 16.1	63.9 ± 16.1	0.944
Male sex	64 (58.2)	106 (62.7)	0.448
Mortality (60 days)	73 (66.4)	158 (93.5)	<0.001
APACHE II	23.1 ± 7.7	24.4 ± 8.4	0.196
SOFA score	14.9 ± 4.1	16.2 ± 3.7	0.010
Sepsis	42 (38.2)	78 (46.2)	0.189
Septic shock	62 (56.4)	132 (78.1)	<0.001
Mechanical ventilation	82 (74.5)	142 (84)	0.052
MAP (mm Hg)	56 ± 11	51 ± 9	<0.001
pH	7.32 ± 0.14	7.32 ± 0.14	0.718
Potassium (mEq/L)	4.7 ± 1.5	4.4 ± 1.1	0.063
BUN (mg/dL)	73 ± 48	68 ± 50	0.394
Creatinine (mg/dL)	4.8 ± 4.1	4.5 ± 3.6	0.423
Urine output (L/24 h)	0.3 ± 0.4	0.2 ± 0.4	0.149
Platelets ($\times 10^3$/mL)	168 ± 119	150 ± 109	0.182
RIFLE classification			
Nonclassified	7 (6.4)	9 (5.3)	0.762
Risk	10 (9.1)	10 (5.9)	
Injury	10 (9.1)	11 (6.5)	
Failure	63 (57.3)	110 (65.1)	
Loss	9 (8.2)	11 (6.5)	
ESKD	11 (10)	18 (10.7)	
AKIN			
1	14 (12.7)	15 (8.9)	0.393
2	11 (10)	10 (5.9)	
3	79 (71.8)	135 (79.9)	

Data are presented as mean ± standard deviation or as number (%). P values are for Student's t-test or chi-square test.

BUN, blood urea nitrogen; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; NE, norepinephrine; RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease; ESKD, end-stage kidney disease; AKIN, Acute Kidney Injury Network.

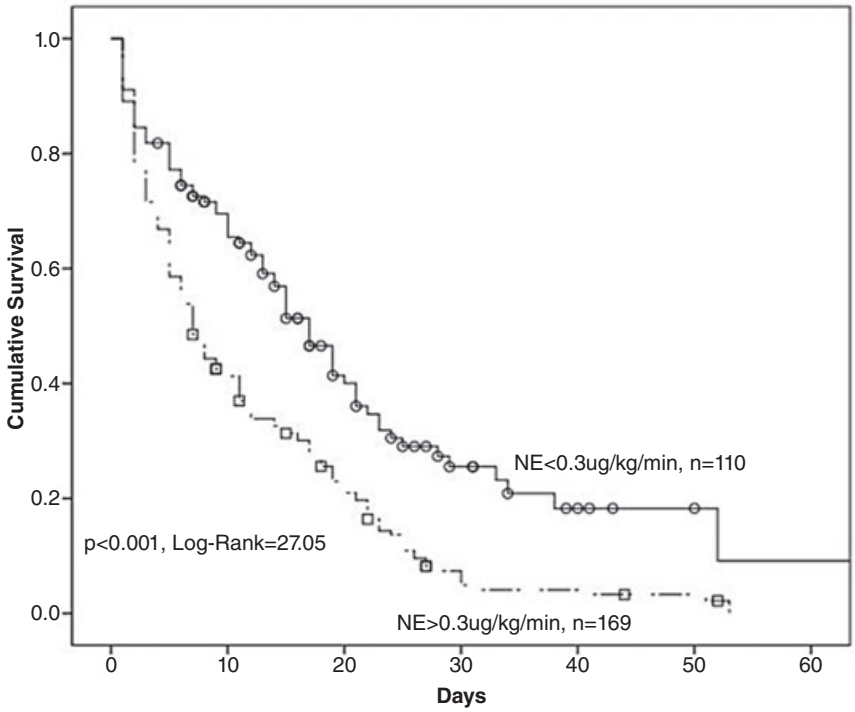


FIG. 3. Kaplan–Meier survival curve for patients with norepinephrine dose of ≥0.3 or <0.3 μg/kg/min.

TABLE 3. *Hazard ratio (HR) of possible prognostic factors in multivariate Cox proportional hazard regression*

	HR	95% CI		*P*
Norepinephrine (≥0.3 μg/kg/min)	1.771	1.247	2.516	0.001
APACHE II	1.035	1.012	1.058	0.003
Platelet (every 10^3/mL higher)	0.997	0.996	0.999	0.003
MAP (every 10 mm Hg increase)	0.992	0.975	1.009	0.346
Dopamine (≥20 μg/kg/min)	0.837	0.603	1.161	0.286
SOFA (every 1 point increase)	1.004	0.940	1.072	0.911
Septic shock	1.190	0.821	1.723	0.358
Mechanical ventilation	0.944	0.598	1.492	0.806
Urine output	1.000	0.999	1.000	0.494
RIFLE	1.868	0.438	7.972	0.399
AKIN	0.526	0.124	2.229	0.383

Norepinephrine, peak norepinephrine dose of ≥0.3 μg/kg/min; dopamine, peak dopamine dose ≥20 μg/kg/min. APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; NE, norepinephrine; RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease; AKIN, Acute Kidney Injury Network.

The high mortality rate (84.9%) in our study may be explained by the high percentage of AKIN classification 3 (76.7%) and RIFLE-F (62%). Because we reviewed all patients treated with CRRT in medical ICU, acute kidney injury patients with stable hemodynamic status treated by intermittent hemodialysis who have a better survival rate were not included in our cohort. A similar mortality rate (69 and 76%) of patients with RIFLE-F was also shown in previous studies (20,21). Because serum creatinine and urine output are the most important prognostic factors in patients with acute kidney injury (3,9,14,20–22), the high 60-day mortality rate (86%) in our study can be explained by the very low average urine output of 0.3 L/24 h and high serum creatinine (4.8 ± 4.1 mg/dL) in our patients. In the previous studies, the patients had an average urine output of 2 L/24 h and a serum creatinine of 1–2 mg/dL (20–22).

The effect for CRRT in improving survival in critically ill patients remains surrounded by conflicting results (7–9). One of the most advanced indications for CRRT is multiple organ dysfunction in septic patients. The removal of pro-inflammatory mediators permit a blockade of the systemic inflammation, a modulation of the altered immune response, and a restoration of the lost homeostasis (8). In our study, the septic patients had a 90% (108/120) mortality rate, significantly higher than the 77.4% (123/159) mortality rate of patients without sepsis ($P = 0.006$, chi-square test). Another concern regarding acute kidney injury studies is when a stable survival rate is reached. Longer follow-up results in a higher mortality rate and may not reflect the real mortality related to acute kidney injury. Shorter follow-up may not show the real outcomes either. An optimal follow-up period for 60 days for patients with acute kidney injury was suggested by Bell et al. (23). In our study, only six patients died after 60 days, and 97.5% (231/237) of patients died within 60 days.

CONCLUSION

Critically ill patients were treated with a high dose of NE before CRRT; nevertheless, the stage of acute kidney injury has a very high mortality rate. CRRT for acute kidney injury in our cohort may provide little help in the high-risk patients. More studies are needed to determine if CRRT before a very high dose of vasopressor treatment improves patients' outcome.

REFERENCES

1. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
2. Katsaragakis S, Kapralou A, Theodorou D, et al. Refractory septic shock: efficacy and safety of very high doses of norepinephrine. *Methods Find Exp Clin Pharmacol* 2006;28:307–13.
3. Sennoun N, Montemont C, Gibot S, Lacolley P, Levy B. Comparative effects of early versus delayed use of norepinephrine in resuscitated endotoxic shock. *Crit Care Med* 2007;35:1736–40.
4. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877–87.
5. Levy B, Dusang B, Annane D, Gibot S, Bollaert PE. Cardiovascular response to dopamine and early prediction of outcome in septic shock: a prospective multiple-center study. *Crit Care Med* 2005;33:2172–7.
6. Hernandez G, Bruhn A, Romero C, et al. Management of septic shock with a norepinephrine-based haemodynamic algorithm. *Resuscitation* 2005;66:63–9.
7. Bellomo R, Ronco C. Continuous haemofiltration in the intensive care unit. *Crit Care* 2000;4:339–45.
8. Ronco C, Bellomo R, Ricci Z. Continuous renal replacement therapy in critically ill patients. *Nephrol Dial Transplant* 2001;16(Suppl 5):67–72.

9. Cho KC, Himmelfarb J, Paganini E, et al. Survival by dialysis modality in critically ill patients with acute kidney injury. *J Am Soc Nephrol* 2006;17:3132–8.
10. Sieberth HG, Kierdorf HP. Is cytokine removal by continuous hemofiltration feasible? *Kidney Int Suppl* 1999;56:S79–83.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
12. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–10.
13. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8: R204–12.
14. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
15. American College of Chest Physicians/Society of Critical Care Medicine Consensus. Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864–74.
16. Tarantini G, Ramondo A, Isabella G, et al. Pressure response to vasopressors and mortality after direct angioplasty for cardiogenic shock. *Int J Cardiol* 2004;94:197–202.
17. Micek ST, Shah P, Hollands JM, Shah RA, Shannon WD, Kollef MH. Addition of vasopressin to norepinephrine as independent predictor of mortality in patients with refractory septic shock: an observational study. *Surg Infect (Larchmt)* 2007;8:189–200.
18. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28:2758–65.
19. Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med* 2006;32:1782–9.
20. Ricci Z, Ronco C, D'Amico G, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. *Nephrol Dial Transplant* 2006;21: 690–6.
21. Maccariello E, Soares M, Valente C, et al. RIFLE classification in patients with acute kidney injury in need of renal replacement therapy. *Intensive Care Med* 2007;33:597–605.
22. Lopes JA, Fernandes P, Jorge S, et al. Acute kidney injury in intensive care unit patients: a comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit Care* 2008;12:R110.
23. Bell M, Liljestam E, Granath F, Fryckstedt J, Ekbom A, Martling CR. Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. *Nephrol Dial Transplant* 2005;20:354–60.