Determinants of Outcome in Non-Septic Critically Ill Patients with Acute Kidney Injury on Continuous Venovenous Hemofiltration

Mark V. Koning a  Asselina A. Roest a  Marc G. Vervloet b  A.B. Johan Groeneveld a  Shaikh A. Nurmohamed b
Departments of a Intensive Care and b Nephrology, Free University Medical Center, Amsterdam, The Netherlands

Key Words
Acute kidney injury • Continuous venovenous hemofiltration • Mortality • Sepsis • Timing/dose of hemofiltration

Abstract
Background/Aims: In view of ongoing controversy, we wished to study whether patient characteristics and/or continuous venovenous hemofiltration (CVVH) characteristics contribute to the outcome of non-septic critically ill patients with acute kidney injury (AKI). Methods: We retrospectively studied 102 consecutive patients in the intensive care unit (ICU) with non-septic AKI needing CVVH. Patient and CVVH characteristics were evaluated. Primary outcome was mortality up to day 28 after CVVH initiation. Results: Forty-four patients (43%) died during the 28-day period after the start of CVVH. In univariate analyses, non-survivors had more often a cardiovascular reason for ICU admission, greater disease acuity/severity and organ failure, lower initial creatinine levels, less use of heparin and more use of bicarbonate-based substitution fluid. The latter two can be attributed to high lactate levels and bleeding tendency in non-survivors necessitating withholding lactate-buffered fluid and heparin, respectively, according to our clinical protocol. In multivariate analyses, mortality was predicted by disease severity, use of bicarbonate-based fluids and lack of heparin, while initial creatinine and CVVH dose did not contribute. Conclusion: The outcome of non-septic AKI in need of CVVH is more likely to be determined by underlying or concurrent, acute and severe disease rather than by CVVH characteristics, including timing and dose.
Introduction

Acute kidney injury (AKI) is common and associated with a high morbidity and mortality in the critically ill [1–4]. Renal replacement therapy is required in about 6% of patients and this is associated with a rise in mortality to about 60% [2, 4, 5]. Although improved therapy might help to decrease survival, the optimal timing, dose and type of renal replacement therapy, such as continuous venovenous hemofiltration (CVVH), the major treatment in Europe [5], remain to be determined. Although septic AKI may differ from non-septic AKI, and the former may benefit more from higher CVVH dose compared with the latter [4, 6–8], patients have often been lumped together in prospective randomized trials, and as a result, timing, dose and the schedule of renal replacement therapy remain largely inconsistent [6, 8–17]. In a retrospective analysis of both septic and non-septic patients, oligoanuria, acidosis and concomitant organ dysfunction at the time of initiation of renal replacement therapy were associated with high mortality [18]. Another observational retrospective study also did not reveal an effect of dose [19], whereas higher creatinine levels at the start of CVVH suggested that late rather than early treatment was of benefit [7], being in contrast to prospective and sometimes even randomized studies [13, 20–22]. However, treatment guided by urea levels did not improve outcome in another prospective randomized study [15]. The contradicting results may partly relate to differences in patient recruitment and modes of renal replacement therapy across studies. Alternatively, the contribution of CVVH characteristics to outcome may be smaller than that of patient characteristics, including type and severity of the underlying disease and co-morbidity, but these issues have hardly been addressed in large observational studies using different renal replacement therapy modes previously [5, 18, 19]. Our recent retrospective analysis restricted to sepsis-induced AKI requiring CVVH suggested however that the dose delivered, rather than timing, mode of administration, azotemic control and concomitant organ failure, is an independent predictor of outcome [23].

In the current retrospective study, we aimed to evaluate determinants of a favorable outcome in critically ill patients with AKI in need of CVVH. In an attempt to minimize differences attributable to patient selection, only non-septic AKI was studied. Our hypothesis was that outcome in non-septic AKI is determined by both patient and CVVH characteristics.

Patients and Methods

All patients treated with CVVH between November 17, 2004, and January 31, 2006, in the intensive care unit (ICU) of a university hospital were retrospectively studied. AKI was defined as a sudden creatinine and/or urea increase, loss of urine production or decreased renal clearance. Exclusion criteria were other indications for CVVH than AKI, such as a last known creatinine clearance (or estimated glomerular filtration rate using the abbreviated Modification of Diet in Renal Disease formula) <15 ml/min. Patients were excluded from the study if criteria of sepsis occurred within a 48-hour window after the start of CVVH. Sepsis was considered present if patients had clinical evidence of infection and at least two or more of the following conditions; temperature <36.0 or >38.0°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or mechanical ventilation, and/or white blood cells <4.0 or >12.0 × 10^9/l [24].

Therapeutic Protocol

Decisions regarding the time of initiation of CVVH were based on the opinion of the treating physicians and consulting nephrologists. The decision to start CVVH was based on the following parameters: diuresis, plasma urea and creatinine, plasma potassium and bi-
carbonate, and the occurrence of fluid overload. Other decisions included the use of anticoagulation, substitution fluid (lactate, bicarbonate or citrate buffer; table 1), post- or predilution, ultrafiltration and blood flow rates. To prevent frequent clotting of catheters or filters, patients were treated per protocol by heparin in order to reach an activated partial thromboplastin time of 55–65 s. Patients with increased risk of bleeding complications (defined as a platelet count < 40 × 10⁹/l, an activated partial thromboplastin time > 60 s, a prothrombin time test (INR) > 2.0, a recent major bleeding or significant active bleeding were not administered heparin. These patients were treated with anticoagulant-free CVVH (bicarbonate or lactate buffered) until the availability of citrate-based substitution fluid in May 2005, which then became the first choice of treatment in case of a high bleeding risk. Furthermore, the choice of the substitution fluid, lactate or bicarbonate, was based on the occurrence of lactic acidosis. Patients are routinely treated with CVVH with lactate-buffered substitution fluid. In case of severe lactic acidosis (serum lactate > 5 mmol/l), CVVH is performed with bicarbonate-buffered hemofiltration. The clinician almost always chooses predilution because of the possible positive effect on filter lifetime. CVVH is performed using a hemofiltration machine (Diapact; Braun, Melsungen, Germany). Vascular access is secured by inserting an 11-french double-lumen catheter (GamCath; Gambro, Hechingen, Germany) into one of the three large veins (jugular, femoral or subclavian). In all patients, a 1.9-m² highly permeable cellulose triacetate hemofilter is used (Nipro UF205; Nissho, Osaka, Japan). After 72 h, the filters are considered ineffective and are changed on a routine basis. In case of blood clots in the filter, an increased filter membrane pressure, or therapeutic or diagnostic interventions, filters are changed earlier. Blood flow and flow of lactate- or bicarbonate-based substitution fluid were historically routinely set at 180 ml/min and 2 l/h, respectively, with the ultrafiltrate flow set by the treating physicians. When using citrate-buffered substitution solution, the blood and substitution fluid flow is set per protocol at 180 ml/min and 2.4 l/h, respectively. CVVH was predicted to be not needed when diuresis and sufficient creatinine clearance had resumed, on clinical grounds and based on laboratory measurements, which is a commonly applied policy. If patients were indeed not in need of CVVH for > 48 h, AKI was considered to have recovered. If CVVH had to be resumed within 48 h after discontinuation, a second episode of CVVH (after the initial episode) was defined.

**Data Collection**

Patient characteristics, including age, gender, weight, height (for body mass index, BMI), co-morbidities and cause of AKI, were recorded. Data regarding Acute Physiology and Chronic Health Evaluation (APACHE II) and the Sequential Organ Failure Assessment (SOFA) score [1] were collected. The latter score was obtained on admission and day

|     | BH 504® | HF 32 Bl® | HF CitPre® |
|-----|---------|-----------|------------|
| Sodium     | 140     | 140       | 139.9      |
| Potassium  | 1.5     | 2.0       | 3.0        |
| Magnesium  | 0.5     | 0.5       | 0.5        |
| Calcium    | 1.5     | 1.75      | –          |
| Chloride   | 103     | 111.5     | 104.0      |
| Glucose    | 11.0    | 1.0       | 5.0        |
| Citrate    | –       | –         | 39.9       |
| Bicarbonate| –       | 32.0      | –          |
| Lactate    | 42.0    | 3.0       | –          |

Table 1. Composition of the substitution fluids (in mmol/l)
0 (day of CVVH initiation). Co-morbid conditions are defined as follows: hypertension – a diagnosis of hypertension mentioned in the medical record or the use of blood pressure-lowering agents; diabetes mellitus – a diagnosis of diabetes mellitus mentioned in the medical record or the use of insulin or oral glucose-lowering agents; chronic renal failure – a diagnosis of chronic renal failure mentioned in the medical record, without the need of renal replacement therapy (stages 1–4 chronic kidney disease), or chronic obstructive pulmonary disease – a diagnosis of chronic obstructive pulmonary disease mentioned in the medical record or the use of medication for this indication. The reasons for ICU admission were grouped as follows: cardiovascular disease, respiratory insufficiency, metabolic derangement, neurological disorders, hematological disorders, liver failure and gastrointestinal surgery. The reasons of AKI were categorized into four groups: prerenal/ischemic, contrast, rhabdomyolysis and miscellaneous reasons. Data concerning timing of CVVH initiation were retrieved; these include serum creatinine, urea, pH and bicarbonate, potassium and diuresis before CVVH initiation. The following CVVH characteristics were also recorded: the mode of CVVH (pre- or postdilution), blood flow, substitution flow, ultrafiltration flow, type of substitution fluid and of anticoagulation, filter life of all filters used, the hours CVVH actually performed, downtime, and prescribed and delivered doses. Downtime was defined as the interval that CVVH was prescribed but not applied due to circuit clotting or transport to the radiology or operating room. The prescribed and delivered doses were calculated. The former was defined as the ultrafiltration volume delivered per kilogram body weight before admission per hour; it was averaged per day and thus included downtime. The delivered dose was calculated by adjusting the prescribed dose for downtime.

To compensate the effluent dose based on losses due to predilution, the ultrafiltration flow per hour ($Q_{uf}$) was adjusted according to the following formula:

$$
\frac{Q_b \times 60 \times (1 - Hct)}{(Q_b \times 60 \times (1 - Hct) + Q_s)} \times Q_{uf}
$$

where $Q_b = \text{blood flow (ml/min)}$; $Q_s = \text{substitution flow (ml/h)}$ and Hct = hematocrit.

The means for filter life, downtime, flow rate and dose were calculated for each patient per CVVH episode and for all episodes together, as well as the percent use of predilution CVVH, heparin and the different substitution fluids. A group median percentage of 0 thus implies that in most patients the respective mode was not used in all filters per patient.

**Statistical Analysis**

Patients were grouped according to survival on day 28 after CVVH initiation. A power analysis was not performed for this retrospective analysis, but we estimated a mortality rate of 50% for the population in the study interval. The data were often non-normally distributed (Kolmogorov-Smirnov test: $p > 0.05$) and values are therefore summarized as medians and interquartile ranges (e.g. for the percentage of filters on certain modes per patient). The Mann-Whitney U test was used for continuous variables. For categorical data, Fisher’s exact test was used. We performed multiple logistic regression using backward elimination to assess the independent value of initial creatinine and delivered dose to predict 28-day mortality, including variables reaching statistical significance in univariate analyses ($p < 0.05$). The odds ratio and its 95% confidence interval (CI) were calculated. Similarly, we performed multiple proportional hazards (Cox) regression analysis for survival time and calculated hazard ratios (95% CI). We did not include filter time, a major determinant of the dose delivered, but forced initial creatinine and CVVH dose into the models. Exact $p$ values are given if $p > 0.005$, and considered statistically significant if $p < 0.05$. 
### Table 2. Patient characteristics

|                      | Survivors (n = 58) | Non-survivors (n = 44) | p value |
|----------------------|--------------------|------------------------|---------|
| Age, years           | 70.5 (18.0)        | 69.5 (19.0)            | 0.71    |
| Females/males        | 26 (45)/32 (55)    | 16 (30)/28 (70)        | 0.15    |
| Body weight, kg      | 78.5 (18.7)        | 80.0 (18.7)            | 0.78    |
| Body mass index      | 25.4 (4.1)         | 24.7 (4.7)             | 0.20    |
| Co-morbidity         |                    |                        |         |
| Hypertension         | 31 (53)            | 12 (27)                | 0.01    |
| Diabetes mellitus    | 12 (21)            | 7 (16)                 | 0.61    |
| COPD                 | 9 (15)             | 3 (7)                  | 0.22    |
| CRF                  | 8 (14)             | 5 (11)                 | 0.46    |
| APACHE II            | 24.5 (7.2)         | 32.5 (10.7)            | <0.005  |
| SOFA within 24 h     | 9.0 (3.0)          | 10.0 (3.0)             | 0.01    |
| Elective ICU admission | 35 (60)         | 17 (39)                | 0.04    |
| Admission after surgery | 41 (71)       | 21 (48)                | 0.02    |
| Reason for ICU admission |                |                        |         |
| Cardiovascular disease | 24 (41)         | 24 (55)                | 0.01    |
| Respiratory insufficiency | 12 (21)         | 16 (36)                | 0.11    |
| Metabolic derangement | 6 (10)          | 12 (27)                | 0.03    |
| Neurological disorders | 1 (2)           | 8 (18)                 | 0.01    |
| Hematological disorders | 2 (3)           | 8 (14)                 | 0.03    |
| Liver failure        | 3 (5)              | 4 (9)                  | 0.40    |
| Gastrointestinal surgery | 2 (3)           | 2 (4)                  | 0.49    |
| Type of AKI          |                    |                        |         |
| Prerenal/ischemic    | 46 (79)            | 35 (80)                | 0.81    |
| Contrast             | 3 (5)              | 1 (2)                  | 0.46    |
| Rhabdomyolysis       | 4 (7)              | 3 (7)                  | 0.99    |
| Miscellaneous        | 5 (9)              | 5 (11)                 | 0.65    |
| Mechanical ventilation within 24 h | 51 (88) | 43 (98)                | 0.13    |
| Vasoactive drugs within 24 h | 45 (78) | 37 (84)                | 0.46    |
| Lactate within 24 h, mmol/l | 2.7 (2.9) | 6.4 (7.9)              | <0.005  |
| Hospitalization, days | 14.0 (21.0)     | 5.0 (9.0)              | <0.005  |

Median (SD) or number (%) of patients, where appropriate. COPD = Chronic obstructive pulmonary disease; CRF = chronic renal failure.

### Results

#### Patient Characteristics

A hundred and two consecutive patients were included. On day 28, 44 patients (43%) had died. Two patients died after ICU discharge within 28 days after the start of CVVH. Six patients had a second and 1 patient a third episode of CVVH. Fourteen patients received intermittent hemodialysis on the ward after ICU discharge. Outcome groups were comparable except for reasons of admission, their disease acuity and severity, and organ failure (table 2). Lactate levels were higher, and duration of CVVH and hospitalization shorter in non-survivors.

#### CVVH Characteristics

Table 3 shows that in non-survivors, less heparin and lactate-buffered fluids and more bicarbonate-buffered fluids were used. Filter life and the number of filters used were decreased in non-survivors. Ultrafiltrate was somewhat greater in survivors at similar substitution fluid flows, suggesting greater fluid withdrawal. However, neither the prescribed nor
the delivered CVVH dose, ranging between 12 and 46 ml/kg/h, differed among outcome groups. Table 4 shows that non-survivors had more severe metabolic acidosis, with similar oligoanuria, and initial creatinine and urea levels were lower and decreases occurred less often during (less prolonged) CVVH.

### Table 3. Characteristics of CVVH during the ICU stay [median values (SD)]

|                        | Survivors (n = 58) | Non-survivors (n = 44) | p value |
|------------------------|--------------------|------------------------|---------|
| Time from ICU admission to CVVH start, days | 2.0 (1.2) | 1.0 (1.0) | 0.76 |
| SOFA at CVVH initiation | 11.0 (3.0) | 14.0 (4.0) | <0.005 |
| First CVVH episode: duration, h | 81.0 (90.5) | 44.5 (109.5) | <0.005 |
| Filters, n | 3.0 (3.2) | 1.0 (4.7) | 0.01 |
| Mean filter life, h | 34.3 (27.7) | 20.1 (25.2) | 0.01 |
| Mean downtime, h | 1.5 (1.8) | 0 (2.3) | 0.01 |
| Mean blood flow, ml/h | 180 (0) | 180 (0) | 0.42 |
| Mean substitution flow, ml/h | 2,020 (332) | 2,000 (400) | 0.78 |
| Mean ultrafiltration flow, ml/h | 2,099 (350) | 2,040 (400) | 0.04 |
| Percentage on: | | | |
| Predilution | 100 (43) | 100 (30) | 0.95 |
| Heparin | 74 (100) | 0 (83) | <0.005 |
| Citrate | 0 (59) | 0 (11) | 0.24 |
| Bicarbonate | 0 (27) | 55 (100) | <0.005 |
| Lactate | 50 (100) | 0 (69) | 0.01 |
| Mean prescribed dose, ml/kg/h | 23.6 (6.8) | 23.4 (6.0) | 0.99 |
| Mean delivered dose, ml/kg/h | 21.8 (6.7) | 22.2 (6.2) | 0.36 |
| Total CVVH: duration, h | 84 (93) | 45 (110) | <0.005 |
| Filters, n | 3.0 (4.2) | 1.0 (4.7) | 0.01 |
| Mean filter life, h | 33.9 (28.4) | 20.1 (25.2) | 0.01 |
| Mean downtime, h | 1.5 (1.8) | 0 (2.3) | 0.01 |
| Mean blood flow, ml/h | 180 (0) | 180 (0) | 0.54 |
| Mean substitution flow, ml/h | 2,075 (332) | 2,000 (400) | 0.59 |
| Mean ultrafiltration flow, ml/h | 2,108 (347) | 2,040 (400) | 0.03 |
| Percentage on: | | | |
| Predilution | 100 (40) | 100 (30) | 0.88 |
| Heparin | 74 (100) | 0 (83) | <0.005 |
| Citrate | 0 (59) | 0 (11) | 0.24 |
| Bicarbonate | 0 (23) | 55 (100) | <0.005 |
| Lactate | 59 (100) | 0 (84) | 0.01 |
| Mean prescribed dose, ml/kg/h | 23.5 (6.8) | 23.4 (6.0) | 0.99 |
| Mean delivered dose, ml/kg/h | 21.4 (6.7) | 22.2 (6.2) | 0.32 |

Multivariable Analyses

Results of logistic and Cox regression analyses are depicted in table 5. In both models, initial lactate, changes in creatinine/urea or CVVH dose did not contribute to mortality prediction. In any case, both models suggest that mortality is determined by the underlying disease determining the mode of CVVH and anticoagulation rather than by timing, as judged from initial creatinine values, and dose. As data from patients with a poor prognosis can skew the results, we also analyzed the data after excluding patients who deceased within 48 h (n = 13). The results, however, p ≤ 0.05 were similar regarding predicting contributions (p = 0.05 or less) by APACHE II score, and percentage on heparin and bicarbonate, but not regarding initial creatinine or CVVH dose.
Discussion

This single-center retrospective study suggests that patient rather than CVVH characteristics contribute to the outcome of non-septic, critically ill patients with AKI on CVVH. This contrasts with the beneficial effects of a higher CVVH dose in the septic patients studied by us recently in the same time frame and with similar methodology [23].

At the start of CVVH, creatinine and urea levels were higher in survivors than in non-survivors. Although this suggests that CVVH start was postponed in survivors compared to non-survivors, as observed before [7], the difference disappeared in multivariable analyses, suggesting that timing was not a determinant of outcome in our patients [cf. 9, 21], in contrast to suggestions that early institution may improve outcome [14, 20, 22]. The lower blood pH in non-survivors than in survivors can be attributed to higher lactate levels rather than more progressive renal failure. Since, per protocol, bicarbonate-buffered fluid is preferred to lactate-buffered fluid in case of lactic acidosis, the use of bicarbonate-buffered fluid predicted mortality in our models, and this is unlikely caused by a detrimental effect of the solution

Table 4. Renal metabolism prior to and during CVVH [median values (SD)]

|                          | Survivors (n = 58) | Non-survivors (n = 44) | p value |
|--------------------------|-------------------|------------------------|---------|
| Within 24 h prior to CVVH initiation |                    |                        |         |
| Diuresis, ml/h           | 13.7 (16.5)       | 12.0 (19.7)            | 0.89    |
| pH                       | 7.26 (0.14)       | 7.19 (0.15)            | <0.005  |
| Bicarbonate, mmol/l      | 17.5 (5.0)        | 14.0 (4.4)             | <0.005  |
| Potassium, mmol/l        | 5.1 (1.1)         | 5.1 (1.1)              | 0.94    |
| Creatinine, μmol/l       | 285 (129)         | 236 (120)              | 0.01    |
| Urea, mmol/l             | 17.8 (11.4)       | 14.2 (13.4)            | 0.16    |
| During CVVH              |                    |                        |         |
| Highest creatinine, μmol/l | 285 (99)         | 177 (135)              | 0.01    |
| Lowest creatinine, μmol/l | 140 (80)         | 110 (84)               | 0.20    |
| Change in creatinine, μmol/l | 130 (117)       | 32 (123)               | <0.005  |
| Highest urea, mmol/l     | 18.5 (10.9)       | 10.3 (12.5)            | 0.04    |
| Lowest urea, mmol/l      | 9.9 (5.6)         | 10.3 (10.9)            | 0.82    |
| Change in urea, mmol/l   | 5.7 (12.1)        | 1.0 (2.7)              | 0.04    |

Table 5. Multivariable (logistic and Cox regression) analyses of determinants of mortality in non-septic AKI patients needing CVVH

|                          | Odds ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
|--------------------------|---------------------|---------|-----------------------|---------|
| APACHE II                | 1.16 (1.06–1.27)    | 0.001   | 1.09 (1.04–1.14)      | 0.001   |
| Initial creatinine, μmol/l | 0.99 (0.99–1.00)  | 0.18    | 0.99 (0.99–1.11)      | 0.14    |
| On heparin               | 0.98 (0.96–0.99)    | 0.007   | 0.99 (0.99–1.00)      | 0.04    |
| Substitution fluid       |                     |         |                       |         |
| Lactate buffered         | 1.02 (1.00–1.04)    | 0.04    | not calculated        | 0.25    |
| Bicarbonate buffered     | 1.03 (1.01–1.05)    | 0.003   | 1.01 (0.99–1.01)      | 0.03    |
| Delivered dose of CVVH, ml/kg/h | 1.10 (0.99–1.21) | 0.07    | not calculated        | 0.25    |

For logistic regression: Hosmer-Lemeshow test $\chi^2$ 7.4, d.f. 8, p = 0.50, indicating good calibration.
itself [25]. The absence of anticoagulation with heparin also predicted mortality, which is withheld in case of a bleeding tendency, which may be more severe in non-survivors. We cannot exclude that this contributed to the lower survival times of filters in non-survivors or that heparin has even exerted beneficial effects in our non-septic patients. The greater fall in creatinine and urea levels in survivors can be explained by the longer duration of CVVH. Downtime was decreased in non-survivors, which may be explained by the fact that in many patients in this group only one filter was used, which results in zero downtime.

Taken together, our results suggest that CVVH characteristics such as timing, dose and azotemic control did not determine outcome, while crude outcome and its patient-specific determinants of our study cohort roughly agree with other studies [1–5, 18, 19, 22]. While large prospective studies either suggest or deny a benefit of higher- compared to standard-dose CVVH, many studies suggest that high-dose CVVH more likely benefits septic than non-septic patients, as judged from post hoc analyses, in the absence of prior stratified randomization [6, 8]. Hence, a higher dose may, in line with observational studies [26] and our own results [23], potentially be of benefit in septic patients with AKI only. Although underdosing (<20 ml/kg/h) is a potential threat [16, 23], this may, apparently, not have substantially affected outcome in our non-septic patients.

Obviously, the limitations of our study include its retrospective nature and the relatively small number of patients, so that conclusions should be drawn cautiously and a small effect of CVVH characteristics on outcome cannot completely be excluded. They nevertheless represent a ‘real-life’ situation in a patient cohort treated with a single renal replacement therapy mode, and the observations may help to design and power future studies investigating timing and dose of CVVH in the critically ill. The results did not prompt us to change current CVVH practice for non-septic patients.

In conclusion, our retrospective data suggest that patient characteristics rather than the timing, dose and mode of CVVH and azotemic control are predominant determinants of outcome in critically ill non-septic patients with AKI.

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Disclosure Statement

The authors declare that they have no competing interests.

References

1 De Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli A, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26: 915–921.

2 Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813–818.
3 Bagshaw SM, George C, Bellomo R, ANZICS Database Management Committee: Changes in incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 2007;11:R68.

4 Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML: Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med 2009;37:2552–2558.

5 Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA: Continuous renal replacement therapy: a worldwide practice survey. The Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Intensive Care Med 2007;33:1563–1570.

6 Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different dosages in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. Lancet 2000;355:26–30.

7 Cerdá J, Cerdá M, Kilcullen P, Prendergast J: In severe acute kidney injury, a higher serum creatinine is paradoxically associated with better patient survival. Nephrol Dial Transplant 2007;22:2781–2784.

8 Renal Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal replacement therapy in critically ill patients. N Engl J Med 2009;361:1627–1638.

9 Bauer M, Marzi I, Ziegenfuss T, Riegel W: Prophylactic hemofiltration in severely traumatized patients: effects on post-traumatic organ dysfunction syndrome. Intensive Care Med 2001;27:376–383.

10 Saudan P, Niederberger M, De Siegneux S, Romand J, Perneger T, Martin PY: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312–1317.

11 Tolwani AJ, Campbell RC, Stefan BS, Lai KR, Oster RA, Wille KM: Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 2008;19:1233–1238.

12 VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O’Connor TZ, Chertow GM, Crowley ST, Choudhury DJ, Fink K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S,Star RA, Peduzzi P: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2009;359:7–20.

13 Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network: Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA 2008;299:793–805.

14 Gibney RTN, Bagshaw SM, Kutsogiannis DJ, Johnston C: When should renal replacement therapy for acute kidney injury be initiated and discontinued? Blood Purif 2008;26:473–484.

15 Faulhaber-Walter R, Hafer C, Jahr N, Vahlbruch J, Hoy L, Haller H, Fliser D, Kielstein JT: The Hanover Dialysis Outcome Study: Comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. Nephrol Dial Transplant 2009;24:2179–2186.

16 Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NKJ, University of Toronto Acute Kidney Injury Research Group: High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. Crit Care Med 2010;38:1360–1369.

17 Jun M, Heerspink HJ, Ninomiya T, Gallagher M, Bellomo R, Myburgh J, Finfer S, Palevsky PM, Kellum JA, Perkovic V, Cass A: Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2010;5:956–963.

18 Ostermann M, Chang RWS: Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Crit Care 2009;13:R175.

19 Vesconci S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monit G, Marinho A, Mariano F, Formica M, Marchesi M, Robert R, Livigni S, Ronco C, DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI Study Group): Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care 2009;13:R57.

20 Liu KD, Himmelfarb J, Paganini E, Ikizler TA, Soroko SH, Mehta RL, Chertow GM: Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 2006;1:915–919.

21 Bouman CSC, Oudemans-van Straaten HM, Schultz MJ, Vroom MB: Hemofiltration in sepsis and systemic inflammatory response syndrome: the role of dosing and timing. J Crit Care 2007;22:1–12.
22 Bagshaw SM, Uchinno S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 2009; 24:129–140.

23 Nurmohamed SA, Koning MV, Vervloet MG, Groeneveld ABJ: Delivered dose of continuous venovenous hemofiltration predicts outcome in septic patients with acute injury: a retrospective study. J Crit Care 2011;26:213–220.

24 Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, International Sepsis Definitions Conference: 2001 SCCM/ESICM/ACC/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29:530–538.

25 Barenbrock M, Hausberg M, Matzkies F, De la Motte S, Schaefer RM: Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. Kidney Int 2000;58:1751–1757.

26 Honoré PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, Hanique G, Matson JR: Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 2000;28:3581–3587.