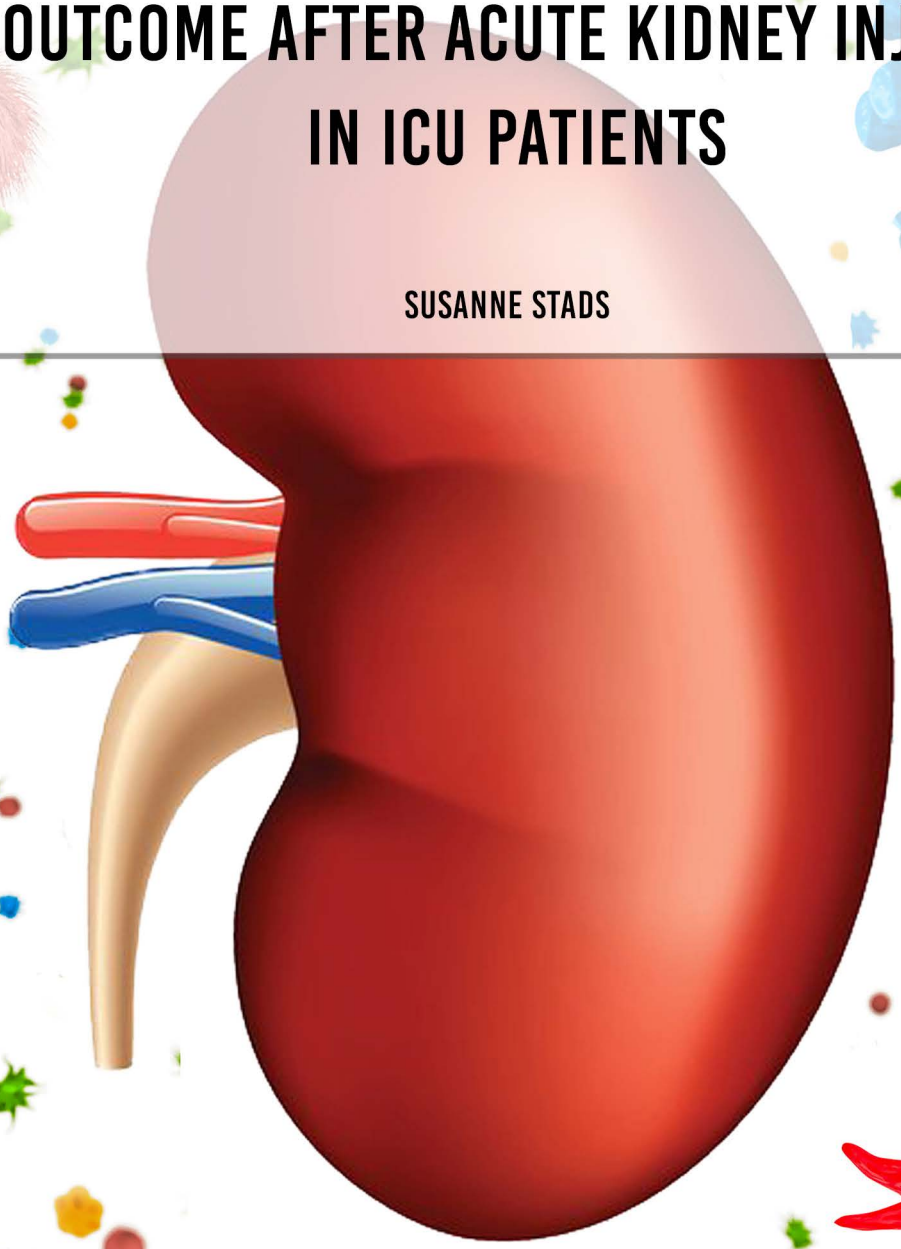
OUTCOME AFTER ACUTE KIDNEY INJURY IN ICU PATIENTS

SUSANNE STADS



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CHAPTER 1

General introduction and outline of the thesis

Susanne Stads

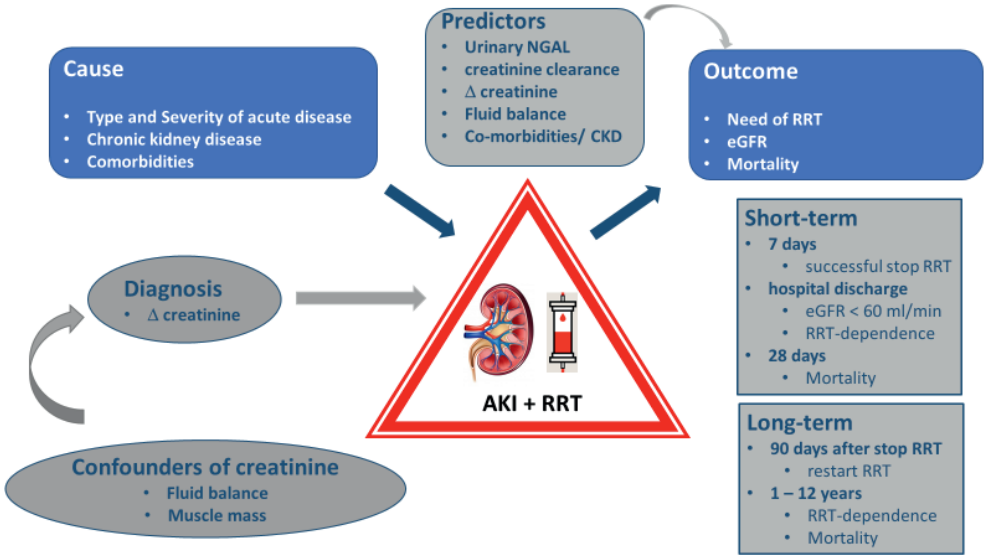
General introduction

Acute kidney injury and renal replacement therapy – background

Acute kidney injury (AKI) is a common complication of critical illness. The incidence of AKI varies widely depending on the definition, but up to 60% of the intensive care unit (ICU) patients develop AKI [1, 2]. AKI is associated with high morbidity and mortality [1-4]. Around two thirds of the AKI patients need renal replacement therapy (RRT) during their ICU stay [1]. Nowadays, RRT is performed as continuous renal replacement therapy (CRRT) in the majority of critically ill patients in the Netherlands. Despite improved recognition and treatment, mortality rates remain between 27% and 60%, depending on the definition, cause, reason of ICU admission and whether RRT is required [1-3, 5, 6].

After an episode of AKI, renal function might recover but this is not always the case. In some patients renal function does not recover or recovers only partially, and these patients have an increased risk for progression to chronic kidney disease (CKD) and subsequently end-stage-renal-disease (ESRD) [7]. Importantly, chronic kidney disease itself is a risk factor for AKI as well. Patients with acute on chronic kidney disease have a higher risk of developing end-stage-renal-disease than those with AKI without prior CKD. Independent of AKI, chronic kidney disease in itself often progresses to ESRD [8]. In this thesis we studied several aspects determining short-term and long-term outcome after AKI. (Fig. 1)

Figure 1 schematic presentation of diagnosis, causes and predictors of short-term and long-term outcome after RRT-requiring AKI



NGAL, Neutrophil gelatinase-associated lipocalin; CKD, chronic kidney disease; AKI, acute kidney injury; RRT, renal replacement therapy; eGFR estimated glomerular filtration rate

AKI – definition and pitfalls

In 2005 uniform standards for definition and classification of AKI were developed by key-members of societies in critical care and nephrology together with additional experts (Acute Kidney Injury Network, AKIN). A staging system for AKI was developed including quantitative changes in serum creatinine and urine output [9]. This staging system expands upon the previously developed Risk, Injury, Failure, Loss, End stage kidney disease (RIFLE) classification [10] and uses the ratio of actual serum creatinine to pre-admission serum creatinine (Δ creatinine) and/or urine output, thereby defining three stages of AKI severity [9] Table 1.

Table 1 AKI stage defined by AKIN criteria

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 26.4 µmol/L (or 0.3 mg/dl) or increase to more than or equal to 150% – 200% from baseline	Less than 0.5 ml/kg/hr for more than 6 hours
2	Increase in serum creatinine of more than 200% - 300% from baseline	Less than 0.5 ml/kg/hr for more than 12 hours
3	Increase in serum creatinine of more than 300% from baseline or serum creatinine of more than or equal to 354 µmol/L (4.0 mg/dl) with an acute increase of at least 44 µmol/L (0.5 mg/dl)	Less than 0.3 ml/kg/hr for 24 hours or anuria for 12 hours

Only one criterium (serum creatinine or urine output) has to be fulfilled for a stage

These AKIN criteria are used to design and compare studies on AKI in the ICU and to evaluate potential prevention and treatment strategies. However, the use of this AKI classification has some limitations. Plasma creatinine concentration, the cornerstone of AKI staging, is not only determined by renal excretion, but also by haemodilution (caused by fluid accumulation) and by creatinine generation, e.g. by muscle mass. Lower creatinine levels due to fluid overload or low creatinine generation may therefore underestimate true renal function impairment in critically ill patients. The dilution of serum creatinine by fluid accumulation leads to underestimation of severity of AKI and delays the identification of a 50% increase in serum creatinine in critically ill patients [11]. It has therefore been suggested to correct creatinine for AKI-staging for fluid-balance [11-13].

Short-term outcome after AKI

Patients surviving an episode of AKI often have incomplete recovery of renal function and sometimes require restart of RRT after initial discontinuation of CRRT. Only a few studies evaluated predictors for successful discontinuation of CRRT, but up to now no uniform criteria for discontinuation of CRRT are defined [1, 14]. In daily practice, CRRT is discontinued on an individual basis: when urinary output increases or when the CRRT session ends and the attending physician presumes that renal function will recover because other organ functions improve. Predicting short-term successful discontinuation

in patients in whom CRRT has been stopped may support decision-making and prevent potentially harmful complications of over- and undertreatment.
Currently, it is not sure which clinical characteristics or biomarkers are associated with renal dysfunction at hospital discharge or restart of RRT after AKI. Such predictors could be important to indicate which patients should be monitored more closely for prevention and treatment of complications of renal dysfunction and restart of RRT.

Long-term outcome after AKI

After an episode of AKI, patients are at risk for further renal function deterioration in the long-term and can develop chronic kidney disease and ESRD, requiring chronic RRT [7, 8, 15, 16]. Even patients who seem to have complete recovery of renal function after AKI, have a two-fold increased risk for "de novo" CKD [7]. And progressive CKD without AKI is associated with increased mortality as well [8, 17]. Thus, acute kidney injury and chronic kidney disease seem to be an integrated syndrome. Patients with a history of CKD are at risk for development of AKI and severe AKI is associated with CKD, ESRD and mortality.
In contrast to patients with known CKD, only a small proportion of patients experiencing an episode of AKI receive nephrological follow-up, despite the high mortality and incidence of ESRD in this population [18]. Therefore it may be beneficial to identify patients at risk for further renal function deterioration after AKI to take preventive measures and to restart RRT timely [19].

Biomarkers for AKI and renal recovery

Nowadays interest for biomarkers rises. Neutrophil gelatinase-associated lipocalin (NGAL) measured at ICU admission has high potential for the prediction of AKI and need of CRRT [20-27]. After renal injury, NGAL is secreted into blood and urine as early as 2 hours [28], whereas the rise in creatinine takes days. While serum creatinine is a marker of renal function, NGAL reflects renal injury. Up to now no studies tested NGAL after discontinuation of CRRT for the prediction of need of early or late restart of RRT.

Aim and outline of the thesis

The aim of this thesis was to evaluate predictors for short-term and long-term outcome after AKI. In **chapter two** of this thesis we analysed risk factors for mortality after CRRT and questioned whether fluid balance-adjusted initiation creatinine was a better predictor of mortality than uncorrected creatinine. We therefore performed a post-hoc analysis on data of the multicentre CASH-trial, comparing citrate to heparin anticoagulation during continuous venovenous hemofiltration (CVVH) [29].
In previous studies, renal recovery was associated with lower age, less severe organ failure, shorter duration of CRRT, higher creatinine clearance or urine output during CRRT and decreasing plasma NGAL on the first day of RIFLE-F [1, 6, 14, 30-36]. However, none of these studies evaluated clinical risk factors or biomarkers *after* discontinuation

of CRRT. To evaluate short-term (7-day) and long-term (90-day) predictors of successful discontinuation or restart of RRT *after* initial discontinuation, we performed a prospective multicentre observational study in 4 intensive care units in the Netherlands (Erasmus Medical Centre, Ikazia Hospital, Amphia Hospital and Noordwest Ziekenhuisgroep). In **chapter three** we focussed on the prediction of short-term successful discontinuation of CRRT and evaluated renal and non-renal predictors after discontinuation of CRRT. And in **chapter five** we aimed to determine whether renal markers independently predicted restart of RRT within 90 days after initial discontinuation of CRRT.

Identification of determinants related to the degree of renal dysfunction at hospital discharge may be useful to prevent further renal damage and treat complications of chronic kidney disease. In **chapter four** we performed a single centre retrospective cohort study including adult patients with "RRT-requiring AKI" admitted to the ICU from 1994 until 2010 to evaluate predictors of renal function at hospital discharge.

In community-based populations, a decreased estimated glomerular filtration rate (eGFR) seems associated with an increased risk of progressive deterioration of renal function, death, cardiovascular events and hospitalization [17, 37]. Patients who experienced an episode of RRT-requiring AKI are at high risk for progression to chronic kidney disease [38]. In **chapter six** we evaluated whether the degree of renal dysfunction at hospital discharge after an episode of "RRT-requiring AKI" in the ICU was a risk factor for long-term renal and overall survival in our population as well. We therefore performed a single centre retrospective cohort study evaluating adult patients who received CRRT for AKI in the ICU between 1994 and 2010.

The majority of ICU patients developing AKI have co-morbidities, such as diabetes, heart failure and a history of CKD that may substantially influence both mortality and renal function deterioration [39-42]. However to what extent the risk for ESRD and mortality is associated with co-morbidities or with the renal insult itself is unknown. In **chapter seven** we compared the association between "RRT-requiring AKI" and mortality and renal survival in critically ill patients with and without co-morbidities in the retrospective cohort of RRT-requiring AKI patients between 1994 and 2010.

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PART A

Short-term outcome

CHAPTER 2

2

Fluid balance-adjusted creatinine at initiation of continuous venovenous hemofiltration and mortality. A post-hoc analysis of a multicenter randomized controlled trial

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Abstract

Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high mortality. The creatinine-based stage of AKI is considered when deciding to start or delay RRT. However, creatinine is not only determined by renal function (excretion), but also by dilution (fluid balance) and creatinine generation (muscle mass). The aim of this study was to explore whether fluid balance-adjusted creatinine at initiation of RRT is related to 28-day mortality independent of other markers of AKI, surrogates of muscle mass and severity of disease.

We performed a post-hoc analysis on data from the multicentre CASH trial comparing citrate to heparin anticoagulation during continuous venovenous hemofiltration (CVVH). To determine whether fluid balance-adjusted creatinine was associated with 28-day mortality, we performed a logistic regression analysis adjusting for confounders of creatinine generation (age, gender, body weight), other markers of AKI (creatinine, urine output) and severity of disease.

Of the 139 patients, 32 patients were excluded. Of the 107 included patients, 36 died at 28 days (34%). Non-survivors were older, had higher APACHE II and inclusion SOFA scores, lower pH and bicarbonate, lower creatinine and fluid balance-adjusted creatinine at CVVH initiation. In multivariate analysis lower fluid balance-adjusted creatinine (OR 0.996, 95% CI 0.993-0.999, p = 0.019), but not unadjusted creatinine, remained associated with 28-day mortality together with bicarbonate (OR 0.869, 95% CI 0.769-0.982, P = 0.024), while the APACHE II score non-significantly contributed to the model.

In this post-hoc analysis of a multicentre trial, low fluid balance-adjusted creatinine at CVVH initiation was associated with 28-day mortality, independent of other markers of AKI, organ failure, and surrogates of muscle mass, while unadjusted creatinine was not. More tools are needed for better understanding of the complex determinants of "AKI classification", "CVVH initiation" and their relation with mortality, fluid balance is only one.

Introduction

Acute kidney injury (AKI) in critically ill patients is an independent risk factor for increased morbidity and mortality. Despite improved recognition and treatment, mortality rates remain between 40 and 60% [1]. Nowadays, AKI is staged by the ratio of actual serum creatinine to pre-admission serum creatinine (Risk, Injury, Failure, Loss, End stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN), Kidney Disease: Improving Global Outcomes (KDIGO)), thereby defining three stages of AKI severity [2-5]. Several studies explored the relation between creatinine-based criteria of AKI at initiation of continuous renal replacement therapy (CRRT) and mortality. Bagshaw et al. found that a lower creatinine, was associated with high mortality [6]. Recently, two randomized controlled trials evaluated the effect of creatinine-based criteria to initiate CRRT on mortality using the KDIGO stage of AKI and found controversial results: either a survival benefit for starting at a lower stage of AKI (stage 2) [7], or no difference in mortality when starting at stage 3 (early) or later when complications developed [8]. Two observational studies reported that a lower creatinine at initiation of CRRT had a poor prognosis [9, 10]. However, the use of AKI stage, as a marker for severity of AKI and initiation of RRT has several limitations. Plasma creatinine concentration, the cornerstone of AKI staging, is not only determined by renal excretion, but also by hemodilution (caused by fluid accumulation) and by creatinine generation, e.g. by muscle mass. Lower creatinine levels due to fluid overload or low creatinine generation therefore underestimate true renal function impairment in critically ill patients. In none of the above mentioned studies creatinine was adjusted for fluid balance [6-10].

The effect of fluid balance on AKI classification and outcomes was initially evaluated in a post-hoc analysis of the Fluid and Catheter Treatment Trial [11]. The study showed that patients who had AKI after adjustment for fluid balance (but not before) had worse outcomes than patients who had no AKI before and after adjustment for fluid balance. The modulating effect of fluid overload on the diagnosis of AKI using serum creatinine was recently evaluated by Macedo et al. [12]. They concluded that dilution of serum creatinine by fluid accumulation leads to underestimation of severity of AKI and delays the identification of a 50% increase in serum creatinine in critically ill patients. They developed a formula to adjust serum creatinine for fluid accumulation .

The aim of the present explorative study was to evaluate whether fluid balance-adjusted serum creatinine at CRRT initiation is related to mortality independent of other markers of severity of AKI, surrogate markers of muscle mass (age, sex, race and body weight) and severity of disease.

Methods

We performed a post-hoc analysis of data from a multicenter randomized controlled trial, comparing citrate and heparin anticoagulation during continuous venovenous hemofiltration (CVVH) [13]. Mortality between groups was not different. The study included patients requiring CVVH for AKI in 10 participating ICUs in the Netherlands. The study was performed in accordance with the declaration of Helsinki. The study was registered at clinicaltrials.gov number NCT00209378. The ethical committee VU medical Center approved this study. The local medical ethical committees of the participating centers approved this study. Written informed consent was obtained from all participants or their legal representative.

Study population

Between April 2005 and March 2011, patients were prospectively screened for inclusion in the CASH trial. The study included adult patients requiring CVVH for AKI and excluded patients older than 80 years, patients with an increased bleeding risk, with a known heparin induced thrombocytopenia (HIT) and patients needing therapeutic systemic anticoagulation. Patients were randomized to receive heparin or citrate anticoagulation for CVVH in predilution mode, with predilution replacement flow rates between 2000 and 4000 ml/h, according to local guidelines. For the present study, patients were post-hoc excluded when no creatinine at initiation of CVVH was available, or when a documented diagnosis of intrinsic renal disease (such as renal artery stenosis, diabetic nephropathy, nephrotic syndrome or nephrosclerosis) was documented in the medical record. The reason to exclude these patients was that the cause of worsening renal function could have been related to the underlying renal disease and not to critical illness-related AKI. The diagnosis of AKI was made by the attending physician and the decision to initiate CVVH was based on the local protocol. Data were collected using the hospital patient data management system.

Data collection

The following baseline data were collected: age, gender, weight and race as surrogates for muscle mass, reason for ICU admission and cause of AKI (presumed as ischemic, septic or other/toxic). At initiation of CVVH the following data were obtained: number of days at ICU before CVVH initiation, cumulative fluid balance 3 days prior to initiation, diuresis 24 hours prior to initiation, severity scores: APACHE (Acute physiology and Chronic Health Evaluation) II score at ICU admission and SOFA (Sequential Organ Failure Assessment) score at CVVH initiation, creatinine at ICU admission (µmol/L), creatinine at initiation of CVVH (µmol/L). Creatinine corrected for 3 day cumulative fluid balance was calculated according to the formula defined by Macedo et al. [12]. Adjusted creatinine = initiation creatinine x ((hospital admission weight (kg) x 0.6 + ∑ (3 day cumulative fluid balance(L)))/

(hospital admission weight x 0.6)). The KDIGO stage at initiation was calculated using only the delta creatinine criteria according to the KDIGO guidelines [2]. Unfortunately no pre-morbid creatinine was available in this post-hoc analysis. We therefore used admission creatinine as baseline creatinine. When patients were admitted with a single high creatinine and need of direct RRT, the attending physician diagnosed AKI, when there was no history of chronic kidney disease and the patient also had low urine output and other uremic symptoms. The initiation of RRT classified these patients directly to KDIGO 3 [5].

Endpoints

The primary endpoint was mortality at 28 days after CVVH initiation.

Statistical analysis

Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed variables are expressed as mean (standard deviation), non-normally distributed variables as median [interquartile range], and categorical data as number and percentage. Unpaired Student's t-test, Mann-Whitney-U test, Chi-square test or Fisher exact test was used, where appropriate. Statistical significance was defined as $p < 0.05$.

To determine the association between fluid balance-adjusted serum creatinine and 28-day mortality, logistic regression analysis was performed using backward stepwise likelihood ratio including a maximum of n/10 variables choosing those variables that had a $p<0.10$ in univariate analysis as confounders [14] , including fluid balance because of its known association with mortality [15, 16]. For diuresis, a z-score was calculated to obtain the OR for the change per standard deviation in logistic regression. A p-value of 0.10 was used for entry and removal.

ROC curve analysis was used to define the cut-off value of fluid balance-adjusted creatinine at CVVH initiation with best prediction for 28-day mortality in MedCalc®, version 15.6.1 using the Youden index. This cut-off value was used to plot Kaplan-Meier curves comparing the time to survival between patients with low adjusted CVVH initiation creatinine to patients with high adjusted CVVH initiation creatinine. The log-rank test was used to demonstrate differences.

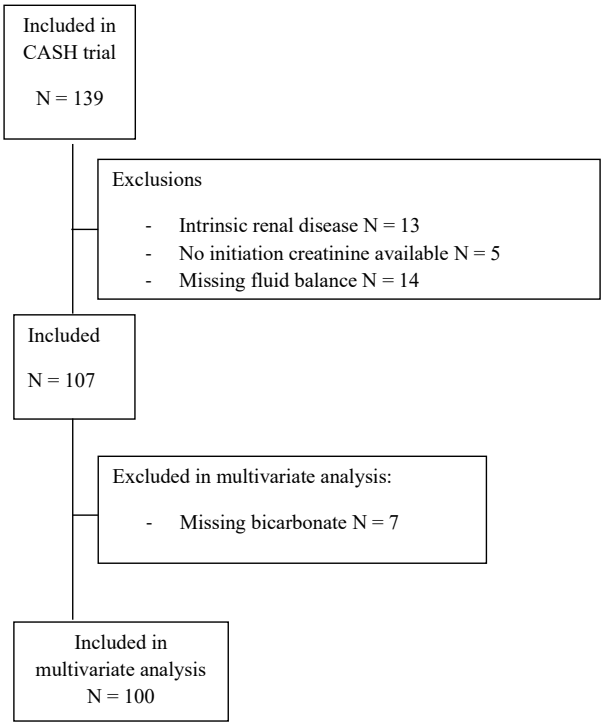
Results

Flowchart

Of the 139 patients included in the CASH trial, 32 patients were excluded, 13 because of a history of intrinsic renal disease, 5 patients because there was no creatinine available at the day of CVVH initiation and 14 patients because fluid balance was not available, so creatinine could not be corrected for fluid balance. In 7 patients bicarbonate was not available, these additional 7 patients were not included in the multivariate analysis (Fig

1). Altogether, 107 patients were included in the primary analysis and 100 patients in the multivariate analysis.

Fig 1. Flowchart of included and excluded patients



Patient characteristics according to 28-day outcome

Thirty-six out of the 107 patients (34%) did not survive at day 28. Patients who died were older (72 [15] vs. 64 [15] years, p = 0.016), had higher APACHE II scores (25 (9) vs. 22 (7), p = 0.043), lower bicarbonate (17.8 (4.3) mmol/L vs. 20.4 (4.1) mmol/L, p = 0.005), lower creatinine (278 (122) µmol/L vs. 347 (155) µmol/L, p = 0.022), and a lower fluid balance-adjusted creatinine at initiation (313 (132) µmol/L vs. 388 (168) µmol/L, p = 0.022) compared to patients alive at 28 days. Urine output, KDIGO stage, fluid balance, gender, weight, admission creatinine, reason for ICU admission, days in the ICU, predilution dose and cause of AKI, were not significantly different between groups. Baseline characteristics are shown in table 1.

Relation between fluid balance-adjusted creatinine at CVVH initiation and 28-day mortality

To determine the association between fluid balance-adjusted creatinine and 28-day mortality, variables that were potentially associated with mortality were first tested in

Table 1 Baseline characteristics of cohort, according to 28-day outcome

	Alive at 28 days, n = 71	Dead at 28 days, n = 36	P-value
Age, years	64 [15]	72 [15]	0.016
Male gender, nr (%)	50 (70)	22 (61)	0.332
Race, white, nr (%)	47 (64)	23 (64)	0.813
Weight, kg	83 [24]	86 [28]	0.789
Reason ICU admission, nr (%)			
Circulatory failure	14 (20)	9 (25)	0.636
Respiratory failure	33 (46)	16 (44)	
Trauma	3 (4)	1 (3)	
Post CPR	2 (3)	3 (8)	
Post-operative	19 (27)	7 (20)	
Cause of acute kidney injury, nr (%)			
Sepsis	31 (44)	14 (39)	0.731
Ischemic	38 (53)	20 (56)	
Other	2 (3)	2 (5)	
Creatinine admission, µmol/L	121 [110]	118 [168]	0.275
APACHE II	22 (7)	25 (9)	0.043
SOFA score	10 [5]	11 (4)	0.130
ICU admission before CVVH, days	2 [4]	3 [5]	0.594
Potassium, mmol/L	4.7 (0.8)	4.7 (0.7)	0.822
pH	7.29 (0.11)	7.25 (0.11)	0.090
Bicarbonate, mmol/L	20.4 (4.1)	17.8 (4.3)	0.005
At start CRRT			
Cumulative fluid balance 3 days before start, ml	5556 [6484]	7102 (6142)	0.609
Diuresis in 24 hr prior to CVVH, ml	341 [851]	410 [1043]	0.617
Creatinine start CVVH, µmol/L	347 (155)	278 (122)	0.022
Fluid balance-adjusted creatinine at start, µmol/L	388 (168)	313 (132)	0.022
Predilution dose, ml/kg/hr	22 (5)	21 (6)	0.751
KDIGO stage, nr (%):	71 (100)	36 (100)	0.541
KDIGO 1	10 (14)	6 (17)	
KDIGO 2	14 (20)	10 (28)	
KDIGO 3	47 (66)	20 (55)	

Mean (standard deviation) for normally distributed variables, median [interquartile range] for non-normally distributed variables, number (percentage) when appropriate; CPR, cardiopulmonary resuscitation; APACHE II, acute physiology and chronic health evaluation score; SOFA, sequential organ failure assessment; CVVH continuous venovenous hemofiltration, KDIGO, kidney disease: improving global outcomes.

univariate logistic regression analysis. In this analysis lower bicarbonate (OR 0.853, 95% CI 0.758 – 0.960, p = 0.008), lower creatinine at CVVH initiation (OR 0.996, 95% CI 0.993 - 1.000, p = 0.026), and lower fluid balance-adjusted creatinine at initiation (OR 0.997, 95% CI 0.994 – 1.000, p = 0.026) were associated with mortality (table 2). The relation with APACHE score tended to significance (OR 1.058, 95% CI 1.000 – 1.119, p = 0.050).

Table 2 Univariate logistic regression analysis of variables associated with 28 day mortality.

	OR	95 % CI	p-value
Age, years	1.039	1.000 – 1.081	0.053
Male gender	0.660	0.284 – 1.532	0.333
Race, white	0.903	0.390 – 2.091	0.813
Weight, kg	1.010	0.994 – 1.026	0.210
Creatinine at start CVVH, µmol/L	0.996	0.993 – 1.000	0.026
Cumulative fluid balance 3 days before start CVVH	1.000	1.000 – 1.000	0.382
Apache II	1.058	1.000 – 1.112	0.050
SOFA day 0	1.113	0.986 – 1.256	0.084
pH	0.035	0.001 – 1.761	0.093
Bicarbonate, mmol/L	0.853	0.758 – 0.960	0.008
Diuresis (z-score)	1.121	0.727 – 1.728	0.605
Fluid balance-adjusted creatinine at start, µmol/L	0.997	0.994 – 1.000	0.026
KDIGO stage			
KDIGO 1	1		0.543
KDIGO 2	1.190	0.325 – 4.356	0.792
KDIGO 3	0.709	0.227 – 2.216	0.554

APACHE II, acute physiology and chronic health evaluation score, OR, Odds ratio, SOFA, sequential organ failure assessment, , KDIGO, kidney disease: improving global outcomes. For continuous variables the odds ratios are per unit increase. For diuresis, Z-transformation was performed; this odds ratio is per standard deviation increase.

Subsequently, logistic regression was performed including both creatinine and fluid balance-adjusted creatinine, APACHE II score, bicarbonate and fluid balance known to be associated with mortality [15, 16]. APACHE score was included as marker of severity of disease and not SOFA score, because of the lower p-value of APACHE in univariate analysis. Age was not included because age is a component of the APACHE score. After covariate adjustment lower fluid balance-adjusted initiation creatinine (OR 0.996, 95% CI 0.993 – 0.999, p = 0.019), but not unadjusted creatinine (lost in second step, first step: OR 1.021, 95% CI 0.987 – 1.056, p 0.228), remained independently associated with 28-day mortality together with lower bicarbonate (OR 0.869, 95% CI 0.769 – 0.982, p = 0.024), while APACHE II score non-significantly contributed to the model (table 3).

Table 3 Multivariate logistic regression analysis of variables associated with 28-day mortality.

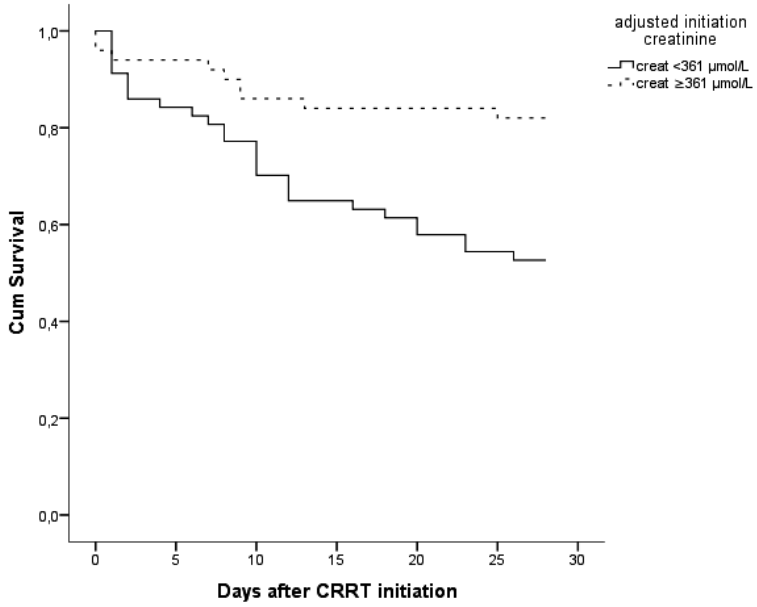
	OR	95 % CI	p-value
APACHE II score	1.060	0.994 – 1.129	0.075
Bicarbonate, mmol/L	0.869	0.769 – 0.982	0.024
Fluid balance-adjusted creatinine start, µmol/L	0.996	0.993 – 0.999	0.019

OR, Odds ratio. The odds ratios are per unit increase.
Variables included: unadjusted creatinine, cumulative fluid balance, APACHE II score, Bicarbonate, adjusted creatinine.
Variables removed: step 2: unadjusted creatinine was lost, step 3: cumulative fluid balance was lost.

To determine the cut-off value of the adjusted creatinine at initiation with the best association with 28-day mortality, ROC-curve analysis was performed. In this analysis, a fluid balance-adjusted creatinine of 361 µmol/L appeared to be associated best with 28-day mortality.

Kaplan-Meier survival curve analysis showed a significant difference between survival curves for patients with CVVH initiation at an adjusted creatinine below 361 µmol/L and those equal to or above 361 µmol/L (log-rank p = 0.002) (Fig 2). Patients with CVVH initiation at lower fluid balance-adjusted creatinine levels than 361 µmol/L had poorer survival.

Fig 2. 28-day survival curves according to the optimal fluid balance-adjusted creatinine at initiation of CVVH



Creat < 361µmol/L	57	48	44	37	35	31	30
Creat ≥ 361µmol/L	50	47	43	42	42	42	41

Discussion

Key findings

In this post-hoc analysis of the database of a prospective randomized controlled multi-center trial, we found that lower fluid balance-adjusted creatinine at initiation of CVVH was independently associated with higher 28-day mortality while unadjusted creatinine (after covariate correction) and KDIGO staging were not. This association was independent

of muscle mass-related confounders of creatinine (age, body weight, race), markers of severity of AKI (bicarbonate, urine output, creatinine, KDIGO criteria) and severity of disease. The optimal cut-off value in the present population for a fluid balance-adjusted creatinine was 361 µmol/L. Mortality was higher in the patients in whom CVVH was initiated at a fluid balance-adjusted creatinine below 361 µmol/L.
The interpretation of low fluid balance-adjusted creatinine is complex because creatinine is a marker of the balance between creatinine generation (muscle mass) and creatinine excretion (renal function). Low serum creatinine can therefore be considered as a low muscle mass or as an earlier stage of AKI. The presently found relation may therefore indicate that either initiation of CRRT at an earlier stage of AKI or low muscle mass at CRRT initiation are associated with higher mortality, or both.

The role of fluid balance

Apart from muscle mass and severity of AKI, fluid overload is an important confounder for mortality. Fluid overload is a dual confounder. Fluid overload itself is a severe complication of critical illness and independently associated with worse outcome, especially in patients with AKI [15-18]. Furthermore, fluid overload dilutes serum creatinine and thereby underestimates the severity of AKI and delays its diagnosis [12]. In a post-hoc analysis of the ARDS network trial, patients who met the criteria for AKI after correction for fluid balance (and not before) had a greater mortality than those who did not meet AKI criteria (before and after correction) and those who had AKI before but not after adjustment for fluid balance [11]. In another study, patients in whom AKI was diagnosed only after adjustment for fluid balance had higher mortality than patients without AKI [19]. To account for these dual effects of fluid balance, we both adjusted creatinine for fluid balance and added fluid balance as an independent factor in the multivariate logistic regression analysis.

Creatinine generation

Previous studies have shown an association between reduced creatinine generation during hemodialysis [20], low serum creatinine at ICU admission (< 30 µmol/L) and low peak plasma creatinine concentrations (< 60 µmol/L) with mortality [21, 22]. That low creatinine may reflect reduced muscle mass has been demonstrated by Baxmann et al. using cystatin C as a marker of renal function [23]. To adjust for the confounding of serum creatinine by low muscle mass, we added surrogates for muscle mass in our multivariate regression analysis. Age is one of the determinants of the APACHE II score and therefore covered by adding APACHE II score in the multivariate analysis. Age has dual effects. A higher age is associated with higher mortality per se, while on the other hand muscle mass declines with aging. Body weight, gender and race were not included because we found no association with 28-day mortality in univariate analysis. We do however admit that the present correction for confounders of muscle mass is insufficient. Low body weight does not necessarily implicate low muscle mass and high body weight may be

associated with low muscle mass (sarcopenic obesity). Furthermore, the relation between high age and low muscle mass is not straightforward. Thus, whether the present results suggest that low muscle mass at CVVH initiation is associated with increased mortality cannot be excluded.

Creatinine excretion

Serum creatinine is primarily conceived as a marker of renal excretory function and the different AKI classifications are based on this concept. Remarkably, while low fluid balance-adjusted creatinine was associated with mortality, neither unadjusted creatinine nor the stage of AKI according to the KDIGO criteria was associated with mortality in this study. The determination of AKI stage was as reliable as possible because we excluded patients with missing creatinine before initiation of CVVH. As recently discussed by Chawla et al. it is important to consider the timeframe of development of kidney injury to accurately classify these patients [5]. However, because premorbid creatinine values were not available we used baseline instead of pre-admission creatinine which can be conceived as limitation. In patients with a high admission creatinine and direct need of RRT the attending physician diagnosed AKI (and not CKD), based on clinical data. These patients were staged as KDIGO 3, because of immediate initiation of RRT. Nevertheless, neither KDIGO nor the previous AKI classifications (RIFLE, AKIN) consider the confounding of fluid balance.

Even when our results would suggest that initiation of CRRT at an earlier stage of AKI is associated with higher mortality, the translation of these results to clinical practice is difficult. In the present study, timing was left to the considerations of the physician in charge and it is well known that CRRT is initiated at an earlier stage of AKI in the most severely ill patients with hemodynamic instability, severe fluid overload or severe acidosis. Low bicarbonate was an independent predictor of mortality in our study. Thus, the stage of AKI will never be the sole criterion used to decide when to initiate CRRT in daily practice, the severity of illness and renal and non-renal complications like fluid overload and acidosis are always considered. Randomized controlled trials should account for this confounding.

Timing of CRRT using creatinine based criteria

The results of studies investigating timing of CRRT using creatinine based definitions are controversial. Two systematic reviews cautiously suggested early CRRT initiation might be associated with better survival [24, 25]. However, these reviews were mainly based on low quality heterogeneous studies. In a recently published randomized controlled trial in surgical patients, initiation of CRRT at a lower creatinine (at KDIGO stage 2) was associated with lower mortality [7]. In contrast, a multicenter randomized controlled trial including patients with AKI requiring mechanical ventilation or catecholamine infusion and without potentially AKI-related life-threatening complications, found no difference in mortality

between early (KDIGO stage 3) and late initiation of RRT (when a conventional indication developed, after diagnosing KDIGO stage 3) [8]. Similarly, a multicenter randomized feasibility trial found no difference in mortality between early (within 12 hours after KDGIO stage 2) and late initiation of RRT (when a conventional indication developed, after 12 hours reaching KDIGO stage 2) either [26]. In the two latter trials, serum creatinine concentration at initiation of RRT was not different between groups, and a substantial proportion of late patients did not receive RRT because of dying or renal recovery. In contrast and in agreement with our results, two observational studies reported that a lower creatinine at initiation of CRRT was associated with higher mortality [9, 10]. Recently two meta-analysis of high quality trials analyzed the impact of early or late RRT initiation on outcome [27, 28]. After exclusion of studies reporting incomplete baseline demographic data, studies without severity of illness assessment or studies with differences between cohorts at baseline, no survival benefit for early RRT initiation was found, supporting the importance of considering severity of disease when initiating CRRT. However, none of the previous studies on timing, using creatinine as a compound of AKI stage or as a solitary value, was adjusted for fluid balance. In the present study, we corrected for disease severity and baseline characteristics, as well as for the non-renal confounders of creatinine, for other markers of timing and for severity of disease, suggesting that low fluid balance-adjusted creatinine could partially be interpreted as a marker of early timing of CRRT, and that, if this were the case, early timing in this population was associated with mortality.
In contrast to previous studies, urinary output [21, 29] and days in ICU [6] were not related to mortality in our population. Urinary output may be confounded by the use of diuretics and oliguria does not necessarily implicate the presence of AKI [30].

Strengths and limitations

Important limitations of our study are the small sample size, limiting its statistical power. Furthermore, the initiation of CVVH was not protocollized and was therefore biased. CRRT might have been started earlier in the sicker patients explaining the higher mortality. Moreover, this study was not designed to evaluate fluid balance-adjusted creatinine. Patients who needed systemic anticoagulation or had an otherwise increased risk of bleeding were excluded in the CASH trial. As a result, we included less surgical patients and less patients with septic AKI limiting the generalizability of our results. The database could, however, be used because mortality between randomized groups was not different [13]. Unfortunately we had no data on fluid balance more than three days prior to CRRT initiation. However, median stay in the ICU was 2 days, thus for the majority of patients fluid balance from admission was available. Furthermore, fluid balance may not precisely estimate fluid status, because part of the fluids may be lost by perspiration or wounds. Also we did not have an independent measure of muscle mass and had no data on premorbid creatinine. Finally, due to missing values, 7 patients were excluded in the multivariate analysis. Nevertheless, our cohort is comparable to other studies regarding

disease severity, indicated by SOFA and APACHE II scores, age, vasopressor dependency and proportion of mechanically ventilated patients [6, 31, 32]. Altogether, the present study can only signal the pitfalls related to the interpretation of serum creatinine being more than a marker of renal function [33].

Our study has several strengths. The use of fluid balance-adjusted creatinine to stage AKI is unique in the available literature, and strongly recommended since recent studies showed underestimation and misclassification of AKI if uncorrected creatinine is used [11, 12, 19]. Confounding is further minimized, because we adjusted creatinine for surrogate markers of muscle mass, such as age, body weight and race. Despite these adjustments, the relation between low creatinine and mortality as shown in our study insufficiently differentiates between an earlier initiation of CVVH, a low muscle mass or both as risk factors for dying in this population.

Conclusions

In conclusion, in this post-hoc analysis of a multicenter study we found that a low fluid balance-adjusted creatinine at initiation of CVVH was associated with increased 28-day mortality independent of surrogates of muscle mass and severity of organ failure, while unadjusted creatinine and KDIGO stage were not. Because we only used surrogates for muscle mass and fluid status, the present study insufficiently differentiates whether a lower muscle mass or earlier initiation of CVVH or both are associated with mortality. Our results cannot be translated to clinical practice, but are hypothesis generating. They suggest that future studies on determinants of mortality should take fluid balance into account when investigating AKI stage as a criterion for timing of CRRT, include better markers of muscle mass such as bioimpedance analysis, and account for severity of disease and acidosis.

Acknowledgement

We sincerely regret that Johan Groeneveld who contributed to the concept of this study has recently died. We miss his sharp and witty research input.

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CHAPTER 3

Predictors of short-term successful discontinuation of continuous renal replacement therapy: results from a prospective multicentre study

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Abstract

Background: Prediction of successful discontinuation of continuous renal replacement therapy (CRRT) might reduce complications of over- and under-treatment. The aim of this study was to identify renal and non-renal predictors of short-term successful discontinuation of CRRT in patients in whom CRRT was stopped because renal recovery was expected and who were still in the Intensive Care Unit (ICU) at day 2 after stop CRRT.

Methods: Prospective multicentre observational study in 92 patients alive after discontinuation of CRRT for acute kidney injury (AKI), still in the ICU and free from renal replacement therapy (RRT) at day 2 after discontinuation. Successful discontinuation was defined as alive and free from RRT at day 7 after stop CRRT. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and clinical variables were collected. Logistic regression and Receiver Operator Characteristic (ROC) curve analysis were performed to determine the best predictive and discriminative variables.

Results: Discontinuation of CRRT was successful in 61/92 patients (66%). Patients with successful discontinuation of CRRT had higher day 2 urine output, better renal function indicated by higher creatinine clearance (6-h) or lower creatinine ratio (day 2/day 0), less often vasopressors, lower urinary NGAL, shorter duration of CRRT and lower cumulative fluid balance (day 0-2). In multivariate analysis renal function determined by creatinine clearance (Odds Ratio (OR) 1.066, 95% confidence interval (CI) 1.022 – 1.111, p = 0.003) or by creatinine ratio (day 2/day 0) (OR 0.149, 95% CI 0.037 – 0.583, p = 0.006) and non-renal sequential organ failure assessment (SOFA) score (OR 0.822, 95% CI 0.678 – 0.996, p = 0.045) were independently associated with successful discontinuation of CRRT. The area under the curve of creatinine clearance to predict successful discontinuation was 0.791, optimal cut-off of 11 ml/min (95% CI 6 – 16 ml/min) and of creatinine ratio 0.819 (95% CI 0.732 – 0.907) optimal cut-off of 1.41 (95% CI 1.27 – 1.59).

Conclusion: In this prospective multicentre study we found higher creatinine clearance or lower creatinine ratio as best predictors of short-term successful discontinuation of CRRT, with a creatinine ratio of 1.41 (95% CI 1.27 – 1.59) as optimal cut-off. This study provides a practical bedside tool for clinical decision making.

Background

Acute kidney injury (AKI) is a common complication of critical illness and patients requiring renal replacement therapy have excess mortality even when adjusted for severity of disease [1-4]. The optimal timing to start continuous renal replacement therapy (CRRT) has been investigated in several studies. The urinary biomarker Neutrophil gelatinase-associated lipocalin (NGAL) has high potential as an early predictor of severe AKI [5, 6]. However, only few studies are available on the use of biomarkers to predict successful discontinuation of CRRT [7-9].

In daily practice, CRRT is discontinued on an individual basis: when urinary output increases or when the CRRT session ends and the attending physician supposes that renal function will recover because other organ functions improve. Previous studies found that lower age, less severe organ failure, shorter duration of CRRT, higher creatinine clearance or urine output during CRRT and decreasing plasma NGAL on the first day of RIFLE-F were associated with recovery [4, 7-15]. Clinical reasons for re-initiation of CRRT are fluid overload, hyperkalaemia and azotaemia [15]. However, none of these studies evaluated biomarkers at discontinuation of CRRT.

Predicting short-term successful discontinuation in patients in whom CRRT has been stopped may prevent potentially harmful complications of over- and under treatment. We hypothesized that high urine output, high endogenous creatinine clearance or low creatinine ratio, low urinary NGAL, no vasopressor use and low non-renal sequential organ failure assessment (SOFA) score after discontinuation are associated with successful discontinuation of CRRT. The objectives of the present study were to identify renal and non-renal predictors for short-term successful discontinuation.

Methods

Study design

We performed a prospective multicentre observational study in 4 intensive care units (ICUs) in the Netherlands (Erasmus (University) Medical Centre, Rotterdam, Ikazia Hospital Rotterdam, Amphia Hospital Breda and Medical Centre Alkmaar). Patients were included from May 2013 until September 2015. The protocol was approved by the medical ethics committee of the Erasmus Medical Centre and the local ethical committees. Written informed consent was obtained from all participants or their legal representative.

Patients

All patients aged 18 years or older, alive and still admitted to the ICU at day 2 after discontinuation of CRRT were screened for eligibility. Patients with end-stage-renal-disease (CKD 5) with or without chronic renal replacement therapy, and patients receiving CRRT for other reasons than acute renal failure (e.g. liver failure, intoxications) were

excluded. Patients discharged from the ICU before day 2 were excluded from analysis, because primary study variables could not be collected from these patients.

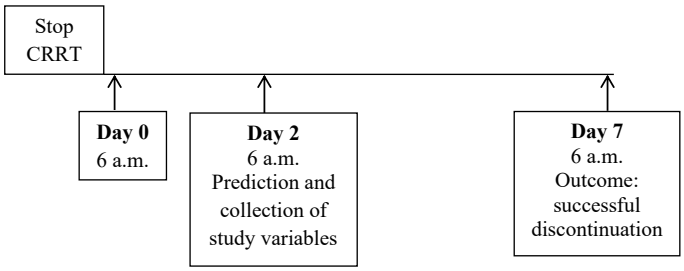
Sample size calculation

For evaluation of predictors of short-term successful discontinuation, we defined five primary study variables (urine output, renal function determined by calculated creatinine clearance or creatinine ratio, urinary NGAL, vasopressor use and non-renal SOFA score) which were hypothesized predictive and two secondary study variables (duration of CRRT and cumulative fluid balance) which were derived from the literature. We planned to test a total of 7 variables in multivariate regression analysis and therefore aimed to include at least 70 evaluable patients as suggested by Altman ("no more than n/10 variables, where n is the sample size" [16]). Because of expected exclusions caused by early discharge and missing urine samples we aimed to include 90 patients.

Study protocol and measurements

Successful discontinuation was defined as alive and free from RRT at day 7 after discontinuation. We chose 2 days after discontinuation of CRRT as time point to predict whether discontinuation of CRRT would be successful for the subsequent 5 days to include only those patients for whom the prediction of successful discontinuation has direct logistical consequences for the unit, and to evaluate only the patients in whom CRRT was discontinued because of expected renal recovery and not those in whom CRRT was temporarily discontinued for logistical reasons (such as CT scan or surgery) or switch of dialysis modality to intermittent haemodialysis. Day 0 was defined as the first 6 a.m. after discontinuation of CRRT. Day 7 as the day at which the outcome successful discontinuation was determined (Fig. 1). The decision to (re)initiate or discontinue renal replacement therapy in the ICU was made according to the decision of the local team. CRRT was performed according to the local protocol of the hospital as continuous venovenous hemofiltration (CVVH) or continuous venovenous haemodialysis (CVVHD) and delivered dose was 20-35 ml/kg/hour. We used polyethersulfone, acrylonitrile/ sodium methallyl sulfonate polymer membranes with a surface area of 1.8 m^2 – 1.9 m^2 and an in vitro cut-off point of 30 - 55 kDa, depending on local availability of materials.

Figure 1 study outline



Study variables

The following *primary study variables* were collected at day 2: urine output, renal function determined by 6-hour endogenous creatinine clearance and incremental creatinine ratio, urinary NGAL concentration (when diuresis was > 200 ml/day) normalized to urinary creatinine concentration, vasopressor use and non-renal SOFA score. Renal function was determined by calculation of creatinine clearance according to the following formula: ((urinary creatinine concentration * urine volume)/ plasma creatinine concentration)/ 360, and calculation of the incremental creatinine ratio between day 2 and day 0 (at discontinuation) (creatinine day 2/day 0).The following *secondary study variables* were collected on day 2 as well: duration of CRRT (as found in previous studies [10, 11, 14, 15]) and cumulative fluid balance from day 0 until day 2 (as used in clinical practice as reason for restart).

Other measurements

The following variables were determined at start of CRRT: demographic data, preadmission creatinine (defined as creatinine 1 month prior to admission or more without disease), preadmission estimated glomerular filtration rate (eGFR) (calculated with CKD-EPI formula [17]), previous kidney disease, reason for ICU admission (post-operative, respiratory failure, sepsis, post cardiac arrest, neurologic, cardiac failure), disease severity scores (Acute Physiology And Chronic Health Evaluation (APACHE) III, Simplified Acute Physiology Score (SAPS) III), cause of AKI (defined as sepsis, toxic, primary renal disease, ischemic/other).

Endpoints

The primary endpoint was successful discontinuation, defined as alive and free from any form of RRT at day 7 after stop CRRT.

Assays

For determination of NGAL, a tube collected from a 6 hour urine portion was stored in the refrigerator for a maximum of 72 hours. As soon as possible the sample was centrifuged for 10 minutes at 2000G at 4˚C and the supernatant was stored at -80˚C for determination of urinary NGAL later. Urinary NGAL was determined by immunoassay using the Architect ci4100 (Abbott Diagnostics, Abbott Park, IL, US), we used the Urine NGAL Rgt 100T (1P37-25), NGAL Calibrator (1P37-01), NGAL Controle (1P37-10) according to manufacturer's specifications. NGAL values were normalized to creatinine concentration and expressed as (ng/ml)/creatinine (mmol/L).

Statistical analysis

Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed variables are expressed as mean (standard deviation), non-normally distributed variables as median [25th and 75th percentile], and categorical data as number

and percentage. Unpaired Student's t-test, Mann-Whitney-U test or Chi-square test was used, where appropriate. Statistical significance was defined as $p < 0.05$.

To determine the association between the primary study variables (urine output, endogenous creatinine clearance, urinary NGAL, use of vasopressors and non-renal SOFA score) and the secondary study variables (duration of CRRT and fluid balance day 0-2) with successful discontinuation of CRRT, univariate logistic regression analysis was performed and subsequent multivariate analysis was performed. For all analyses, multicollinearity was checked with a maximum variance inflation factor (VIF) of 10.

A ROC curve was drawn for the best discriminative variable of successful discontinuation of CRRT. The area under the receiver operator characteristic curve (AUC) was calculated to discriminate for successful discontinuation of CRRT. The Youden index was calculated to determine the optimal cut-off to discriminate for successful discontinuation. The confidence interval for the optimal cut-off was calculated using bootstrapping with 1000 random samples using the bias corrected and accelerated method.

Results

Flowchart

Of the 490 patients receiving CRRT during the study period, 57 patients met the exclusion criteria, 155 patients died during CRRT, 13 patients were transferred to another hospital during CRRT, 110 patients were discharged from the ICU before the predefined sampling point at day 2, 25 patients had missing primary study variables and in 38 patients CRRT was discontinued because of switch of modality to intermittent haemodialysis. Among the 92 included patients, 61 patients (66%) experienced successful discontinuation of CRRT at day 7, 21 patients (23%) needed re-initiation of RRT before day 7, and 10 patients (11%) died within 7 days after discontinuation of CRRT (fig. 2). Of the 173 excluded patients who were alive and on the ICU at discontinuation of CRRT, 105 patients (61% of excluded patients) experienced successful discontinuation, 58 patients (33% of excluded patients) needed re-initiation of RRT and 10 patients (6% of excluded patients) died within 7 days (fig. 2). In 38/58 patients needing restart of RRT, CRRT was discontinued for switch to intermittent haemodialysis.

Differences between included and excluded patients are depicted in table 1. Excluded patients had worse preadmission renal function compared to included patients. Furthermore re-initiation of intermittent haemodialysis was needed in 38 patients (22%) of the excluded patients compared to 4 patients (4%) of the included patients.

Figure 2 Flowchart of included and excluded patients

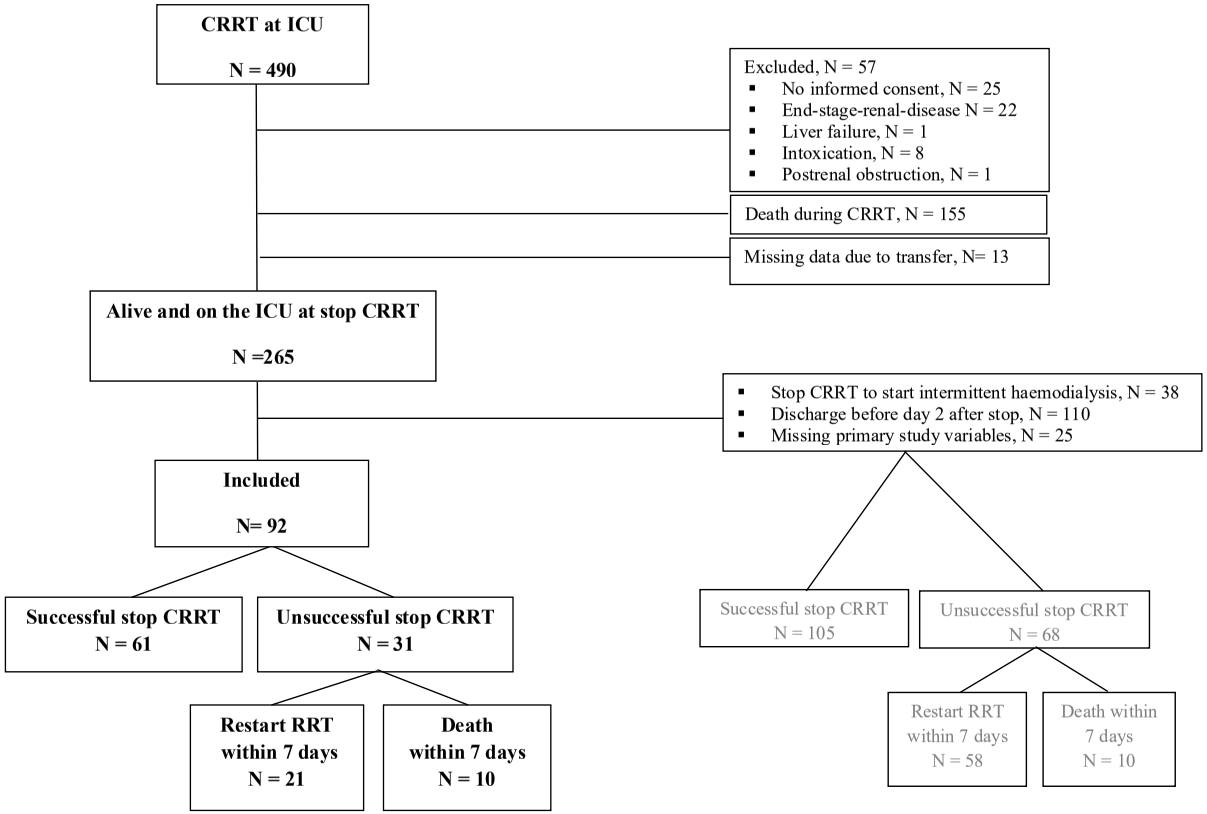


Table 1 Baseline characteristics for included and excluded patients

	Included patients n = 92	**Excluded patients n = 173**	**P-value**
Age (years)	66 [55, 74]	64 [57, 74]	0.620
Male gender, nr (%)	55 (60)	126 (73)	0.030
Weight (kg)	82 (16)	80 [71 , 95]	0.693
BMI (kg/m^2)	25.7 [23.5, 30.3]	27.0 [23.7, 30.9]	0.522
Previous kidney disease, nr (%)	20 (22)	57 (32)	0.056
Preadmission creatinine, µmol/L	96 [74, 127]	103 [83, 149]	0.030
Preadmission eGFR (CKD-EPI), (ml/min/1.73m^2)	67.8 (26.2)	60.8 (26.7)	0.047
Cause of AKI, nr (%)			
Sepsis	34 (37)	51 (30)	0.052
Toxic	4 (4)	24 (14)	
Primary renal disease	2 (2)	8 (5)	
Ischemic/ other	52 (57)	90 (52)	
Reason for ICU admission, nr (%)			
Post-operative	32 (35)	53 (31)	0.470
Respiratory failure	15 (16)	24 (14)	
Sepsis	17 (19)	30 (17)	
Post cardiac arrest	7 (7)	14 (8)	
Cardiac failure	9 (10)	20 (12)	
Other	12 (13)	32 (19)	
SAPS III admission	53 (16)	54 (15)	0.313
APACHE III admission	89 (31)	81 [66, 103]	0.188
Mechanical ventilation at initiation of CRRT	69 (75)	109 (63)	0.107
Vasopressor at initiation of CRRT	74 (80)	117 (68)	0.041
Successful stop CRRT, nr (%)			
Yes	60 (65)	105 (61)	0.001
No, restart of CRRT	18 (20)	20 (11)	
No, restart of IHD	4 (4)	38 (22)	
No, death	10 (11)	10 (6)	

Mean (standard deviation) for normally distributed variables, median [25th and 75th percentile] for non-normally distributed variables, number (percentage) when appropriate. BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; AKI, acute kidney injury; ICU, intensive care unit; SAPS III, simplified acute physiology score; APACHE III, acute physiology and chronic health evaluation score; CRRT, continuous renal replacement therapy; IHD, intermittent haemodialysis.

Patient characteristics according to successful or unsuccessful discontinuation

Demographic and baseline characteristics at CRRT initiation were not significantly different between patients with successful and unsuccessful discontinuation of CRRT (table 2). Accordingly, events during and after CRRT, such as new infections, the use of nephrotoxic medication or intravenous contrast, use of diuretics and the use of citrate anticoagulation were not significantly different between patients with successful and unsuccessful discontinuation of CRRT (table 2).

Table 2 Demographic and baseline characteristics at start of CRRT and events during CRRT or after CRRT according to successful or unsuccessful discontinuation

	All patients n =92	**Successful stop CRRT n= 61 (66%)**	**Unsuccessful stop CRRT n= 31 (34%)**	**P-value**
Age (years)	66 [55, 74]	62 (13)	64 (14)	0.275
Male gender, nr (%)	55 (60)	38 (62)	17 (55)	0.491
Weight (kg)	82 (16)	84 (17)	79 (15)	0.153
BMI (kg/m^2)	25.7 [23.5, 30.3]	26.5 [23.9, 32.1]	25.1 [22.9, 27.7]	0.146
Previous kidney disease, nr (%)	20 (22)	10 (16)	10 (32)	0.081
Preadmission creatinine, µmol/L	96 [74, 127]	101 (39)	96 [71, 139]	0.599
Preadmission eGFR (CKD-EPI), (ml/min/1.73m^2)	67.8 (26.2)	69.5 (25.1)	64.1 (46.0)	0.375
Cause of AKI, nr (%)				
Sepsis	34 (37)	19 (31)	15 (48)	0.058
Toxic	4 (4)	3 (5)	1 (3)	
Primary renal disease	2 (2)	0 (0)	2 (7)	
Ischemic/ other	52 (57)	39 (64)	13 (42)	
Reason for ICU admission, nr (%)				
Post-operative	32 (35)	20 (33)	12 (39)	0.185
Respiratory failure	15 (16)	10 (17)	5 (16)	
Sepsis	17 (19)	8 (13)	9 (29)	
Post cardiac arrest	7 (7)	7 (11)	0 (0)	
Cardiac failure	9 (10)	7 (11)	2 (6)	
Other	12 (13)	9 (15)	3 (10)	
SAPS III admission	53 (16)	52 (15)	55 (18)	0.470
APACHE III admission	89 (31)	88 (29)	91 (36)	0.624
Mechanical ventilation at initiation of CRRT	69 (75)	45 (74)	24 (77)	0.702
Vasopressor at initiation of CRRT	74 (80)	49 (80)	25 (81)	0.971

Events during or after CRRT				
Infection day -4 until day 0, nr (%)	21 (23)	14 (24)	7 (23)	0.936
Infection day 0 until day 7 after stop CRRT, nr (%)	17 (19)	9 (15)	8 (26)	0.197
Citrate anticoagulation, nr (%)	74 (80)	49 (80)	25 (81)	0.971
Nephrotoxic medication or IV contrast, day -4 until day 0, nr (%)	68 (75)	43 (71)	25 (81)	0.350
Nephrotoxic medication or IV contrast, day 0 until day 7 after stop, nr (%)	62 (67)	43 (71)	19 (61)	0.374
Diuretics day 0 until day 2, nr (%)	73 (80)	45 (74)	28 (90)	0.064

Mean (standard deviation) for normally distributed variables, median [25th and 75th percentile] for non-normally distributed variables, number (percentage) when appropriate. BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; AKI, acute kidney injury; ICU, intensive care unit; SAPS III, simplified acute physiology score; APACHE III, acute physiology and chronic health evaluation score; CRRT, continuous renal replacement therapy.

At day 2 after stop CRRT, patients with successful discontinuation of CRRT had higher urine output, 2.424 (1.232) L vs. 1.640 (1.217) L ($p = 0.005$), higher creatinine clearance, 29 [14, 56] ml/min vs. 7 [4, 16] ml/min ($p < 0.001$), lower creatinine ratio (day 2 / day 0), 1.16 [0.91, 1.39] vs. 1.63 [1.42, 1.82] ($p <0.001$), lower urinary NGAL(ng/ml)/creatinine (mmol/L), 80 [10, 249] vs. 583 [203, 1027] (ng/ml)/ creatinine (mmol/L) ($p = 0.002$), less often vasopressors 10 (16%) vs. 12 (39%) ($p = 0.018$) compared to patients with unsuccessful discontinuation of CRRT. Furthermore, patients with successful discontinuation of CRRT had shorter duration of CRRT, 4 [3, 9] days vs. 7 [4, 17] days ($p = 0.014$), and negative cumulative fluid balance between day 0 and 2, -1.284 (2.884) L vs. 1.250 (2.942) L ($p < 0.001$) (table 3).

Association between day 2 variables and successful discontinuation of CRRT

In univariate regression analysis we found a significant association between successful discontinuation of CRRT and higher day 2 urine output (OR 1.777, 95% CI 1.168 – 2.704, $p = 0.007$), higher creatinine clearance (OR 1.069, 95% CI 1.030 – 1.109, $p < 0.001$), lower incremental creatinine ratio (day 2/ day 0) (OR 0.100, 95% CI 0.027 – 0.370, $p = 0.001$), lower urinary NGAL (ng/ml)/creatinine (mmol/L) (OR 0.998, 95% CI 0.997 – 1.000, $p = 0.025$), no vasopressor use (OR 0.310, 95% CI 0.115 – 0.836, $p = 0.021$), shorter CRRT duration (OR 0.926, 95% CI 0.868 – 0.987, $p = 0.018$) and lower cumulative fluid balance (OR 0.734, 95% CI 0.618 – 0.876, $p = 0.001$). Non-renal SOFA score was associated with successful discontinuation although non-significantly (table 4).

Table 3 Potential predictors of successful discontinuation collected on day 2

	All patients n = 92	Successful stop CRRT n= 61 (66%)	Unsuccessful stop CRRT n= 31 (34%)	P-value
Primary study variables				
Urine output (L)	2.160 (1.276)	2.424 (1.232)	1.640 (1.217)	0.005
Creatinine clearance, ml/min	20 [7, 41]	29 [14, 56]	7 [4, 16]	<0.001
Creatinine ratio (day 2/ day 0)	1.35 [1.06, 1.63]	1.16 [0.91, 1.39]	1.63 [1.42, 1.81]	<0.001
Urinary NGAL (ng/ml)/ creatinine (mmol/L) (n =63)	152 [15, 601]	80 [10, 249]	583 [203, 1027]	0.002
Vasopressor use, nr (%)	22 (24)	10 (16)	12 (39)	0.018
Non-renal SOFA score	4 [3, 7]	4 [3, 5]	6 (3)	0.080
Secondary study variables				
Duration of CRRT (days)	5 [3, 10]	4 [3, 9]	7 [4, 17]	0.014
Cumulative fluid balance, day 0-2 (L)	-0.430 (3.129)	-1.284 (2.884)	1.250 (2.942)	<0.001

Mean (standard deviation) for normally distributed variables, median [25th and 75th percentile] for non-normally distributed variables, number (percentage) when appropriate. NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; CRRT, continuous renal replacement therapy.

Table 4 Univariate analysis of variables associated with successful discontinuation (n = 92)

	OR	95% CI	P-value
Primary study variables			
Urine output (L) (day 2)	1.777	1.168 – 2.704	0.007
Creatinine clearance, ml/min (day 2)	1.069	1.030 – 1.109	<0.001
Creatinine ratio (day 0 / day2)	0.100	0.027 – 0.370	0.001
Urinary NGAL (ng/ml)/creatinine (mmol/L) (day 2) (n = 63)	0.998	0.997 – 1.000	0.025
Vasopressor use (day 2)	0.310	0.115 – 0.836	0.021
Non-renal SOFA score (day 2)	0.854	0.729 - 1.001	0.052
Secondary study variables			
Duration of CRRT (days)	0.926	0.868 – 0.987	0.018
Cumulative fluid balance, day 0-2 (L)	0.734	0.618 – 0.876	0.001

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; CRRT continuous renal replacement therapy.

Urinary NGAL was only available in 63 patients. Reasons for missing values were anuria or failure to collect or store the urine portion. The primary multivariate analysis was

performed in the entire group (n = 92), because inclusion of urinary NGAL would cause a substantial loss of data. The analysis showed that a higher day 2 calculated creatinine clearance (OR 1.066, 95% CI 1.022 – 1.111, p = 0.003), and a lower non-renal SOFA score (OR 0.822, 95% CI 0.678 – 0.996, p = 0.045) were significantly associated with successful discontinuation of CRRT, a negative fluid balance contributed non-significantly (OR 0.848, 95% CI 0.708 – 1.014, p = 0.071) (Table 5A).

Table 5A Primary multivariate analysis of variables associated with successful discontinuation of CRRT (n = 92)

	OR	95% CI	P-value
Creatinine clearance, ml/min (day 2)	1.066	1.022 – 1.111	0.003
Non-renal SOFA (day 2)	0.822	0.678 – 0.996	0.045
Cumulative fluid balance, day 0-2 (L)	0.848	0.708 – 1.014	0.071

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval; SOFA, sequential organ failure assessment
Variables included: Urine output (day 2), creatinine clearance (day 2), vasopressor use (day 2), non-renal SOFA score (day 2), duration of CRRT (days), cumulative fluid balance, day 0-2
Variables removed: step 2: Urine output (day 2) was lost, step 3: duration of CRRT was lost, step 4: Vasopressor use (day 2) was lost.
Nagelkerke R^2 of final model 0.415

A second multivariate analysis in the entire group (n = 92) including incremental creatinine ratio (day 2/ day 0) instead of creatinine clearance, showed that a lower creatinine ratio (day 2/ day 0) (OR 0.149, 95% CI 0.038 – 0.583, p = 0.006) and a lower non-renal SOFA score (OR 0.836, 95% CI 0.700 – 1.000, p = 0.049) were significantly associated with successful discontinuation of CRRT, a negative fluid balance contributed non-significantly (OR 0.830, 95% CI 0.686 – 1.005, p = 0. 057) (Table 5B). The Nagelkerke R^2 of the latter model was lower than that of the model including creatinine clearance. There was no significant collinearity, the VIF were < 3 for all combinations of variables.

Table 5B Second multivariate analysis of variables associated with successful discontinuation of CRRT (n= 92)

	OR	95% CI	P-value
Creatinine ratio (day 2 / day 0)	0.149	0.038 – 0.583	0.006
Non-renal SOFA (day 2)	0.836	0.700 – 1.000	0.049
Cumulative fluid balance, day 0-2 (L)	0.830	0.686 – 1.005	0.057

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval; SOFA, sequential organ failure assessment
Variables included: Urine output (day 2), creatinine ratio (day 2 / day 0), vasopressor use (day 2), non-renal SOFA score (day 2), duration of CRRT (days), cumulative fluid balance, day 0-2
Variables removed: step 2: Vasopressor use (day 2) was lost, step 3: duration of CRRT was lost, step 4: Urine output (day 2) was lost.
Nagelkerke R^2 of final model 0.356

A sensitivity analysis was performed in the group in which urinary NGAL(ng/ml)/creatinine (mmol/L) was available (n=63). In this analysis a higher creatinine clearance (OR 1.088, 95% CI 1.028-1.151), p=0.004, and lower non-renal SOFA (OR 0.764, 95% CI 0.604-0.765), p=0.024, were significant predictors of successful discontinuation. Urinary NGAL (ng/ml)/ creatinine (mmol/L) was removed in step 3 (Table 6).

Table 6 Multivariate sensitivity analysis including only the patients with available urinary NGAL (63 patients)

	OR	95% CI	P-value
Creatinine clearance, ml/min (day 2)	1.088	1.028 – 1.151	0.004
Non-renal SOFA (day 2)	0.764	0.604 – 0.965	0.024

OR, Odds ratio; The odds ratios are per unit increase; SOFA, sequential organ failure assessment
Variables included: Urine output (day 2), creatinine clearance, ml/min (day 2), Urinary NGAL (day 2) (ng/ml)/creatinine (mmol/L), vasopressor use (day 2), non-renal SOFA score (day 2), cumulative fluid balance day 0-2, duration of CRRT (days)
Variables removed: step 2: Urine output (day 2) was lost, step 3: Urinary NGAL (ng/ml)/creatinine (mmol/L) (day 2) was lost, step 4: Vasopressor use (day 2) was lost, step 5: duration of CRRT was lost, Step 6: cumulative fluid balance day 0-2 was lost.
Nagelkerke R^2 of final model (n = 63) 0.406

Discrimination of renal function determined as creatinine clearance or creatinine ratio (day 2/day 0) to predict successful discontinuation of CRRT

The AUC of the ROC curve for creatinine clearance to discriminate for short-term successful discontinuation of CRRT was 0.791 (95% CI 0.697 – 0.885) (fig. 3A), with an optimal cut-off of 11 ml/min (95% CI 6 – 16 ml/min), sensitivity 0.84, specificity 0.68, positive predictive value of 84% and negative predictive value of 68%. The AUC of the ROC curve of the final model, including creatinine clearance, non-renal SOFA score and cumulative fluid balance, was 0.838 (95% CI 0.757 – 0.919) (fig. 3A).

The AUC of the ROC curve for creatinine ratio (day 2/day 0) to discriminate for short-term successful discontinuation of CRRT was 0.819 (95% CI 0.732 – 0.907) (fig. 3B),with an optimal cut-off of 1.41 (95% CI 1.27 – 1.59), sensitivity 0.80, specificity 0.81, positive predictive value 89% and negative predictive value of 68%. The AUC of the ROC curve of the final model including creatinine ratio (day 2/ day 0), non-renal SOFA score and cumulative fluid balance is 0.840 (0.756 – 0.925) (fig. 3B).

Figure 3 ROC curves for the prediction of successful discontinuation of CRRT

Fig 3A

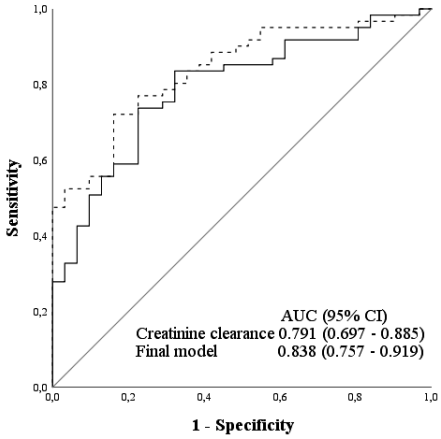
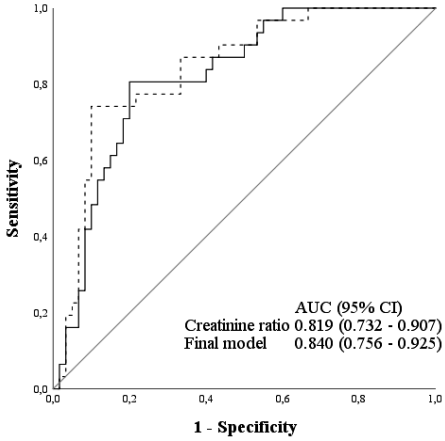


Fig 3B



3A ROC curve for creatinine clearance and final model. Creatinine clearance (black solid line) and the final model including creatinine clearance, non-renal SOFA score and cumulative fluid balance (dotted line).

3B ROC curve for creatinine ratio (day 2/day 0) and final model. Creatinine ratio (day 2/ day 0) (black solid line) and the final model including creatinine ratio (day 2/ day 0), non-renal SOFA score and cumulative fluid balance (dotted line)

Discussion

In this prospective multicentre study in critically ill patients receiving CRRT for AKI, we found that a better renal function determined by a higher day 2 creatinine clearance or a lower creatinine ratio (day 2/ day 0) and a lower non-renal SOFA score after discontinuation of CRRT were independently associated with successful discontinuation of CRRT at day 7. A less positive fluid balance improved the model, but the association was not significant. With an AUC of 0.791, the discrimination of creatinine clearance was good, with an optimal cut off for successful discontinuation of 11 ml/min (95% CI 6 – 16 ml/min), and with an AUC of 0.819, the discrimination of creatinine ratio (day 2/day 0) was also good, with an optimal cut-off for successful discontinuation of 1.41 (95% CI 1.27 – 1.59) . On univariate analysis, urine output, urinary NGAL (ng/ml)/creatinine (mmol/L), duration of CRRT and vasopressor use were significantly associated with successful discontinuation, but these variables were removed in multivariate analysis. Of interest, in patients with successful discontinuation cumulative fluid balance (day 0-2) was negative, while in patients with unsuccessful discontinuation cumulative fluid balance (day 0-2) was positive, whereas the use of diuretics was not significantly different between patients exhibiting successful vs. unsuccessful discontinuation. The latter were apparently not able to remove fluid due to insufficient renal function, persistent associated organ failure or both.

Nowadays there are no guidelines on when CRRT in the ICU can be discontinued. Physicians decide on individual basis, based on bedside parameters or logistic factors, for example when the patient has to undergo a CT scan or when the circuit has to be replaced. In the present study, previously defined variables were prospectively collected from all included patients. The finding that calculated creatinine clearance from a 6-h portion was the best predictor is important because it is an easy and cheap marker and available within hours. When creatinine clearance is higher than 16 ml/min, the upper limit of the 95% confidence interval, successful discontinuation is likely. In case of doubt, when creatinine is within the 95% confidence limits, SOFA score and fluid balance can be considered. A higher SOFA score or a more positive fluid balance could be an argument for restart.

The creatinine ratio (day 2/ day 0) was also predictive, however, the multivariate model including creatinine clearance was more sensitive. Creatinine ratio is presently used to classify the severity of AKI according to the KDIGO guidelines during its development [18]. In these guidelines a creatinine ratio from 1.5 - 1.9 times baseline is defined as AKI stage 1. In the present study we found that an incremental creatinine ratio (day 2/day 0) below 1.41 discriminated for short-term successful discontinuation. Our study therefore provides practical and plausible tools for clinical decision making.

Up to now, only retrospective studies or a post hoc analysis evaluated the association between variables at discontinuation of CRRT and successful discontinuation. Urine output was the best predictor of successful discontinuation of CRRT in two studies evaluating current practice on discontinuation of CRRT [10, 11]. Only one study also evaluated the association between creatinine clearance and successful discontinuation of CRRT. This study used a 2-h creatinine clearance and found an optimal cut-off of 23 ml/min. However, this retrospective study evaluated calculated creatinine clearance in the 12 hours preceding discontinuation and did not evaluate the contribution of SOFA score to the final model. Furthermore the reasons to re-initiate RRT might have been different [13]. We prospectively confirmed that measuring creatinine clearance is the best predictor of short-term successful discontinuation.

Urinary NGAL was lower in patients with successful discontinuation, suggesting less kidney damage. However, contrary to expectation the association between urinary NGAL and successful discontinuation was non-significant in multivariate analysis. Urinary NGAL is a promising early biomarker predicting AKI and need of RRT [5, 19, 20]. When determined 24 hours after AKI diagnosis, a decline in plasma NGAL was associated with renal recovery after 48 hours [7]. Interestingly, kinetic eGFR calculation after initial resuscitation discriminated better for renal recovery from AKI without RRT than urinary biomarkers NGAL or [TIMP-2]*[IGFBP7]. Creatinine clearance, creatinine ratio (day 2/ day 0) and kinetic eGFR reflect actual renal function while NGAL and [TIMP-2]*[IGFBP7] reflect renal damage and cell cycle arrest respectively. Thus a marker of renal function seems more predictive than a marker of renal damage.

In multivariate analysis non-renal SOFA score was associated with successful discontinuation of CRRT as well, suggesting that patients with less severe illness at discontinuation of CRRT are more likely to experience successful discontinuation of CRRT. A high severity of disease has been reported as being associated with non-recovery of renal function or re-initiation of CRRT before [12, 14]. Our study is the first to evaluate the role of fluid balance as a marker of successful discontinuation. Incorporating fluid balance in the model improved its prediction, although not significantly.

Our study has several limitations, first despite screening a large group of patients receiving CRRT only a small group was included in the final analysis, mainly because of mortality during or shortly after discontinuation of CRRT, and early discharge to the ward. Therefore we compared the excluded patients who were alive and on the ICU at discontinuation with the included patients and found that in a large group of the excluded patients (38/173), CRRT was discontinued for switch to intermittent haemodialysis and not because of expected recovery of renal function. Furthermore these excluded patients had worse preadmission renal function. This may have caused bias, but these patients did not fulfil the inclusion criterion of expected renal recovery. Because of our small sample size, the multivariate model might be overfitted. However sample size calculation was based on the suggestion of Altman to include a minimum of 70 patients to evaluate 7 variables in multivariate analysis [16]. Furthermore multicollinearity between variables may have affected the results, this was tested and appeared not to be an issue. Unfortunately urinary NGAL concentrations were determined in only 63 patients, because urine production was less than 200 ml/day (which was deemed unreliable) or because of logistic reasons, such as failure to collect or store the urine portion. We cannot exclude that urinary NGAL would be predictive in a larger cohort, but the relation with creatinine clearance and creatinine ratio (day 2/day 0) seems stronger. Furthermore, if urine output is less than 200 ml/day, creatinine clearance is likely low as well. Nevertheless, the group of patients with successful discontinuation was large enough to demonstrate that creatinine clearance or creatinine ratio (day 2/ day 0) and non-renal SOFA score were significant predictors for patients still in the ICU and these relations are clinically plausible. A third limitation is that we do not have data on the day CRRT is discontinued, but on day 2 after discontinuation. The reason that we chose day 2 was that the population still in the ICU is of interest for the intensivist. Our study has several strengths, to our knowledge this is the first prospective multicentre study evaluating predictors of successful discontinuation of CRRT. Second, our study provides a practical tool for the clinician to evaluate whether discontinuation of CRRT will be successful or not, and therefore prevent potentially harmful complications associated with over- or under-treatment of CRRT.

Conclusions

The present prospective multicentre study found that a calculated 6-h creatinine clearance, a creatinine ratio (day 2/ day 0) and non-renal SOFA score at day 2 after discontinuation independently predicted short-term successful discontinuation of CRRT, while urinary NGAL did not. In our cohort, a creatinine clearance of 11 ml/min (95% CI 6 – 16 ml/min) and a creatinine ratio (day 2/ day 0) of 1.41 (1.27 -1.59) had the optimal cut-off. The study therefore provides a practical bedside tool: discontinuation of CRRT will likely be successful if creatinine clearance is more than 16 ml/min or incremental creatinine ratio (day 2/ day 0) is below 1.27, especially in patients with lower non-renal SOFA score and when fluid balance becomes negative.

Acknowledgements

We sincerely regret that Johan Groeneveld who contributed to the concept of this study has died. We miss his sharp and witty research input.

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CHAPTER 4

4

Determinants of renal function at hospital discharge of patients treated with renal replacement therapy in the intensive care unit

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Abstract

Purpose: Identification of risk factors for impaired renal function at hospital discharge in critically ill patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT).

Methods: A single-center retrospective cohort study was performed evaluating demographic and clinical parameters as potential risk factors for a modest to severely impaired renal function at hospital discharge in patients with AKI requiring RRT in the intensive care unit.

Results: Of the 353 patients in our cohort, 90 (25.5%) patients had pre-existing chronic kidney disease (CKD). An estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2 at hospital discharge occurred in 64.0% of which 63.7% without known renal impairment before hospital admission and 8.2% of all cases left the hospital dialysis-dependent. Multivariable logistic regression showed that age (OR = 1.051, P < 0.001), serum creatinine concentration at start of RRT (OR = 1.004, P < 0.001) and administration of iodine-containing contrast fluid (OR = 0.830, P = 0.045) were associated with an eGFR ≤ 60 ml/min/1.73m^2. Furthermore, a medical history of CKD (OR = 5.865, P < 0.001) was associated with dialysis dependence.

Conclusions: Elderly and patients with pre-existing CKD are at a high risk for modest to severely impaired renal function at hospital discharge after AKI requiring RRT.

Introduction

Acute kidney injury (AKI) frequently complicates the clinical course of critically ill patients admitted to an intensive care unit (ICU) and constitutes an independent predictor for patient survival [1-3]. Severe AKI requiring renal replacement therapy (RRT) occurs in about 5% of the ICU population and is, depending on the definition used, associated with a very high in-hospital mortality rate [4], ranging from 38% to 80% [5-12]. Part of this group of patients that survive their ICU stay will have permanent loss of renal function and 9% to 13.8% will remain dialysis dependent after hospital discharge [4,6].

In addition, any permanent loss of renal function will be a subsequent risk factor for progressive deterioration of renal function in the years after hospital discharge. This constitutes a substantial risk for reaching end-stage renal disease requiring RRT. In addition, any stage of chronic kidney disease (CKD), in particular when the glomerular filtration rate drops below 60 ml/min/1.73m^2 (CKD stage 3–5) has unequivocally been associated with increased mortality [13]. Therefore, the degree of renal recovery in RRT-requiring critically ill patients that survive their hospital stay is of pivotal importance for renal and overall survival thereafter.

In AKI survivors, risk factors associated with progression to CKD after hospital discharge have been identified and include advanced age, diabetes mellitus, decreased baseline glomerular filtration rate and the severity of AKI [14]. However, besides pre-existing CKD it is not well known which factors predict renal function at hospital discharge [15,16]. In particular, little is known about the factors that are associated with the degree of CKD at hospital discharge in RRT-requiring ICU patients. This group of patients will be at a particular high risk for incomplete recovery of renal function and will probably benefit most from any treatment strategies that can promote renal recovery or at least protect the kidneys from further injury. Therefore, identification of clinical determinants related to the degree of CKD at hospital discharge may be of potential use to develop such strategies.

In the present study, the clinical determinants for the degree of CKD at hospital discharge in a large group of critically ill patients treated with RRT during their ICU stay were analyzed.

Materials and methods

Setting

The data were obtained from a retrospective cohort study involving patients from the ICU of a large tertiary care center (Erasmus Medical Center in Rotterdam, the Netherlands). Patients with AKI requiring RRT were treated with continuous arteriovenous haemodialysis or with continuous venovenous haemofiltration. Intermittent haemodialysis is not used in the Erasmus Medical Center for the treatment of AKI in the ICU setting. RRT was prescribed by the attending nephrologist and delivered by the hemodialysis nursing team.

Study population

All consecutive admitted critically ill patients, treated with continuous renal replacement therapy (RRT) between January 1994 and April 2010, were evaluated. Patients with end-stage renal disease dependent on RRT, patients with a kidney transplant and patients with another solid organ transplantation were excluded. The recently published Kidney Disease: Improving Global Outcome serum creatinine criteria were used to evaluate the presence of AKI [17]. Furthermore, for the sake of homogeneity patients with acute vasculitis, glomerulonephritis, interstitial nephritis or thrombotic microangiopathy were excluded and only patients with presumed isolated acute tubulus necrosis were included for analysis. Clinical and demographical data were collected consisting age, sex, comorbidity, cause of AKI, kind of ICU admission, primary indication for ICU admission, non-renal SOFA score, administrations of intravenous iodine-containing contrast during hospital admission and length of ICU stay. Serum creatinine concentrations were determined at baseline (1-6 months before hospital admission), hospital admission, at start of RRT and at hospital discharge. Serum creatinine concentrations at baseline and hospital discharge were used to calculate the estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula [18]. We did not calculate the eGFR from the serum creatinine concentrations at hospital admission or at the time of start RRT as the renal function was not stable and essentially unknown at these time-points. The patients were grouped according to their eGFR at baseline and at discharge from the hospital based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for staging the degree of loss of renal function [19]. Patients were categorized to a separate RRT group if they remained dialysis dependent for at least 3 months and were subsequently registered in RENINE (Dutch abbreviation for REgistratie NIerfunctievervanging NEderland), the Dutch national database for patients on chronic RRT. For statistical analysis, a cutoff eGFR $\leq$ 60 ml/min/1.73m^2 was selected because below this value there is a graded association between eGFR and mortality, cardiovascular events and hospitalization [13]. This study was approved by the medical ethical review board of the Erasmus Medical Centre, which waived the requirement of informed consent, because of its retrospective nature.

Definitions

AKI was defined as an absolute increase in serum creatinine $\geq$ 26.5 µmol/L within 48 hours or a 50% increase in serum creatinine within 7 days before RRT initiation. Owing to the need for dialysis, patients that met the criteria were considered AKI stage 3 [17].

The patient charts were used to identify whether patients were known to have pre-existing CKD or comorbidity like diabetes mellitus, hypertension, or cardiovascular disease. Pre-existing CKD was defined as any documented impairment of renal function within the year before admission to the ICU or a known baseline eGFR $\leq$ 60 ml/min/1.73m^2. Renal function in patients not documented with pre-existing CKD was considered normal. The cause of AKI was categorized as: sepsis, ischemia, drug-associated and other. Sepsis was

defined as the presence of symptoms of systemic inflammatory response syndrome in combination with the persistence of a documented or presumed infection leading to AKI. Ischemia was defined as AKI due to circulatory dysfunction leading to hypotension and ischemia. All patients suffering from AKI due to toxic drugs, contrast and other chemicals that are toxic to the kidney were categorized within the " drug-associated" group. Patients that experienced an episode of AKI due to any other cause then aforementioned, including rhabdomyolysis, tumor lysis syndrome and hemolysis elevated liver enzymes and low platelets (HELLP) syndrome were categorized within the " other" group.
The indication for ICU admission was categorically grouped as: sepsis, thoracic surgery (all surgical interventions within the thoracic cavity), cardiac disease/fluid overload, postoperative other, other/intoxication and traumatic injury.
During hospital admission all radiological investigations with intravenous iodine-containing radiopaque contrast were registered, consisting of computed tomographic scans and cardiac catheterizations.

Statistical analysis

Continuous parameters were expressed as mean ± SD and compared by the Student T-test. Categorical parameters were expressed as number and percentage and compared by χ2-test. A predefined set of variables was chosen for analysis of association with eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge (only including patients without CKD). These variables were: age, sex, diabetes mellitus, hypertension, cardiovascular disease, cause of AKI, kind of ICU admission (surgical/medical), length of ICU stay, non-renal SOFA score, the number of administrations with intravenous iodine-containing radiological contrast, the serum creatinine concentration at admission to the ICU and at the start of RRT. Parameters with an unadjusted P ≤ 0.1 were included in a multivariable logistic regression for the outcome of an eGFR ≤ 60 at hospital discharge. Irrespective of P-value the demographic data age and sex were included in the multivariable analysis. Furthermore, all multivariable analyses were adjusted for the year when RRT was performed. Where analysis on eGFR at hospital discharge only included patients with a considered normal baseline renal function, a similar analysis on dialysis dependence at hospital discharge was performed including patients with pre-existing CKD.
Statistical significance was defined as a 2-tailed P ≤ 0.05. Analyses were performed with statistical software SPSS version 19.0, copyright 1989, 2010 SPSS Inc (Chicago, IL), an IBM company.

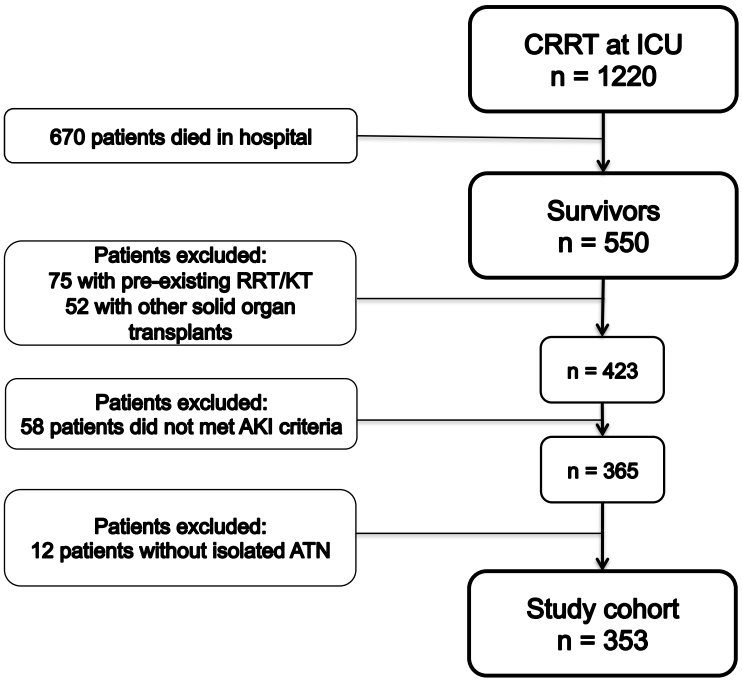
Results

Study population and eGFR at hospital discharge

A total of 1220 patients treated with continuous RRT during ICU admission were recruited. Of these, 670 patients died in hospital yielding an in-hospital mortality rate of

54.9%. Patients that died during hospital admission were excluded for further analysis. After exclusion of patients with RRT, kidney transplant or any other kind of solid organ transplantation, 423 patients remained of which 365 met the AKI criteria. Furthermore, 12 patients were excluded without isolated acute tubulus necrosis (Figure 1). Ninety patients (25.5%) of the 353 patients in the study cohort were known with pre-existing CKD. Clinical characteristics for this study population are given in Table 1. The most common cause of AKI was ischemia (55.2%), followed by sepsis (31.2%), drug-associated (9.1%) and 4.5% of the patients had another cause of AKI. The main reason for admitting patients to the ICU was thoracic surgery (32.9%), followed by other/intoxication (17.3%), sepsis (16.7%), cardiac disease/fluid overload (13.0%), post-operative other (16.1%) and trauma (4.0%).

Figure 1 Flowchart of study population



Patients treated with continuous renal replacement therapy (CRRT) in the intensive care unit (ICU) within the period 1994–2010. The study cohort consists of patients that are discharged from the hospital with exclusion of patients with pre-existing RRT, kidney transplantation (KT), any other solid organ transplantation, patients that did not meet the Kidney Disease: Improving Global Outcome (KDIGO) acute kidney injury (AKI) criteria or patients without isolated acute tubulus necrosis (ATN).

Baseline serum creatinine values were available in 119 cases (33.7%). The mean baseline serum creatinine was 140.7 µmol/L, which is caused by the overrepresentation of patients known with CKD within this group (67/119). At hospital admission, at start of RRT and

at hospital discharge serum creatinine values were 206.5, 496.7 and 175.4 µmol/L, respectively.

Table 1 Clinical and demographical characteristics of study population

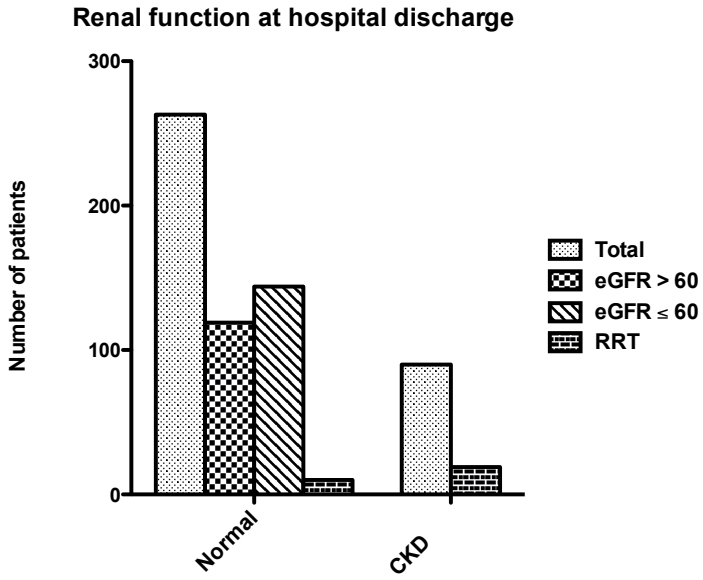
Number of patients	353
Age (y)	59.5 ± 14.9
Sex (male)	241 (68.3)
Medical history	
Chronic kidney disease	90 (25.5)
Diabetes Mellitus	90 (25.5)
Cardio vascular disease	199 (56.4)
Hypertension	110 (31.2)
Cause of AKI	
Sepsis	110 (31.2)
Ischemia	195 (55.2)
Drug-associated	32 (9.1)
Other	16 (4.5)
Surgical/Medical (surgical)	240 (68.0)
Indication for ICU admission	
Sepsis	59 (16.7)
Thoracic surgery	116 (32.9)
Cardiac disease/fluid overload	46 (13.0)
Post-operative other	57 (16.1)
Other/intoxication	61 (17.3)
Trauma	14 (4.0)
Sofa score*	8.2 ± 3.5
Length of ICU stay (d)	29.5 ± 28.4
Serum creatinine (µmol/L)	
Baseline**	140.7 ± 99.2
Hospital admission	206.5 ± 172.8
Start RRT	496.7 ± 190.8
Hospital discharge	175.4 ± 149.4
eGFR (ml/min/1.73m^2)	
Hospital discharge	59.0 ± 51.5
Iodine-containing contrast fluid (administrations)	1.5 ± 2.0
RRT dependent at hospital discharge	29 (8.2)

Categorical variables are expressed as the number of patients and percentage; continuous variables are expressed as mean and standard deviation (SD), where appropriate. AKI = acute kidney injury; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

*Only available in 137 patients **Only available in 119 patients

Of all patients 18.1% left the hospital with an eGFR ≥ 90 ml/min/1.73m^2, 17.8% with an eGFR between 60 and 90 ml/min/1.73m^2, 32.9% with an eGFR between 30 and 60 ml/min/1.73m^2, 17.0% with an eGFR between 15 and 30 ml/min/1.73m^2, 5.9% with an eGFR ≤ 15 ml/min/1.73m^2 without the need of dialysis at hospital discharge and 8.2% while being treated with intermittent hemodialysis. In total, 226 (64.0%) left the hospital with an eGFR ≤ 60 ml/min/1.73m^2 of which 144 (63.7%) were not known with renal impairment before hospital admission. Of all patients with pre-existing CKD, 21.1% left the hospital dialysis-dependent. This group constituted 65.5% of the total number of patients dependent on dialysis at discharge from the hospital (Figure 2). Of the 119 patients with a known baseline eGFR, 67 patients (56.3%) returned to their original class of eGFR, while 52 patients (43.7%) showed significant loss of eGFR resulting in dialysis dependence in 14.3%. Within this latter group of 52 patients, 51.9% were known with CKD.

Figure 2 Renal function at hospital discharge stratified by pre-existing kidney disease



Number of patients categorized by renal function at hospital discharge (total, eGFR (estimated glomerular filtration rate) > 60 ml/min/1.73m^2, eGFR ≤ 60 ml/min/1.73m^2, renal replacement therapy (RRT).

Determinants of renal function at hospital discharge

Univariable analysis of the clinical parameters for their relation with an eGFR ≤ 60 ml/min/1.73m^2 at the time of hospital discharge identified an association for age, cardiovascular disease, hypertension, length of ICU stay, serum creatinine concentration

at hospital admission and at start of RRT and administration of iodine-containing contrast fluid (Table 2).

Table 2 Univariable analysis of the association between clinical variables and eGFR ≤ 60 ml/min/1.73m^2 at time of discharge from the hospital

	Odds ratio (eGFR ≤ 60)	95%-CI	P-value
Age (y)	1.044	1.026 – 1.063	<0.001
Sex (Male)	1.462	0.854 – 2.503	0.166
Medical history			
Diabetes Mellitus	1.248	0.655 – 2.343	0.490
Cardio vascular disease	1.967	1.202 – 3.219	0.007
Hypertension	2.167	1.180 – 3.891	0.013
Cause of AKI			
Sepsis	0.750	0.449 – 1.254	0.273
Ischemia	1.360	0.835 – 2.213	0.217
Drug-associated	1.082	0.457 – 2.563	0.858
Other	0.709	0.152 – 1.154	0.519
Surgical/Medical (surgical)	0.924	0.249 – 2.015	0.768
Sofa score	0.931	0.836 – 1.037	0.193
Length of ICU stay (d)	0.987	0.978 – 0.996	0.006
Serum creatinine (µmol/L)			
Hospital admission	1.002	1.000 – 1.003	0.030
Start RRT	1.002	1.001 – 1.004	0.001
Iodine-containing contrast fluid (administrations)	0.797	0.699 – 0.909	0.001

AKI = acute kidney injury; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

After multivariable analysis, three parameters remained associated with an eGFR ≤ 60 ml/min/1.73m^2 at time of hospital discharge (Table 3); age (OR = 1.051, P < 0.001), serum creatinine concentration at start of RRT (OR = 1.004, P < 0.001), and administration of iodine-containing contrast fluid (OR = 0.830, P = 0.045).

Table 3 Multivariable logistic regression analysis for the association between clinical variables and eGFR ≤ 60 ml/min/1.73m^2 at time of discharge from the hospital

	Odds ratio (eGFR ≤ 60)	95%-CI	P-value
Age (y)	1.051	1.028 – 1.076	<0.001
Serum creatinine at start of RRT (µmol/L)	1.004	1.002 – 1.006	<0.001
Iodine-containing contrast fluid (administrations)	0.830	0.692 – 0.996	0.045

eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

A multivariable regression analysis for the outcome dialysis dependence at discharge from the hospital revealed that only a medical history of CKD (OR = 5.865, P < 0.001) was associated, but the age of the patient and the serum creatinine concentration at start of RRT lost its predictive value.

Discussion

This is the first study that reports on risk factors in critically ill patients with RRT-requiring AKI for an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge. We found within this cohort that age and serum creatinine concentration at start of RRT were the major independent predictors for a modest impaired eGFR at hospital discharge. The independent predictor for dialysis dependence at hospital discharge was a medical history of CKD. In addition, our results clearly show that AKI requiring RRT in critically ill patients has a major impact on eGFR at hospital discharge. Only 45% of the surviving patients with a normal renal function before hospital admission left the hospital with an eGFR < 60 ml/min/1.73m^2, which may even be an overestimation, as serum creatinine levels will probably be lowered because of loss of muscle mass.

The overall in-hospital mortality rate was 54.9%, which is comparable to previous reports [5-12]. Among survivors, 29 patients (8.2%) left the hospital while being dependent on chronic RRT, which is also in accordance with the results from other studies [4,6,20]. Of this group about 2 out of 3 patients were known with pre-existing CKD and more than one fifth of the patients with pre-existing CKD needed further RRT at hospital discharge. These findings were reflected by a high OR for dialysis dependence at hospital discharge (OR = 5.9) in association with pre-existing CKD.

AKI leading to RRT is the most severe form of acute kidney injury but a number of studies have pointed out that AKI of any stage has a major impact on subsequent renal function and survival [21-27]. In addition, the outcome of patients with pre-existing CKD who have survived RRT at the ICU will probably be even worse as recent studies have shown that a pre-existing impairment of kidney function has a major impact on the patient's prognosis [20,28,29]. For instance, 2 large cohort studies showed that patients with known CKD

that suffered from AKI in an ICU had a significantly higher risk for mortality and chronic dialysis dependence compared to patients without renal impairment before hospital admission [28,29]. One of these studies identified CKD itself as a strong risk factor for the development of AKI [29]. Thus, these patients are not only at a high risk to develop AKI but also have a much higher risk for being dialysis dependent at discharge from the hospital. Given our data, it is necessary that critically ill with CKD should be monitored closely to protect their renal function as much as possible.

Besides the major effect of age on renal function (OR = 1.051), another interesting finding is the association between serum creatinine concentration at the time of RRT initiation and an eGFR ≤ 60 ml/min/1.73m^2 at time of hospital discharge (OR = 1.004). Of course the renal function reflected by serum creatinine concentration at the initiation of RRT is unknown and the actual GFR may be close to zero. However, serum creatinine concentration may be a reflection of the timing of RRT in these patients and it might be that an early initiation of RRT is beneficial. To the best of our knowledge there are no studies on timing of RRT and association with deterioration in renal function as outcome, but there are studies that focused on dialysis dependency at hospital discharge. Two recent meta-analyses showed that early initiation of RRT is associated with a trend to better renal outcome [30,31]. However both meta-analyses mentioned that the studies included used many different definitions of " early versus late" initiation of RRT. Our data cannot provide the answer to this intriguing possibility as, e.g., it is possible that patients that received early treatment would also recover renal function with conservative therapy and had a less severe hit of AKI leading to a better renal function at hospital discharge.

In our study, none of the underlying causes of AKI represented an independent predictor. However, several studies have suggested a trend towards better renal recovery and dialysis free survival in patients suffering from septic AKI in comparison to those who suffered from other causes [32-34]. For instance, a study by Bagshaw et al demonstrated that patients suffering from septic AKI left the hospital with a lower serum creatinine (106 vs 121 µmol/L, P = 0.01) and dialysis dependence (9% vs 14%, P = 0.52) compared to non-septic AKI patients [33]. In our study, AKI caused by sepsis had a trend towards a better prognosis in the univariable statistical analysis (OR < 1), but these results were not statistical significant. Therefore, further research on this particular subject seems necessary before firm conclusions can be drawn.

We included the number of investigations involving intravenous iodine-containing contrast fluid in our model as this represents a potential nephrotoxic factor. Taking into count the retrospect nature and long-term observation period the data obtained have a limited level of detail, as we could not document the full amount of iodine containing contrast fluid administered. Remarkably, we found a significant tendency to an OR < 1 for the relation between the contrast dose a patient received during hospital admission and an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge. A possible explanation might be that patients with limited renal recovery after RRT in the ICU were considered to have a

contraindication for contrast to protect their residual renal function and therefore ruled out for radiologic investigations involving iodine-containing contrast fluid. Furthermore, it may be a reflection of overall clinical condition. The possibility exists that patients with a better clinical condition were more likely to undergo an investigation with contrast fluid, because they were stable enough for transportation to, for instance, a computed tomographic unit.

Our study has several important limitations. First, the data are collected in a single tertiary care center, which can make the results less transposable to other clinical situations. However, as mentioned before, the overall mortality of patients and the percentage of patients receiving RRT after hospital discharge are remarkably similar to previous studies. This supports the notion that the data of the present study may represent common associations and risk factors for the degree of CKD in patients surviving RRT at the ICU.

Additionally, the present study has a long recruitment period, which may bias the results. Therefore, all multivariable analyses are adjusted for the year when RRT was performed.

The patient group categorized as having no CKD was defined by the absence of documented impairment of renal function. We cannot account for the possibility that some patients with CKD previously unknown were also included, as we were only able to find baseline serum creatinine levels in the minority of patients. Given these limitations, it was clear that pre-existing CKD is a major risk factor for chronic dialysis dependence after hospital discharge.

Furthermore, we used the eGFR at hospital discharge as the primary outcome in this study, which is not a fixed time point and therefore could bias the results. However, a fixed time point has several disadvantages. Some patients could still be in the ICU while others were already discharged at a certain time point and therefore are less comparable. We think that measuring outcome at hospital discharge is a valid point in time as from this point patients are considered clinically stable and decisions are made regarding their follow-up at the outpatient clinic. Our results indicate that at least nephrological care is mandatory in the majority of patients.

Conclusions

Only a minority of patients that survive an episode of AKI requiring RRT have a normal renal function at time of hospital discharge. The elderly patient and particular the patient with pre-existent CKD runs a high risk for modest to severely impaired renal function at hospital discharge. This will have a major negative effect on quality of life and life expectancy. Therefore, these patients should be monitored closely and every effort should be made to conserve residual renal function. After discharge from the hospital, close observation of the renal function by a nephrologist seems warranted in most patients.

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PART B

Long-term outcome

CHAPTER 5

5

Predictors of 90-day restart of renal replacement therapy after discontinuation of continuous renal replacement therapy, a prospective multicentre study

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Abstract

Background: Restart of renal replacement therapy (RRT) after initial discontinuation of continuous renal replacement therapy (CRRT) is frequently needed. The aim of the present study was to evaluate whether renal markers after discontinuation of CRRT can predict restart of RRT within 90 days.

Methods: Prospective multicentre observational study in 90 patients, alive, still on the ICU at day 2 after discontinuation of CRRT for expected recovery with urinary NGAL available. The endpoint was restart of RRT within 90 days. Baseline and renal characteristics were compared between outcome groups no restart or restart of RRT. Logistic regression and Receiver Operator Characteristic curve analysis were performed to determine the best predictive and discriminative variables.

Results: Restart of RRT was needed in 32/90 (36%) patients. Compared to patients not restarting, patients restarting RRT demonstrated a higher day-2 urinary NGAL, lower day-2 urine output and higher incremental creatinine ratio (day-2/day-0). In multivariate analysis only incremental creatinine ratio (day-2/day-0) remained independently associated with restart of RRT (OR 5.28, 95% CI 1.45 – 19.31, p = 0.012). The area under curve (AUC) for incremental creatinine ratio to discriminate for restart of RRT was 0.76 (95% CI 0.64 – 0.88). The optimal cut-off was 1.49 (95% CI 1.44 – 1.62).

Conclusion: In this prospective multicentre study, incremental creatinine ratio (day-2/day-0) was the best predictor for restart of RRT. Patients with an incremental creatinine ratio at day 2 of 1.5 times creatinine at discontinuation are likely to need RRT within 90 days. These patients might benefit from nephrological follow up.

Introduction

Acute kidney injury (AKI) is a common complication of critical illness. If renal replacement therapy (RRT) is required, patients have excess mortality even when adjusted for severity of disease [1-4]. Among survivors, renal function might not recover and patients may sooner or later need chronic RRT. Currently, no clinical characteristics or biomarkers are known to predict restart of RRT. Identification of patients at risk and close nephrological follow-up may be important to take preventive measures and restart RRT timely.
Neutrophil gelatinase-associated lipocalin (NGAL) at ICU admission has high potential as predictor for AKI [5-11] and need of CRRT [9, 12-14]. After renal injury, NGAL is secreted into blood and urine within 2 hours [15], whereas the rise in creatinine takes days. While serum creatinine is a marker of renal function, NGAL reflects renal injury. Evaluation of NGAL at ICU admission as a predictor for dialysis dependency *after* an episode of AKI has shown disappointing results [16, 17]. However different types of NGAL and commercial kits for determination of NGAL are available and therefore results might not be comparable. Only a few studies evaluated NGAL later during ICU admission. In patients after out-of-hospital-cardiac-arrest, NGAL at day 2-3 was better associated with AKI and mortality than NGAL at admission [5, 18]. In sepsis, NGAL at day 7 was associated with 28-day mortality [12]. However, NGAL after discontinuation of CRRT and its association with restart of RRT was not tested. We previously found that incremental creatinine ratio after discontinuation, but not urinary NGAL was independently associated with short-term successful discontinuation of CRRT (no restart of RRT for 7 days) [19] However, identification of the patients at risk for long-term restart is also important because these patients need close nephrological follow-up after ICU discharge to take protective measures for the kidney, adjust medications and delay restart or prepare the patient for chronic dialysis.
The aim of this study was to evaluate whether urinary NGAL, urine output and incremental creatinine ratio measured after discontinuation of CRRT can predict restart of RRT within 90 days.

Methods

Study design

We performed a prospective multicentre observational study in 4 ICUs in the Netherlands (additional file 1) to evaluate short-term (7-day) [19] and long-term (90-day) predictors of restarting RRT after initial discontinuation for expected renal recovery. Patients were included from May 2013 until September 2015. The protocol was approved by the medical ethics committee of Erasmus Medical Centre and local medical ethical committees of participating centres. Written informed consent was obtained from all participants or legal representatives.

Study endpoint

The endpoint of study was restart of RRT within 90 days after initial discontinuation of CRRT for AKI.

Patients

All patients, aged 18 years or older, alive and still on the ICU at day 2 after discontinuation of CRRT for renal reasons with expected renal recovery, excluding patients in whom CRRT was discontinued for logistic reasons, such as a CT scan or operation, patients with known end-stage-renal-disease (CKD-5) and those in whom CRRT was discontinued to switch to intermittent haemodialysis, were screened for inclusion. Patients discharged from the ICU before day 2 after discontinuation of CRRT were excluded, because day 2 study variables could not be reliably collected.

Study protocol and measurements

The decision to initiate, discontinue or restart RRT was made by the attending team of physicians and was not defined by protocol. Reason was that there is no consensus and there are no guidelines for restart of RRT. This decision is generally based on a combination of reasons. CRRT was performed according to the local protocol of the hospital as CVVH or CVVHD, delivered dose was 20-35 ml/kg/hour. Day 0 was defined as the first 6 a.m. after discontinuation of CRRT. At day 2 after initial discontinuation of CRRT three renal markers were determined: urinary NGAL, urine output and the incremental creatinine ratio between day 2 and day 0 (at discontinuation) (creatinine day 2/day 0), and the non-renal SOFA score. The assay for determination of urinary NGAL is specified in additional file 1.

We additionally collected: age, sex, weight, BMI, preadmission eGFR (calculated with CKD-EPI formula [20]), history of chronic kidney disease (CKD) and other co-morbidities, reason for ICU admission, disease severity scores (Acute Physiology And Chronic Health Evaluation (APACHE) III, Simplified Acute Physiology Score (SAPS) III), cause of AKI, main reason for restart and use of diuretics (day 0-2), radiocontrast agents or nephrotoxic medication (day 0-7). Nephrotoxic medication was scored according to the local pharmacological guide and a list of this medication is added in additional file 2.

Statistical analysis

Sample size calculation was based on an expected incidence of restart of RRT of 30% [21]. To evaluate the prediction of the renal markers (urinary NGAL, urine output and incremental creatinine ratio (day 2/ day 0)), we aimed to include 90 patients using the number of events/10 rule. Patients not restarting RRT were compared to patients restarting temporary or chronic RRT within 90 days. Variables were tested for normal distribution using the Shapiro-Wilk test. Continuous variables are expressed as mean (standard deviation) or median [25th and 75th percentile] and categorical data as number

and percentage. Unpaired Student's t-test, Mann-Whitney-U test or Chi-square test was used, where appropriate. Statistical significance was defined as $p < 0.05$. To assess the relation between renal markers and other potential predictors of restarting RRT within 90 days, univariate analysis was performed. Subsequently, multivariate analysis was performed, including the three above defined renal markers alone, and after adjustment for preadmission eGFR and non-renal SOFA score. We also performed a sensitivity analysis including the patients with missing NGAL concentrations and determined the relation between the main reasons for restart and the three renal predictors at day 2. For all analyses, multicollinearity was checked with a maximum variance inflation factor (VIF) of 10.

A ROC curve was drawn for the best discriminative variable for restart of RRT. The area under the receiver operator characteristic curve (AUROC) was calculated to discriminate for restart of RRT. The Youden index was calculated to determine the optimal cut-off to discriminate for restart of RRT. The 95% confidence interval (CI) for the optimal cut-off was calculated using bootstrapping with 1000 random samples using the bias corrected and accelerated method.

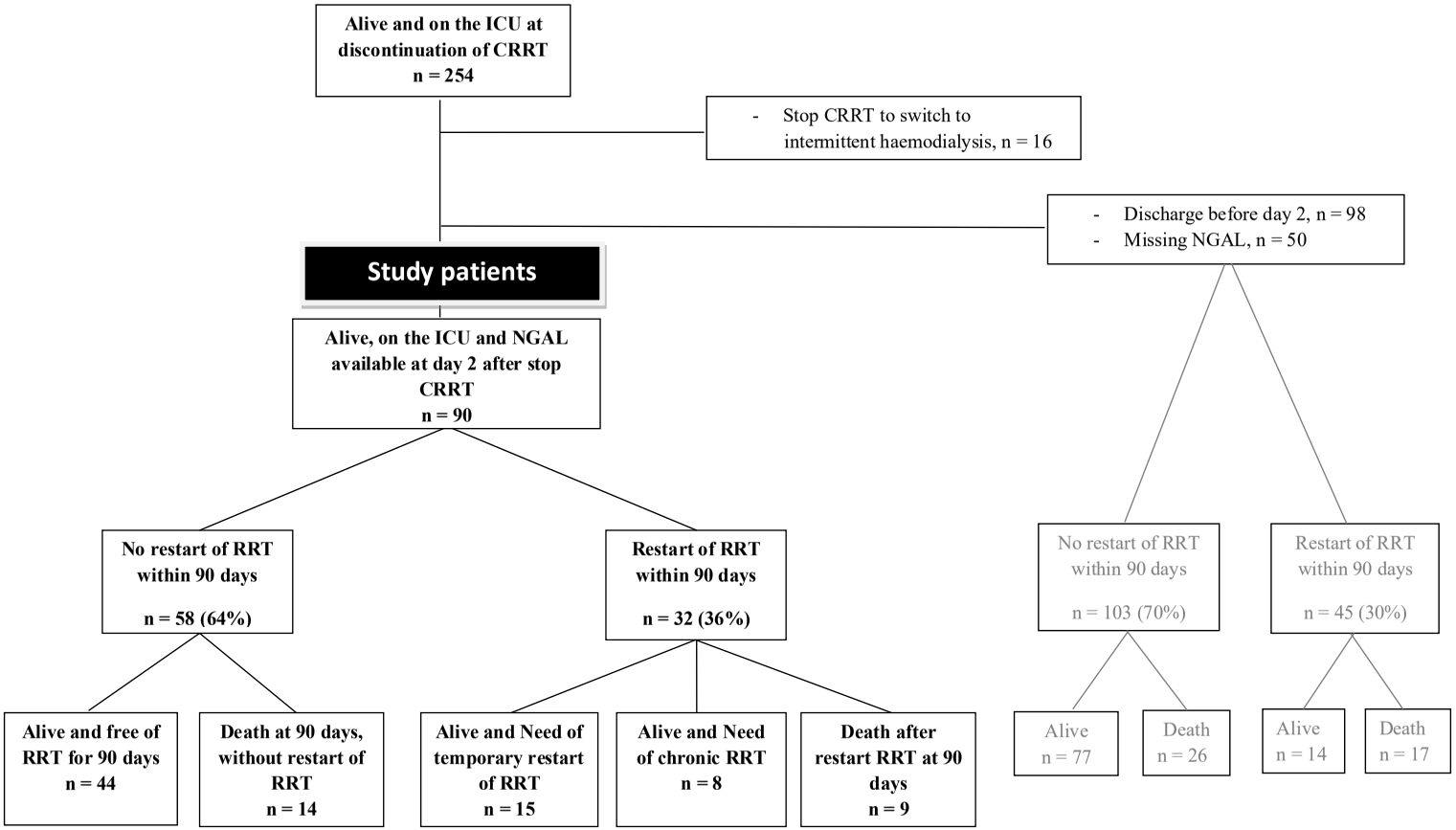
Results

Of the 254 patients on the ICU at discontinuation of CRRT, 90 patients were alive, still at the ICU and had urinary NGAL determined on day 2 after discontinuation of CRRT (see figure 1). Of these 90 patients, 32 (36%) patients restarted RRT, while 58 (64%) did not restart RRT within 90 days after initial discontinuation. Among the 32 patients restarting RRT, 15/32 only temporary needed RRT, whereas 8/32 became dependent of chronic RRT. Nine of these 32 patients died after restarting RRT.

11/32 patients restarted RRT because of fluid overload, 6/32 restarted RRT because of oliguria, 14/32 restarted RRT because of azotaemia or a rise in creatinine and 1/32 restarted RRT because of hyperkalaemia. Among the 58 patients not restarting RRT 14 patients died within 90 days. The clinical course of the 90 study patients and associated NGAL concentrations are shown in figure 2.

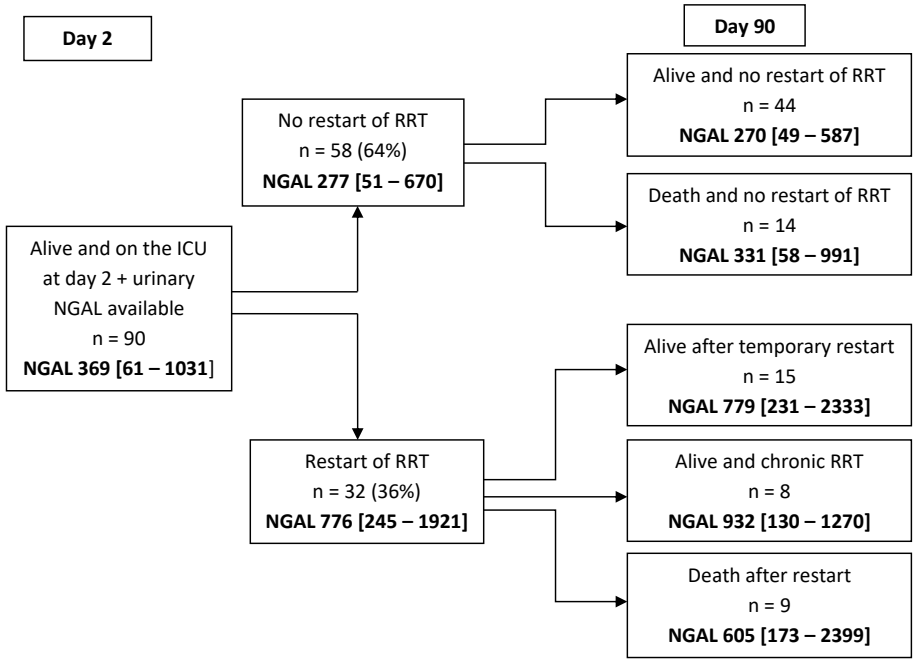
RRT was restarted at a median of 4 [3 – 10] days, range 2 - 50. In 11/32 patients RRT was restarted more than 7 days after discontinuation of CRRT and in 6/32 patients RRT was restarted after ICU discharge (range 1 - 41 days after ICU discharge). The cumulative number of patients restarting RRT after initial discontinuation of CRRT is shown in figure 3. In the majority of patients RRT was restarted within 18 days. Among the 148 excluded patients (because of discharge from the ICU before day 2 after discontinuation of CRRT (N = 98) or because of missing NGAL (N = 50)), 45 (30%) restarted RRT within 90 days.

Figure 1 Flowchart



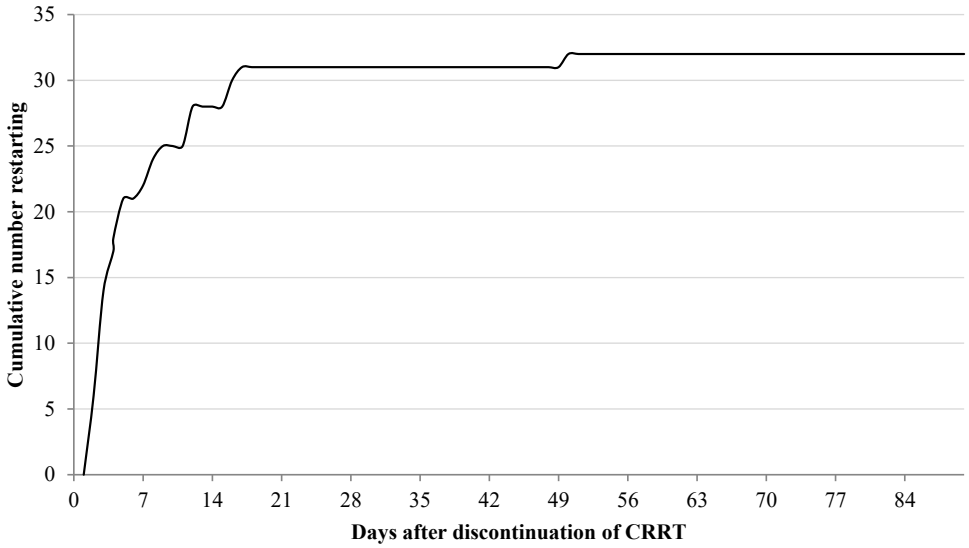
ICU, intensive care unit; CRRT, continuous renal replacement therapy; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy

Figure 2 Clinical course of the study patients and associated NGAL concentrations



NGAL, neutrophil gelatinase-associated lipocalin, NGAL results in median [25th – 75th percentile], ICU, intensive care unit; RRT, renal replacement therapy; NGAL is expressed in ng/ml.

Figure 3 Cumulative number of patients restarting RRT



RRT, renal replacement therapy; CRRT, continuous renal replacement therapy

To assess characteristics of patients restarting RRT, this group was compared to patients not restarting RRT within 90 days after initial discontinuation of CRRT. Characteristics of these groups are presented in table 1 and were not different.

Table 1 Patient and disease characteristics of the patients according to restart of RRT within 90 days or not

	No restart of RRT, n = 58	**Restart of RRT, n = 32**	**P-value**
Age, years	61 [51 - 70]	60 (15)	0.610
Male gender, nr (%)	39 (67)	21 (66)	0.876
Weight, kg	81 (14)	83 (19)	0.646
BMI, kg/m^2	25.4 [23.1 – 29.8]	26.6 (5.7)	0.830
History kidney disease, nr (%)	11 (19)	11 (34)	0.103
Hypertension, nr (%)	19 (33)	9 (28)	0.649
Diabetes Mellitus, nr (%)	8 (14)	6 (19)	0.535
History of malignancy, nr (%)	16 (28)	8 (25)	0.722
History of cardiovascular disease, nr (%)	21 (36)	15 (47)	0.323
History of Pulmonary disease, nr (%)	13 (22)	11 (34)	0.219
Reason ICU admission, nr (%)			
Post-operative	18 (31)	12 (37)	0.684
Respiratory failure	8 (14)	4 (13)	
Sepsis	8 (14)	7 (21)	
Post cardiac arrest	8 (14)	4 (13)	
Cardiac failure	9 (15)	4 (13)	
Other	7 (12)	1 (3)	
Cause of AKI, nr (%)			
Sepsis	16 (27)	13 (41)	0.103
Intrinsic	0 (0)	2 (6)	
Toxic	3 (6)	2 (6)	
Ischemic/ Other	39 (67)	15 (47)	
SAPS III at ICU admission	52 (16)	56 (17)	0.313
APACHE III at ICU admission	87 (32)	88 (36)	0.901
Diuretic use day 0-2	44 (76)	25 (81)	0.607
Contrast or nephrotoxic medication day 0-7	54 (93)	28 (88)	0.359

Mean (standard deviation) for normally distributed variables, median [25th – 75th percentile] for non-normally distributed variables, number (percentage) when appropriate. BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; ICU, intensive care unit; AKI, acute kidney injury; SAPS III, simplified acute physiology score; ICU, intensive care unit; APACHE III, acute physiology and chronic health evaluation score.

Potential predictors of restarting RRT within 90 days after initial discontinuation of CRRT

Compared to patients not restarting RRT, patients restarting RRT had a higher day 2 urinary NGAL 776 [245 – 1921] ng/ml vs. 277 [51 - 670] ng/ml, p = 0.005, a lower day 2 urine output 1.783 (1.263) L vs. 2.503 (1.231) L, p = 0.015 and higher incremental creatinine ratio (day 2/day 0) 1.64 [1.52– 1.75] vs. 1.26 [1.01 – 1.46], p < 0.001. Day 2 non-renal SOFA score and preadmission eGFR were not significantly different between groups (table 2).

Table 2 Comparison of potential predictors according to restart within 90 days or not

	No restart of RRT, n= 58	Restart of RRT n = 32	P-value
Study variables			
Day 2 urinary NGAL, ng/ml (n = 90)	277 [51 -670]	776 [245 – 1921]	0.005
Day 2 urine output, liters (n = 81)	2.503 (1.231)	1.783 (1.263)	0.015
Day 2/0 incremental creatinine ratio (n = 81)	1.26 [1.01 – 1.46]	1.64 [1.52 – 1.75]	<0.001
Confounders			
Day 2 non-renal SOFA (n = 82)	4 [2 - 6]	5 (3)	0.883
Preadmission eGFR (CKD-EPI), (ml/min/1.73m^2) (n = 85)	67.1 (25.4)	69.0 [41.2 – 91.7]	0.754

Median [25th – 75th percentile] for continuous variables, number (percentage) when appropriate. NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; RRT, renal replacement therapy; NGAL is expressed in ng/ml.

Regression analysis of potential predictors of restarting RRT

In univariate regression analysis, we found a significant association between restarting RRT within 90 days and lower day 2 urine output (OR 0.60, 95% CI 0.39 – 0.92, p = 0.020), higher incremental creatinine ratio (day 2/day 0) (OR 5.15, 95% CI 1.42 – 18.69, p = 0.013) and a trend for higher day 2 urinary NGAL (OR 1.00, 95% CI 1.00 – 1.00, p = 0.053) (table 3).

Table 3 Univariate analysis of potential predictors of restart of RRT within 90 days

	OR	95% CI	P-value
Urinary NGAL ng/ml (day 2)	1.00	1.00 – 1.00	0.053
Urine output (L) (day 2)	0.60	0.39 – 0.92	0.020
Creatinine ratio (day 2/ day 0)	5.15	1.42 – 18.69	0.013
Non-renal SOFA score (day 2)	0.98	0.84 – 1.15	0.828
Preadmission eGFR	1.00	0.98 – 1.02	0.883

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; NGAL is expressed in ng/ml.

In multivariate regression analysis, only incremental creatinine ratio (day 2/day 0) remained significantly associated with restarting RRT within 90 days (OR 5.28, 95% CI 1.45 – 19.31, p = 0.012) (table 4a).

Table 4a Multivariate analysis of variables associated with restart of RRT within 90 days (n = 90)

	OR	95% CI	P-value
Step 1			
Urinary NGAL (day 2)	1.00	1.00 – 1.00	0.724
Urine output (day 2)	0.77	0.47 – 1.25	0.286
Creatinine ratio (day 2/day 0)	3.94	1.03 – 15.00	0.045
Step 2			
Urine output (day 2)	0.75	0.47 – 1.19	0.221
Creatinine ratio (day 2/day 0)	4.05	1.06 – 15.41	0.040
Step 3			
Creatinine ratio (day 2/day 0)	5.28	1.45 – 19.31	0.012

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval.
Variables included: primary analysis: urinary NGAL (day 2), urine output (day 2), creatinine ratio (day 2/day 0) as confounders: preadmission eGFR, non-renal SOFA score (day 2)

We performed a sensitivity analysis also including the patients with missing urinary NGAL. Among the 140 patients in this group, 52 patients (37%) restarted RRT, 88 patients (63%) did not restart RRT. Also in this analysis only incremental creatinine ratio (day 2/ day 0) remained significantly associated with restarting RRT within 90 days (OR 5.45, 95% CI 1.87 – 15.88, p = 0.002) (table 4b).

Table 4b Multivariate sensitivity analysis of variables associated with restart of RRT within 90 days including the patients with missing NGAL (n = 140)

	OR	95% CI	P-value
Step 1			
Urine output (day 2)	0.79	0.53 – 1.19	0.258
Creatinine ratio (day 2/day 0)	4.36	1.43 – 13.33	0.010
Step 2			
Creatinine ratio (day 2/day 0)	5.45	1.87 – 15.88	0.002

OR, Odds ratio; The odds ratios are per unit increase; 95% CI, 95% confidence interval.
Variables included: primary analysis: urine output (day 2), creatinine ratio (day 2/day 0) as confounders: preadmission eGFR, non-renal SOFA score (day 2)

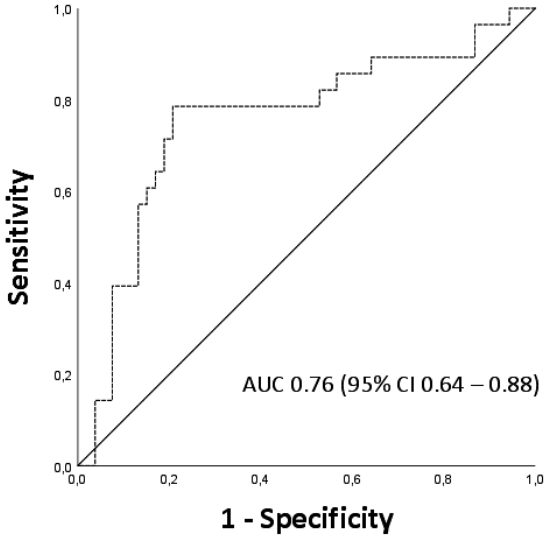
Furthermore we analysed the association between day 2 predictors urine output, urinary NGAL and creatinine ratio (day 2/ day 0) stratified per reason for restart of RRT (fluid overload, oliguria, azotaemia or creatinine rise and hyperkalaemia). We only found an

independent association between restart because of oliguria and day 2 urine output (OR 0.040, 95% CI 0.002 – 0.678, p = 0.026).

Discrimination of incremental creatinine ratio (day 2/day 0) for restart of RRT

The AUROC curve for incremental creatinine ratio (day 2/day 0) to discriminate for restart of RRT within 90 days was 0.76 (95% CI 0.64 – 0.88) (figure 4). The optimal cut-off of the incremental creatinine ratio at day 2 to predict restart of RRT was 1.49 (95% CI 1.44 - 1.62), sensitivity 0.79, specificity 0.79.

Figure 4 ROC curve of creatinine ratio (day 2/day 0) for discrimination of restart of RRT within 90 days



ROC, receiver operating characteristic; RRT, renal replacement therapy; AUC, area under the curve

Discussion

In this prospective multicentre observational study, we found that after initial discontinuation of CRRT for expected renal recovery, the incremental creatinine ratio at day 2 after discontinuation was the only renal marker that independently predicted restart of RRT within 90 days. Urine output and urinary NGAL on day 2 were no independent predictors. This association remained after adjustment for severity of other organ failure and preadmission renal function, which were not related to restart of RRT within 90 days. With an AUROC of 0.76 the discrimination of the incremental creatinine ratio (day 2/day 0) was good. A rise of creatinine by one and a half at day 2 after discontinuation appeared as the optimal cut-off to predict restart of RRT within 90 days.

The main reasons for restart were fluid overload, azotaemia or rise in creatinine and oliguria. When analysing whether the reason for restart was associated with one of the described predictors, we found that only restart because of oliguria was associated with urine output at day 2, while none of the other reasons were associated with the day 2 renal predictors. However, the robustness of this post-hoc analysis can be questioned because subgroups were small. Furthermore, we could only analyse the main reason for restart, while restart of RRT is generally determined by a combination of factors. Big data analysis would be needed to analyse the different combinations of reasons to restart.

The present study shows that two thirds of the patients restarted RRT within the first week after discontinuation for expected renal recovery and the majority restarted in the first three weeks. This finding is in line with previous studies [22, 23]. Interestingly, in our short term restart study [19], the incremental creatinine ratio also appeared as best predictor for restart within the first week. In that study, we found that the incremental creatinine ratio was as good as creatinine clearance, of which the measurement is more complex.

Creatinine ratio is presently used to classify the severity of AKI according to the KDIGO guidelines during its development [24]. In these guidelines, AKI stage 1 is defined as a creatinine ratio from 1.5 - 1.9 times baseline. We found that two days after discontinuation, a creatinine of 1.5 times creatinine at discontinuation was the optimal cut-off to predict restart of RRT, which is similar to the creatinine ratio used to define AKI stage 1. Creatinine ratio after discontinuation of CRRT might therefore be a new and simple tool to identify patients at risk for further renal function deterioration and thus for nephrological follow up.

Unexpectedly, we found no independent association between day 2 urinary NGAL and restart of RRT within 90 days. Although median NGAL concentrations were significantly higher in patients restarting RRT compared to patients not restarting RRT, significance was lost when conventional markers of renal function were included in the analysis. Of interest, we found that neither for short-term (within 7 days) [19] nor for long-term restart, NGAL was independently predictive of restart. This finding is unexpected and has not been reported before in the literature. As mentioned before, urinary NGAL determined at ICU admission is an early marker of renal injury and associated with development of AKI and need of CRRT [5-15]. Previous studies found a poor association between NGAL on admission and late major adverse kidney events [17, 25]. However, none of these studies determined NGAL after discontinuation of CRRT. We demonstrated that the renal injury marker urinary NGAL after discontinuation of CRRT was also not independently associated with restart of RRT. In contrast, the incremental creatinine ratio, a simple renal function marker, was the best predictor. Accordingly, the more complex renal function marker kinetic eGFR also was a better predictor of late major adverse kidney events than urinary NGAL [16]. It therefore seems that after discontinuation of CRRT for expected recovery, the remaining renal function is more important to predict whether the kidney will recover

without restarting RRT than the renal damage marker NGAL, which better predicts the development of AKI.

Another remarkable result was that preadmission eGFR was not significantly different between patients restarting and patients not restarting RRT. This is in seeming contrast to results found in previous studies in which acute on chronic kidney disease was a major risk factor for end-stage-renal-disease [21, 26]. However, we excluded patients with end-stage-renal-disease (CKD 5) and patients in whom CRRT was discontinued to switch to intermittent haemodialysis. Thus patients with the worst preadmission renal function were excluded. This may explain why preadmission eGFR did not differ between the need of RRT groups in our cohort. Independent of CKD, severe AKI, i.e. AKI requiring RRT is a risk factor for incomplete renal recovery and for the development of subsequent end-stage-renal-disease and chronic dialysis [27, 28]. However, in our cohort all included patients had severe AKI because only patients with AKI requiring RRT were included.

Several studies evaluated predictors of restart of RRT or dialysis dependency after AKI. Some studies evaluated risk factors at initiation of CRRT: age, CKD, co-morbidities and severity of disease [21, 26, 29]. Five studies evaluated renal markers at discontinuation and found urine output, 2-hour creatinine clearance and 24-hour urinary creatinine excretion as predictors of successful discontinuation [22, 23, 30-32]. In contrast to the present study, these studies evaluated short-term successful discontinuation (3-15 days). These studies were retrospective in design, included selected populations, such as only surgical patients, and used different modalities of RRT, such as CRRT and intermittent haemodialysis [22, 23, 30-32]. None of these studies evaluated delta creatinine as a predictor. The present prospective study suggests that an incremental creatinine ratio of 1.5 or more two days after discontinuation would be a practical trigger to consult the nephrologist for follow-up.

Nowadays only about 8.5% of patients at risk for further renal function deterioration after an episode of AKI receive referral to a nephrologist. However mortality and incidence of end-stage-renal-disease in this population is high (22%) [33]. In our cohort 6/32 patients (19%) restarted RRT after ICU discharge, especially these patients could benefit from nephrological follow-up, but possibly also those restarting RRT in the ICU. Previous studies found that early nephrological follow up after an episode of AKI is associated with improved survival [34]. The kidney disease: improving global outcomes (KDIGO) guidelines already recommend supportive measures in patients at high risk for AKI or CKD [35]. Therefore it may be beneficial if intensivists and nephrologists cooperate early after discontinuation of CRRT to determine optimal hemodynamic conditions, dose pharmacotherapy thereby reducing potential nephrotoxic events. Thus, the determination of risk factors for restart of RRT early after discontinuation seems important.

Our study has some limitations. First, a large number of patients was excluded because of discharge before day 2 after discontinuation of CRRT or missing NGAL. This might have caused bias, however, these patients had similar rates of restart, and in the multivariate

sensitivity analysis incremental creatinine ratio also was the only independent predictor. Furthermore we evaluated the renal markers at day 2 after discontinuation and not at day 1. The reason was that we aimed to include only patients in whom CRRT was discontinued because of expected recovery of renal function and we did not want to include patients in whom CRRT was temporarily discontinued because of logistic reasons, such as a CT scan or operation. Furthermore we evaluated the incremental creatinine ratio day 2/ day 0, because we supposed that the creatinine ratio day 1/ day 0 might not have been discriminative enough. This was later on also found in another study [16]. Second, death might be a competing endpoint. Patients who died within 90 days could have needed RRT if still alive. We therefore presented the NGAL data in all different subgroups. Patients restarting RRT seemed to have higher NGAL concentrations than those who died without receiving RRT. Third, patients who switched directly from CRRT to intermittent haemodialysis were excluded. However, in these patients RRT was not discontinued because of expected recovery, but for change of RRT modality and they therefore did not fulfil the inclusion criteria. Fourth, restart of RRT was not protocolized, the attending physician decided whether RRT was restarted. Therefore reasons for restart might be different between centres. However, there is currently no consensus on criteria and there are no guidelines describing criteria for restart of RRT. Thus our study describes current practice in 4 Dutch hospitals.

Our study has several strengths. First, we performed a multicentre study, including ICU patients in four hospitals, including an academic hospital, hence our results are highly generalizable. Further, to our knowledge this is the first prospective study determining predictors for restart of RRT after discontinuation of CRRT, which allows the attending physician to select patients who might especially benefit from nephrological follow-up. Finally, creatinine ratio is a simple marker, which is already used to stage developing AKI and therefore well-known and available in clinical practice.

Conclusions

In this prospective multicentre study, in patients alive and still on the ICU at day 2 after discontinuation of CRRT, the incremental creatinine ratio at day 2 after discontinuation predicted restart of RRT within 90 days, independent of urinary NGAL, urinary output, preadmission eGFR and severity of organ failure. The present study suggests that when the rise in creatinine at day 2 after discontinuation of CRRT is 1.5 or more, the patient will likely need restart of RRT within 90 days. We hereby provide a simple and useful tool to select patients who might benefit from nephrological follow up.

Supplementary material

In additional file 1 the participating centres and the assay used for determination of urinary NGAL are described.

In additional file 2 a list of the medication that was scored as nephrotoxic medication is added.

Acknowledgement

We sincerely regret that Johan Groeneveld who contributed to the concept of this study has died. We miss his sharp and witty research input.

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Additional file 1

Participating centres

- Erasmus (University) Medical Centre Rotterdam
- Ikazia Hospital Rotterdam
- Amphia Hospital Breda
- Noordwest Ziekenhuisgroep Alkmaar

Assay for determination of urinary NGAL

For determination of NGAL, a tube collected from a 6-hour urine portion was stored in the refrigerator for a maximum of 72 hours. As soon as possible the sample was centrifuged for 10 minutes at 2000G at 4˚C and the supernatant was stored at -80˚C for determination of urinary NGAL later. Urinary NGAL was determined by immunoassay using the Architect ci4100 (Abbott Diagnostics, Abbott Park, IL, US), we used Urine NGAL Rgt 100T (1P37-25), NGAL Calibrator (1P37-01), NGAL Controle (1P37-10) according to manufacturer's specifications, results are expressed in ng/ml.

Additional File 2: Nephrotoxic medication

Antibiotics/ antiviral drugs/ antimycotics

- vancomycin
- clavulanate
- tazobactam
- cotrimoxazole
- (val)acyclovir
- amphotericin B
- levofloxacin
- micafungin
- daptomycin
- gentamycin
- tobramycin
- amikacin
- clarithromycin
- fluconazole

Diuretics

- furosemide
- bumetanide
- amiloride

Non-steroidal anti-inflammatory drugs

- aceclofenac
- acetylsalicylic acid
- phenylbutazone
- meloxicam
- dexketoprofen
- nabumetone
- parecoxib
- diclofenac
- naproxen
- ibuprofen
- celecoxib
- etoricoxib
- indomethacin
- tiaprofenic acid

ACE-inhibitors/ ATII-antagonists/ renin-antagonists

- captopril
- enalapril
- perindopril
- ramipril
- candesartan
- fosinopril
- lisinopril
- quinapril
- aliskiren
- losartan

Immune-suppressive drugs

- tacrolimus
- ciclosporin

Other

- colchicine
- lamivudine
- zidovudine
- abacavir
- carbamazepine
- cisplatin
- deferoxamine
- methotrexate
- ifosfamide
- gabapentin
- carboplatin

CHAPTER 6

Impaired kidney function at hospital discharge and long-term renal and overall survival in patients who received CRRT

Susanne Stads, Gijs Fortrie, Jasper van Bommel, Robert Zietse, Michiel G. H. Betjes

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Abstract

Background and objectives: Critically ill patients with AKI necessitating renal replacement therapy (RRT) have high in-hospital mortality, and survivors are at risk for kidney dysfunction at hospital discharge. The objective was to evaluate the association between impaired kidney function at hospital discharge with long-term renal and overall survival.

Design, setting, participants and measurements: Degree of kidney dysfunction in relation to long-term effects on renal survival and patient mortality was investigated in a retrospective cohort study of 1220 adults admitted to an intensive care unit who received continuous RRT between 1994 and 2010.

Results: After hospital discharge, median follow-up of survivors (*n*=475) was 8.5 years (range 1-17 years); overall mortality rate was 75%. Only 170 (35%) patients were discharged with an estimated glomerular filtration rate (eGFR) > 60 ml/min per 1.73m^2. Multivariate proportional hazards regression analysis demonstrated that age, nonsurgical type of admission, pre-existing kidney disease, malignancy and eGFR 29-15 ml/min per 1.73m^2 (hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.01 to 2.58) and eGFR <15 ml/min per 1.73m^2 (HR 1.93, 95% CI 1.23 to 3.02) at discharge were independent predictors of increased mortality. Renal survival was significantly associated with degree of kidney dysfunction at discharge. An eGFR 29-15 ml/min per 1.73m^2 (HR 26.26, 95% CI 5.59 to 123.40) and an eGFR <15 ml/min per 1.73m^2 (HR 172.28, 95% CI 37.72 to 786.75) were independent risk factors for initiation of long-term RRT.

Conclusions: Most critically ill patients surviving AKI necessitating RRT have impaired kidney function at hospital discharge. An eGFR <30ml/min per 1.73m^2 is a strong risk factor for decreased long-term survival and poor renal survival.

Introduction

Recently, several studies have shown the interplay between AKI, progressive CKD and long-term mortality [1-6]. A recent study indicated that even patients who seem to have complete recovery of renal function after AKI have a two-fold increased risk for *de novo* CKD, which modified the hazard ratio for mortality [7]. These data confirm the notion that AKI is not an innocent event but rather constitutes a significant risk factor for subsequent development of CKD. In addition, the findings are in accordance with the well-established association between progressive CKD and increased mortality, found in large epidemiological studies [8].

Given these data, it is important to identify the risk factors for death and poor renal recovery after AKI in the intensive care unit (ICU). In addition, the factors associated with CKD at hospital discharge and subsequent development of end stage renal disease (ESRD) or death should be studied. Many studies have identified the following as risk factors for increased mortality after AKI: age older than 65 years, elevated Acute Physiology and Chronic Health Evaluation score (APACHE) score, associated organ dysfunction and the need for continuous renal replacement therapy (CRRT) during ICU stay [9-12]. The need for CRRT during ICU stay is associated with an estimated in-hospital mortality between 14 and 60%, depending on the reason for ICU admission and the cause of renal failure [9, 13]. However, our current knowledge about the long-term effects of AKI that necessitates dialysis in critically ill patients after hospital discharge on mortality and renal survival is far from complete. It is clear that incomplete recovery of renal function, specifically dependence on long-term RRT, after an episode of AKI is associated with increased mortality at follow up [14, 15]. However, definitions of AKI and long-term outcome after an episode of AKI vary among studies, and the degree of kidney function impairment at discharge was not calculated per glomerular filtration rate (GFR) [12, 16].

The objective of this study was to evaluate the degree of renal function at hospital discharge as an independent risk factor for long-term renal survival and overall long-term mortality after an episode of AKI that necessitates RRT in the ICU.

Materials and methods

Setting

A retrospective cohort study was performed in the ICU of a large academic hospital (Erasmus Medical Centre in Rotterdam, The Netherlands). All critically ill patients with AKI who required RRT were treated with continuous arteriovenous hemodialysis (30%) or continuous veno-venous hemofiltration (CVVH). All patients included after 2005 were treated according to the local protocol, anticoagulation was performed using citrate, unless contraindicated, in that case heparin was used as an anticoagulant. Before 2005 the standard anticoagulation used was heparin, unless contraindicated. Intermittent

hemodialysis (IHD) was not performed in this group of patients because most patients in our ICU ward were hemodynamically unstable and the ICU lacks facilities to perform intermittent hemodialysis. The study was approved by the medical ethical review board of the Erasmus Medical Centre, which waived the requirement of informed consent, because of its retrospective nature.

Study population and data collection

All patients older than 18 years receiving CRRT in the ICU between 1994 and 2010 were included in a database. Patients with RRT or a kidney transplant before ICU admission were excluded from analysis (*n*=75). Data were collected using the hospital electronic patient registry (EPR). Long-term RRT after hospital discharge was defined as peritoneal dialysis or hemodialysis for more than 3 months or having received a kidney transplant; these data were obtained from the Dutch national RENINE database (RENINE, The Netherlands) or the hospital electronic patient registry. In the population eligible for analysis, the following clinical and demographic data were collected: age, sex, type and date of ICU admission, medical history, duration of ICU admission, cause of AKI, kidney function at discharge, and the need for long-term RRT after discharge. Most patients were mechanically ventilated during their ICU stay; therefore, it was not possible to test the predictive value of mechanical ventilation on outcome.

Definitions

Type of ICU admission was defined as surgical when any surgical procedure was performed in the period before ICU admission. This included abdominal, trauma, transplantation or thoracic (including cardiac and pulmonary) surgery. Nonsurgical reason for admission included all other admission types, including sepsis, cardiopulmonary resuscitation, cardiac diseases, and intoxication. These are further specified in table 1. For medical history we included data on diabetes mellitus, cardiac disease (defined as myocardial infarction before admission, cardiac valvular disease or heart failure), malignancy, hypertension, cardiac, liver or lung transplantation or pre-existing CKD. Pre-existing CKD was defined as any documented impairment in renal function in the years prior to ICU admission that did not necessitate long-term RRT or kidney transplant. Because information on kidney function impairment was not available at a standardized preadmission time point and for some patients it was not available at all, we did not attempt to categorize these data according to stage of CKD. Preadmission kidney function was considered normal when the patient had documented normal kidney function at the time of admission or within the previous two years, without major events that could have compromised kidney function. Furthermore, we categorized causes of AKI as sepsis, hypotension and toxic/other. Sepsis was defined as the presence of a systemic inflammatory response with a documented or presumed infection. In the group defined as having AKI caused by hypotension, all prerenal causes were included. All patients with AKI due to toxic drugs, contrast agents

and other nephrotoxic substances were categorized in the "toxic/other" group. Patients who experienced AKI as a result of any other cause (*e.g.* rhabdomyolysis, vasculitis or other disorders) were also categorized in this group.

Study outcomes

The main study outcome measures were overall and renal survival; renal survival was defined as the time until long-term RRT. Survival and the need for long-term RRT are reported at six and twelve years after discharge. Furthermore, we evaluated whether degree of kidney dysfunction at discharge was associated with both overall and renal survival. We defined the kidney function at discharge arbitrarily per estimate GFR (eGFR) category, using the Modification of Diet in Renal disease (MDRD) formula for the estimation of GFR. Because the MDRD formula performs best in patients with an eGFR < 60 ml/min per 1.73m^2, we grouped together the patients with eGFR> 60 ml/min per 1.73m^2. The second category is defined as eGFR 30-59 ml/min per 1.73m^2, the third category is defined as eGFR 15-29 ml/min per 1.73m^2 and the last category is defined as eGFR < 15 ml/min per 1.73m^2 with or without the need for long-term RRT at discharge.

Statistical analysis

Continuous variables are expressed as median and range. Categorical variables are expressed as number of cases and percentages. Curves for patient survival and renal survival censored for death were generated for each CKD category by Kaplan-Meier analysis. Log-rank test was used to analyze differences between these curves. Cox regression analysis was used to evaluate independent predictors of long-term mortality. Separate analyses were performed to evaluate changing hazards, for follow-up in the first ninety days and from ninety days to the end of follow-up. Potential risk factors for increased mortality were tested with univariate analysis. When variables were significant in univariate analysis ($p<0.05$), they were included in a multivariate proportional hazards Cox regression analysis using a multiple forward stepwise approach. Statistical significance was defined by a p-value< 0.05. Time-dependent variables were created to evaluate whether hazards were proportionate. Predictive ability of the multivariate proportional hazards model was tested by Harrel's C-statistic. Analyses were performed with statistical software SPSS version 19.0, (SPSS Inc., an IBM company, Chicago, IL).

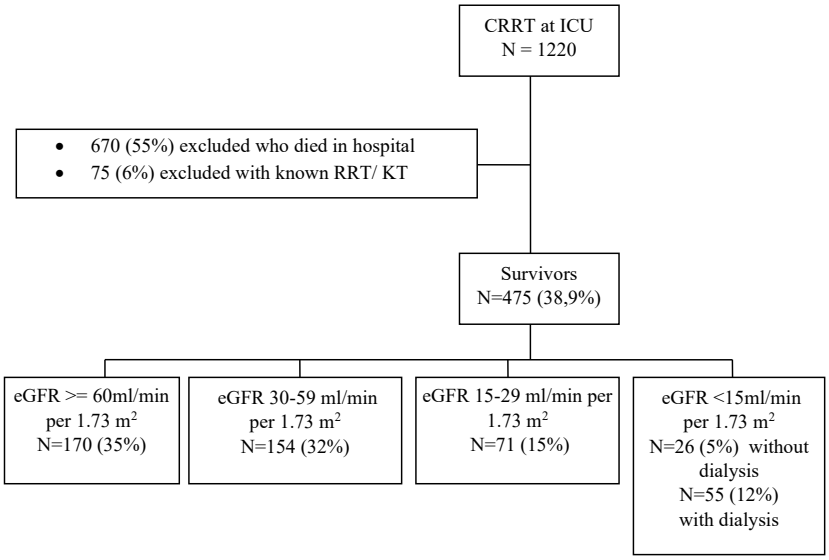
Results

Clinical characteristics of RRT-treated ICU patients discharged from the hospital alive

Between 1994 and 2010, a total of 1220 patients received CRRT in the ICU (figure 1). Seventy-five patients (6%) were known to have received dialysis or have undergone kidney transplantation before hospital admission and were excluded from further analysis. Of the

remaining patients, 670 (55%) died in the hospital. Patients alive at hospital discharge (*n*=475, 39%), were divided in categories according to their eGFR at discharge (figure 1). Median hospital length of stay was 47 days (range: 2-297 days). More than 60% of the patients had eGFR loss at hospital discharge of whom 12% needed RRT at this time.

Figure 1 Flowchart of inclusion and CKD classification at hospital discharge.



eGFR = estimated GFR; KT = kidney transplant; RRT = renal replacement therapy

The baseline characteristics of the 475 patients are depicted in table 1. The largest group of patients was admitted to the ICU after thoracic surgery, followed by 83 patients admitted for sepsis. Table 1 provides all indications for ICU admission, along with medical history of patients before admission. Pre-existing CKD was known in 97 patients (20%) and 229 patients (48%) had normal preadmission kidney function.

Association of long-term patient survival with eGFR at hospital discharge

Follow-up after hospital discharge varied from 1 to 17 years, with a median follow-up of 8.5 years. Survival rates for patients alive at hospital discharge at 6 years and 12 years were 62% and 44%, respectively. Cumulative survival per category was determined by Kaplan-Meier analysis (figure 2). A log-rank test comparing all categories showed a significant difference in patient long-term survival (p-value<0.001).

Compared with patients discharged with an eGFR> 60 ml/min per 1.73m^2, survival curves for patients with an eGFR 15-29 ml/min per 1.73m^2 (hazard ratio (HR) 1.62; 95% confidence interval (CI) 1.01 to 2.58) and an eGFR <15 ml/min per 1.73m^2 at hospital discharge were significantly worse (HR 1.93, 95% CI 1.23 to 3.02). The unadjusted six and twelve year

Table 1 Clinical characteristics of 475 patients treated with renal replacement therapy in the intensive care unit and discharged from the hospital alive.

Characteristic	Value
Median age in years ±SD (yr)	59 (19-84)
Men (%)	314 (66)
Surgical / medical admission (*n/n*)	301/174
Median hospital (range) (*d*)	47 (2-297)
Median ICU (range) (*d*)	18 (1-209)
Cause of AKI, *n* (%)	
Sepsis	119 (25)
Hypotension	191 (40)
Toxic / other	68 (14)
Indication ICU admission, *n* (%)	
Sepsis	83 (17)
Transplantation	41 (9)
Thoracic surgery	118 (25)
Cardiac disease	67 (14)
General surgery	62 (13)
Bleeding	6 (1)
Cardiopulmonary resuscitation	16 (3)
Trauma	14 (3)
Intoxication / other	69 (15)
Medical history, *n* (%)	
CKD	97 (20)
Diabetes mellitus	110 (23)
Cardiovascular disease	241 (50)
Heart transplant	24 (5)
Lung transplant	1 (0.2)
Liver transplant	27 (6)
Malignancy	67 (14)
Liver disease	54 (11)
Hypertension	141 (30)

patient survival rates per category are shown in table 2. Most of the patients discharged with an eGFR < 15 ml/min per 1.73m^2 experienced acute-on-chronic kidney injury (56% of patients in this category had pre-existing CKD).

Figure 2 Kaplan-Meijer curves for survival after hospital discharge, per category at hospital discharge

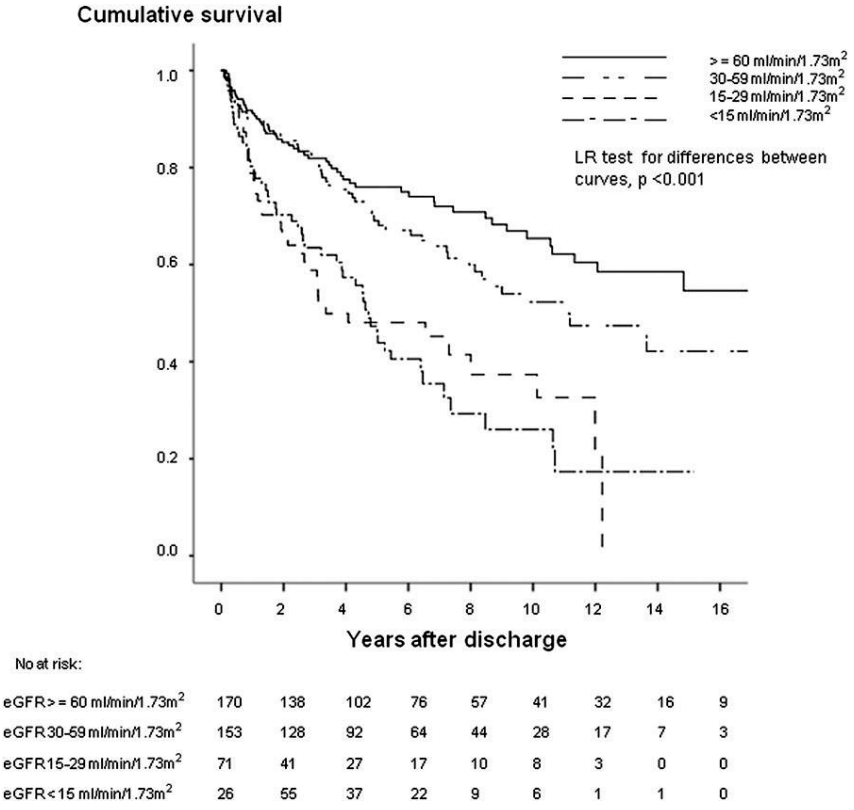


Table 2 Patient and renal survival of 475 patients treated with renal replacement therapy in the intensive care unit and discharged from the hospital alive.

	6-yr overall survival (%)	12-yr overall survival (%)	6-yr renal survival (%)	12-yr renal survival (%)
eGFR > = 60ml/min per 1.73m^2	75	60	100	96
eGFR 30-59 ml/min per 1.73m^2	67	47	95	93
eGFR 15-29 ml/min per 1.73m^2	48	22	86	47
eGFR < 15 ml/min per 1.73m^2	41	17	21	9

Data are given as percentages of initial number of patients alive (overall survival) or without renal replacement therapy (renal survival) at 6 years and 12 years stratified per category at hospital discharge.

Univariate analysis identified several clinical variables associated with worse long-term patient survival, as shown in table 3. Age, date of ICU admission, nonsurgical reason for ICU admission, malignancy and eGFR <30 ml/min per 1.73m^2 at hospital discharge remained significantly associated with patient survival after multivariate proportional hazards analysis (table 3). Separate analysis for the first 90 days after discharge and from 90 days until the end of follow-up, showed that hazards were proportionate during follow-up. The predictive ability of this multivariate proportional hazards model was tested by Harrel C-statistics. We found a concordance of 0.69 (SEM 0.02).

Table 3 Univariate and multivariate analysis of the variables associated with long-term survival.

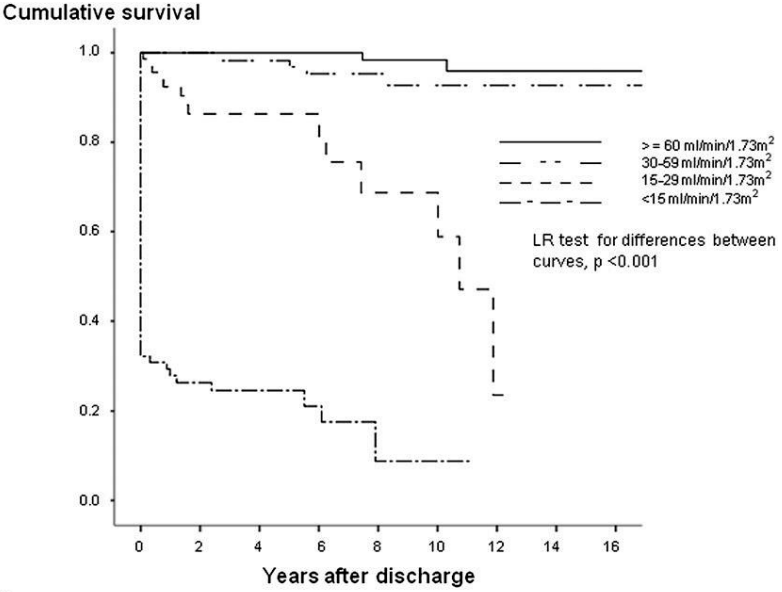
	Univariate analysis		**Multivariate analysis**	
Variable	HR (95 % CI)	p-value	HR (95% CI)	p-value
Age	1.04 (1.03-1.05)	<0.001	1.04 (1.02-1.05)	<0.001
Medical	0.68 (0.51-0.89)	0.01	0.60 (0.43-0.83)	0.002
Kidney function at admission				
Normal	1		1	
Pre-existing CKD	2.21 (1.57-3.09)	<0.001	1.42(0.96-2.10)	0.08
No data available	1.14 (0.82-1.59)	0.44	0.84 (0.58-1.21)	0.34
Admission diagnosis				
Sepsis	0.70 (0.46-1.06)	0.09	0.80 (0.51-1.24)	0.31
Thoracic surgery	1.11 (0.80-1.52)	0.54	0.99 (0.66-1.50)	0.97
Other	1		1	
eGFR at discharge,				
eGFR > = 60 ml/min/1.73m^2	1		1	
eGFR 30-59 ml/min/1.73m^2	1.35 (0.93-1.96)	0.12	1.06 (0.71-1.57)	0.78
eGFR 15-29 ml/min/1.73m^2	2.87 (1.90-4.35)	<0.001	1.62 (1.01-2.58)	0.04
eGFR < 15 ml/min/1.73m^2	2.94 (1.99-4.36)	<0.001	1.93 (1.23-3.02)	0.004
Malignancy	1.85 (1.29-2.65)	0.001	1.73 (1.17-2.55)	0.006
Cardiovascular disease	1.66 (1.25-2.20)	0.001	1.22 (0.85-1.74)	0.28
Diabetes mellitus	1.69 (1.25-2.30)	0.001	1.15 (0.83-1.59)	0.40
Hypertension	1.72 1.29-2.30)	<0.001	0.94 (0.69-1.29)	0.71
Year of admission	0.98 (0.95-1.01)	0.21	0.96 (0.92-0.99)	0.02

Variables tested in multivariate analysis: age, medical admission type, pre-existing CKD, admission diagnosis sepsis, thoracic surgery or other, class of estimated GFR at discharge, malignancy, cardiovascular disease, diabetes mellitus, hypertension and year of admission. HR, hazard ratio; CI, confidence interval; eGFR, estimated GFR (categorical class at discharge, compared with eGFR > = 60ml/min per 1.73m^2).

Association of eGFR at hospital discharge with renal survival.

Renal survival rates after hospital discharge at 6 and 12 years were 83% and 74%, respectively. Comparing renal survival censored for death showed an overall significant difference between eGFR categories (P<0.001) (figure 3).

Figure 3. Kaplan Meier renal survival curves, defined as years after discharge until chronic renal replacement therapy is initiated, censored for death.



No at risk:

eGFR>= 60 ml/min/1.73m^2	170	138	102	76	56	40	32	16	9
eGFR30-59 ml/min/1.73m^2	153	128	90	61	41	27	17	7	3
eGFR15-29 ml/min/1.73m^2	71	36	25	16	9	7	1	0	0
eGFR<15 ml/min/1.73m^2	26	17	11	6	1	1	0	0	0

Compared with patients discharged with an eGFR > 60 ml/min per 1.73m^2, renal survival curves for patients with an eGFR <30 ml/min per 1.73m^2 at hospital discharge were worse (eGFR 15-29 ml/min per 1.73m^2: HR, 27.40, 95% [CI, 5.79 to 129.60]; eGFR<15 ml/min per 1.73m^2: HR, 176.96 [95% CI, 38.59 to 811.50]). The unadjusted six and twelve year renal survival censored for death per eGFR category shows the association between an increased incidence of initiation of RRT and impaired eGFR at hospital discharge (table 2). After multivariate proportional hazards analysis, the following variables were strongly associated with decreased renal survival: pre-existing CKD (compared with patients with documented normal prior kidney function) and an eGFR <30 ml/min per 1.73m^2 at hospital discharge (table 4). Hazards were proportionate during follow-up.

Table 4 Univariate and multivariate analysis of the variables associated with long-term renal survival

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	1.01 (1.00-1.03)	0.14	1.00 (0.98-1.01)	0.66
Medical	0.63 (0.41-0.97)	0.04	1.13 (0.69-1.83)	0.63
Kidney function at admission	1		1	
Normal	9.19 (5.34-15.82)	<0.001	1.82 (1.01-3.33)	0.05
Pre-existing CKD	0.97 (0.49-1.95)	0.94	0.49 (0.23-1.04)	0.06
No data available				
Admission diagnosis				
Sepsis	0.54 (0.28-1.02)	0.06	1.06 (0.54-2.08)	0.88
Thoracic surgery	0.37 (0.19-0.72)	0.003	0.74 (0.34-1.62)	0.46
Other	1		1	
Class of eGFR,				
eGFR > = 60 ml/min/1.73m^2	1		1	
eGFR 30-59 ml/min/1.73m^2	3.18 (0.62- 16.40)	0.17	3.77 (0.72-19.77)	0.12
eGFR 15-29 ml/min/1.73m^2	27.19 (6.09- 121.46)	<0.001	27.40 (5.79-129.60)	<0.001
eGFR < 15 ml/min/1.73m^2	184.69 (43.32- 787.37)	<0.001	176.96 (38.59-811.50)	<0.001
Malignancy	1.51 (0.86-2.65)	0.15	1.56 (0.85-2.85)	0.15
Cardiovascular disease	0.87 (0.56-1.33)	0.51	1.07 (0.65-1.78)	0.79
Diabetes mellitus	1.57 (0.98-2.52)	0.06	0.85 (0.50-1.46)	0.56
Hypertension	3.09 (2.00-4.76)	<0.001	1.29 (0.78-2.15)	0.32
Year of admission	1.00 (0.95-1.05)	0.98	0.98 (0.93-1.04)	0.56

Variables tested in multivariate analysis: age, medical admission type, pre-existing CKD, admission diagnosis sepsis, thoracic surgery or other, class of estimated GFR at discharge, malignancy, cardiovascular disease, diabetes mellitus, hypertension and year of admission. HR, hazard ratio; CI, confidence interval; eGFR, estimated GFR (categorical class at discharge, compared with eGFR > = 60ml/min per 1.73m^2).

The results show that an eGFR< 30 ml/min per 1.73m^2 at hospital discharge is an independent and strong predictor of poor long-term renal survival. The predictive ability of this multivariate proportional hazards model was tested by Harrel C-statistics. We found a concordance of 0.96 (SEM 0.03).

Discussion

The results of this study show that after an episode of AKI necessitating RRT in the ICU, long-term survival and renal survival are both strongly related to the degree of kidney function impairment at hospital discharge. In particular, an eGFR <30 ml/min per 1.73m^2 is an independent predictor of death and worse renal survival at long-term follow-up. About a third of all patients who survive their ICU stay and leave the hospital are discharged with an eGFR <30 ml/min per 1.73m^2. In addition, the majority of patients in our cohort (> 60%) had an impaired kidney function at hospital discharge. Therefore, our findings are clinically relevant because they indicate that most of the patients who have received RRT in the ICU are at risk for CKD and, therefore, further deterioration of kidney function and increased mortality in the years thereafter.

A recently published large systematic review evaluated 15 studies on long-term mortality after an episode of AKI defined by different criteria in different patient populations. Remarkably, none of these studies had patient follow-up as long as or a cohort as diverse as in our study [17]. Overall, it is apparent that an episode of AKI with or without the need for RRT is independently associated with an increased risk (relative risk, 1.6-3.9) for death at follow-up. A meta-analysis performed on 13 cohort studies evaluated the association of AKI with the risk of developing CKD. The results showed that AKI was a strong independent risk factor for development of CKD (HR, 8.8) and ESRD (HR, 3.1) [18].

Some studies have described the relation between impaired kidney function at hospital discharge and long-term survival. In a study performed by Liano et al, patients with complete renal recovery after an episode of AKI were compared with patients who had only partial recovery. Survival was worse in the latter group. However, the degree of renal insufficiency at discharge was not shown, and the study included patients who developed AKI but were not admitted to an ICU or treated with RRT [19].

Only a few studies have evaluated the mortality rate and renal survival of patients who received RRT in the ICU after their hospital discharge [6, 20-22]. The largest study population was described by Wald et al. and consisted of 3769 patients enrolled during a 10-year period; the patients were compared with matched control ICU patients without AKI or RRT [6]. The AKI group had a significantly increased risk for long-term RRT (HR, 3.23), but overall survival (50% mortality after 8 years) was similar to that in the control ICU patient group. In our study, patients discharged with an eGFR <30 ml/min per 1.73m^2 (including patients receiving long-term RRT) showed a persistent association with long-term mortality after multivariate analysis. Only one published study is similar in design to ours [14], that study followed 226 survivors of RRT in the ICU for 5 years. Cumulative survival at 5 years was 47%, and partial recovery of renal function after RRT in the ICU was an independent predictor of poor long-term survival.

Of interest is the lack of association of cardiovascular risk factors, such as hypertension and diabetes mellitus, with survival and between preexisting CKD and survival. The

significance of these relationships was lost in the multivariate analysis in which age and ESRD were the major risk factors for decreased survival. In the large cohort evaluated by Wald et al., patients who needed RRT during the first 30 days after hospital discharge were excluded from analysis [6]. According to our results, this would be the group of patients with worse long-term survival and could therefore at least partly explain the lack of association with mortality in their study. It is possible that some degree of renal recovery may still take place after hospital discharge, leading to underestimation of the true rate of renal recovery; unfortunately data on renal recovery after hospital discharge were not available in our cohort [14, 23].

We cannot conclude with certainty that the association between an eGFR <30 ml/min per 1.73m^2 at hospital discharge and worse long-term survival, implies causality. However, the association persisted even after adjustment for possible covariates that included known risk factors for CKD and progression of CKD, such as age and cardiovascular risk factors and preexisting CKD. Many studies have consistently shown that patients developing ESRD are at higher risk for cardiovascular events and have a higher mortality risk [8, 24, 25]. All these observations agree with data from the general population in which mortality risk exponentially increases when GFR decreases below 60 ml/min per 1.73m^2 [8]. Therefore, prevention of (further) renal function deterioration in patients experiencing AKI by avoiding nephrotoxic drugs as much as possible could improve overall survival and prevent patients from reaching ESRD. Long-term nephrological follow up is necessary for patients who experience incomplete renal recovery after an episode of AKI, especially patients discharged with an eGFR <30 ml/min per 1.73m^2, to minimize the complications of CKD.

Limitations of our study include its retrospective single-center cohort design. We did not calculate GFR by inulin clearance or a 24-hour urine collection but rather used eGFR according to the MDRD formula. Although this formula considers gender and age, it cannot correct for changes in body composition as may be expected in formerly critically ill patients. However, because a substantial loss of muscle mass has most likely occurred in ICU patients, the eGFR at hospital discharge probably overestimates the true GFR and subsequently underestimates the number of patients discharged with an eGFR <30 ml/min per 1.73m^2 . Therefore, the impact of eGFR loss may be even greater than recorded in this study. On the other hand, follow-up of kidney function after discharge is not available in our cohort and some patients may have shown a variable degree of recovery of eGFR over time that we could not account for in our analysis.

Because of the large time span of our patient registry, we depended on the analog and digital patient data management systems that have been used over time. Organ failure scores are available only since 2005 and have not always been used in our ICU; unfortunately it is not possible to analyze the influence of severity of illness on overall and renal survival. In addition, treatment modalities for RRT and overall treatment strategies

for ICU patients have changed over time. Date of admission was therefore included in our multivariate analyses but did not affect the overall conclusions.

The in-hospital mortality rate (55%) in our cohort, the percentage of patients discharged with the need for long-term RRT and the overall survival of our patients after hospital discharge are similar to the results of previous studies [12, 14, 26-29]. Furthermore, our cohort contains a diverse population of ICU patients, including a large group of patients admitted after thoracic surgery and septic patients. We found no differences in survival between admission types after multivariate analysis. Therefore, the patients in our cohort seem to represent an average population of ICU patients.

These findings add credibility to the generalization of our major finding that impaired kidney function at hospital discharge is independently associated with worse long-term overall and renal survival.

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CHAPTER 7

Long-term sequelae of severe acute kidney injury in the critically ill patient without comorbidity: a retrospective cohort study

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Abstract

Background and Objectives: Acute kidney injury (AKI) necessitating renal replacement therapy (RRT) is associated with high mortality and increased risk for end stage renal disease. However, it is unknown if this applies to patients with a preliminary unremarkable medical history. The purpose of this study was to describe overall and renal survival in critically ill patients with AKI necessitating RRT stratified by the presence of comorbidity.

Design, Setting, Participants, and Measurements: A retrospective cohort study was performed, between 1994 and 2010, including all adult critically ill patients with AKI necessitating RRT, stratified by the presence of comorbidity. Logistic regression, survival curve and cox proportional hazards analyses were used to evaluate overall and renal survival. Standardized mortality rate (SMR) analysis was performed to compare long-term survival to the predicted survival in the Dutch population.

Results: Of the 1067 patients included only 96 (9.0%) had no comorbidity. Hospital mortality was 56.6% versus 43.8% in patients with and without comorbidity, respectively. In those who survived hospitalization 10-year survival was 45.0% and 86.0%, respectively. Adjusted for age, sex and year of treatment, absence of comorbidity was not associated with hospital mortality (OR = 0.74, 95%-CI = 0.47-1.15), while absence of comorbidity was associated with better long-term survival (adjusted HR = 0.28, 95%-CI = 0.14-0.58). Compared to the Dutch population, patients without comorbidity had a similar mortality risk (SMR = 1.6, 95%-CI = 0.7-3.2), while this was increased in patients with comorbidity (SMR = 4.8, 95%-CI = 4.1-5.5). Regarding chronic dialysis dependency, 10-year renal survival rates were 76.0% and 92.9% in patients with and without comorbidity, respectively. Absence of comorbidity was associated with better renal survival (adjusted HR = 0.24, 95%-CI = 0.07-0.76).

Conclusions: While hospital mortality remains excessively high, the absence of comorbidity in critically ill patients with RRT-requiring AKI is associated with a relative good long-term prognosis in those who survive hospitalization.

Introduction

Despite improvement in medical care, acute kidney injury (AKI) is a major complication in critically ill patients. Over the past decades a steady increase in incidence of AKI has been reported, while mortality continues to be excessively high [1-5]. The increased incidence of AKI is likely caused by increasing age, a greater burden of comorbidity, pre-existing chronic kidney disease (CKD), the greater use of nephrotoxic drugs and iodine-containing contrast for radiological imaging. Today, AKI occurs in approximately 10-67% of those admitted to the intensive care unit (ICU) [6-13] and in 3-8% renal replacement therapy (RRT) is necessary [6,12]. AKI requiring RRT is associated with a hospital mortality rate around 50-60% and survivors have a substantial risk for end-stage renal disease (ESRD) [3,14–18]. However, an average ICU population is characterized by the heavy burden of comorbidities, which may substantially influence both mortality and renal recovery or even the development of AKI itself [19-21]. In recent literature, the impact of comorbid conditions on renal recovery after AKI and the long-term sequelae is a major topic of discussion [20,22-25]. Given the complex interplay between AKI and comorbidity, it is difficult to determine the true impact of AKI on ESRD and mortality, especially in the long-term. Therefore, overestimation of the risk for these outcomes may occur in subpopulations with lower levels of comorbidity. In particular, in those who are not burdened by any comorbidity. This study describes overall and renal survival in a group of critically ill patients with AKI necessitating RRT stratified by the presence of comorbid conditions.

Materials and methods

Study design and population

A retrospective cohort study was performed including data obtained from patients admitted to a large tertiary care center (Erasmus Medical Center, Rotterdam, The Netherlands). All critically ill patients ≥ 18 years treated with continuous renal replacement therapy (CRRT) between January 1994 and April 2010 were evaluated. Patients with RRT or kidney transplant prior to hospital admission were excluded from analysis. Furthermore, patients in the study population were categorized by the presence of comorbidity in two groups, patients with (comorbid+) and patients without comorbidity (comorbid-). When a patient experienced multiple hospital admissions requiring RRT, only the first hospital admission was used for further analysis. The modalities used for CRRT were continuous arteriovenous hemodialysis (CAVHD) or continuous venovenous haemofiltration (CVVH). Initially, CAVHD was the standard modality for CRRT, which was later gradually replaced by CVVH. CRRT was prescribed by the attending nephrologist and delivered by the hemodialysis nursing team. Intermittent hemodialysis was not performed because most patients in the ICU ward were hemodynamically unstable and the ICU lacks facilities to perform intermittent hemodialysis. The study was approved by the medical ethical review

board of the Erasmus Medical Center, which waived the requirement for informed consent, because of its retrospective design.

Data collection

Data were collected using the hospital electronic patient records (EPR). Detailed clinical and demographic data were collected for patients without comorbidity including primary cause of AKI, type of ICU admission, primary indication for ICU admission, CRRT modality, non-renal SOFA score and number of ICU admission days. Furthermore, at hospital admission, at start of CRRT and at hospital discharge serum creatinine values were collected. Baseline renal function was not known in the majority of patients, as they were not under medical care prior to hospital admission. Given the uncertain relation between serum creatinine concentrations and renal function at hospital admission and start of CRRT we only calculated the estimated glomerular filtration rate (eGFR) at hospital discharge. To determine whether a patient reached ESRD requiring RRT after hospital discharge we used data from the RENINE Foundation. This foundation manages a Dutch national database containing all patients treated with RRT for at least 3 months and therefore considered chronically dependent on RRT.

Definitions

The patient records were used to identify whether patients were known with malignancy, solid organ transplantation, intravenous drug abuse and pre-existing chronic diseases such as CKD, hypertension, diabetes mellitus, liver failure, cardiovascular diseases, autoimmune diseases, chronic obstructive pulmonary disease (COPD), connective tissue diseases and chronic infectious diseases like HIV and hepatitis. Patients without one of these conditions were categorized in the comorbid- group, while patients with one or more of these conditions were categorized in the comorbid+ group. The primary cause of AKI was categorized as: sepsis, ischemia, drug-associated and other. Sepsis was defined in accordance to the Surviving Sepsis Campaign International Guidelines [26]. Ischemia was defined as AKI due to hypotension and pre-renal kidney failure. All patients suffering from AKI due to drugs, contrast and other substances that are nephrotoxic were categorized in the drug-associated group. Patients that experienced an episode of AKI due to any other cause then aforementioned, consisting rhabdomyolysis and glomerulonephritis were categorized in the "other" group. Indications for ICU admittance were categorized as: sepsis, postoperative, traumatic injury, intoxication and other. A postoperative ICU indication was defined as the need for ICU admission for treatment and monitoring due to perioperative hemodynamic instability. Reasons for surgery included acute pancreatitis, stomach and bowel perforations, an intra-abdominal abscess and a total hip prosthesis. For estimation of the GFR we used the modification of diet in renal diseases (MDRD) formula adjusted for age and sex [27].

Study outcomes

Primary study outcomes were overall and renal survival stratified by the presence of comorbidity. Overall survival was divided into hospital mortality and survival after hospital discharge. Renal survival was defined as the time until the need for chronic RRT. Long-term overall and renal survival rates were presented at 1, 5 and 10 years after discharge. In addition, long-term overall survival was compared to the predicted survival in the Dutch population. Secondary, patients without comorbidity were evaluated for independent predictors associated with hospital mortality. Due to the low number of events in patients without comorbidity predictors for overall and renal survival were not evaluated.

Statistical analysis

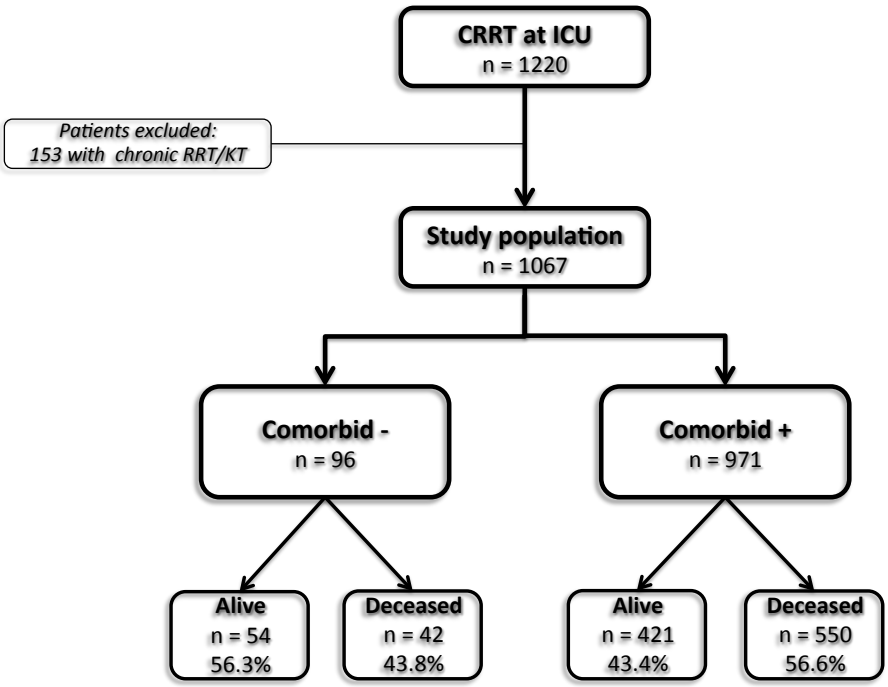
Continuous parameters were expressed as median and interquartile range. Categorical parameters were expressed as number and percentage. Logistic regression analysis adjusted for age, sex and year of treatment was performed to compare hospital mortality in patients with and without comorbidity. In patients without comorbidity, logistic regression analysis was performed to determine independent predictors for hospital mortality. Parameters with a p-value ≤ 0.1 reported by univariable analysis were considered eligible for multivariable analysis. Irrespective of p-value the variables age, sex and year of treatment were included in multivariable analysis. Overall and renal survival after hospital discharge stratified by presence of comorbidity was evaluated by Kaplan-Meier analysis. Log-rank test was used to analyze crude differences pooled over strata and cox proportional hazards analysis was used to adjust for age, sex and year of treatment. The standardized mortality ratio (SMR) was calculated by comparing mortality after hospital discharge with the expected mortality in the general Dutch population. The SMR is the ratio of observed to expected number of deaths. The expected number of deaths is calculated by multiplying the total number of years lived by patients in the study population for each calendar period in each age and sex category by the age and sex specific mortality rates of the Dutch population for each calendar period. A two-tailed p-value ≤ 0.05 was considered significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL, USA) and GraphPad Prism version 5.0a for Mac (Graph-Pad Software, La Jolla, CA, USA)

Results

Study population

A total of 1220 patients treated with CRRT during ICU admission were evaluated during the study period. After exclusion of 153 patients on chronic RRT or with a kidney transplant the study population included 1067 patients of which 96 (9.0%) had no comorbidity (Figure 1).

Figure 1
Flowchart of inclusion and hospital mortality stratified by presence of comorbidity



(C)RRT: (continuous) renal replacement therapy, ICU = intensive care unit, KT = kidney transplant

Clinical characteristics of the patients without comorbidity are presented in Table 1. The median age was 45 years and 55.2% of the patients were of male gender. The most common cause of AKI was sepsis (58.3%) followed by ischemia (25.0%). In the largest group of patients sepsis (37.5%) was also the most frequently indication for ICU admission followed by trauma (31.3%). CAVHD or CVVH were used in 39 (40.6%) and 57 (59.4%) of the patients as modality for CRRT. The median non-renal SOFA score at ICU admission was 10 points and only available in 50 patients. The median serum creatine at hospital admission and start of CRRT were 177 and 427 µmol/L, respectively, and the median length of ICU stay was 21 days.

Table 1 Clinical and demographical characteristics of 96 patients without comorbidity treated with CRRT in the ICU.

Characteristic	Value
Age in years (interquartile range)	45 (35-60)
Male sex (%)	53 (55.2)
Cause of AKI (%)	
Sepsis	56 (58.3)
Ischemia	24 (25.0)
Drug-associated	9 (9.4)
Other	7 (7.3)
Surgical admission (%)	64 (66.7)
Indication for ICU admission (%)	
Sepsis	36 (37.5)
Post-operative	12 (12.5)
Intoxication	10 (10.4)
Trauma	30 (31.3)
Other	8 (8.3)
CRRT modality (%)	
CAVHD	39 (40.6)
CVVH	57 (59.4)
Non-renal SOFA score (interquartile range)*	10 (8-13)
Serum creatinine in µmol/L (interquartile range)	
Hospital admission	177 (94-350)
Start CRRT	427 (298-569)
Days of ICU stay (interquartile range)	21 (11-38)

Categorical variables are expressed as number and percentage; continuous variables are expressed as median and interquartile range. AKI: acute kidney injury; CAVHD, continuous arteriovenous haemodialysis; CVVH, continuous venovenous hemofiltration; ICU, intensive care unit; SOFA, sequential organ failure assessment.
**score available in 50 cases*

Hospital mortality

In the group without comorbidity 42 (43.8%) patients deceased during hospitalization compared to 550 (56.6%) of those with comorbidity, respectively (P = 0.02). Adjusted for age, sex and year of treatment, patients without comorbidity had a similar hospital mortality risk (Odds ratio [OR] = 0.74, 95% confidence interval [CI] = 0.47-1.15). In subgroup analysis on patients without comorbidity, univariable analysis identified several clinical variables associated with hospital mortality presented in Table 2. Only serum creatinine at start of CRRT (OR = 0.96, 95%-CI = 0.93-0.99) and length of ICU stay (OR = 0.96, 95%-CI = 0.94-0.99) remained associated with hospital mortality after multivariable logistic regression analysis.

Table 2 Univariable and multivariable analysis of characteristics associated with hospital mortality in patients without comorbidity

	Univariable analysis		Multivariable analysis	
	OR (95%-CI)	P-value	OR (95%-CI)	P-value
Age in years	1.02 (0.99-1.05)	0.13	1.03 (1.00-1.07)	0.08
Male sex	1.37 (0.60-3.09)	0.45	2.46 (0.67-9.02)	0.18
Surgical admission	1.00 (0.43-2.35)	1.00	-	-
Indication for ICU admission				
Sepsis	1		1	
Post-operative	0.50 (0.13-1.96)	0.32	1.11 (0.21-5.85)	0.90
Intoxication	0.43 (0.10-1.93)	0.27	0.49 (0.09-2.73)	0.42
Trauma	1.14 (0.43-3.02)	0.79	3.17 (0.81-12.37)	0.10
Other	0.14 (0.02-1.28)	0.08	0.44 (0.04-5.46)	0.52
CVVH as CRRT modality	0.60 (0.26-1.36)	0.22	-	-
Non-renal SOFA score*	1.07 (0.93-1.24)	0.36	-	-
Serum creatinine in µmol/L				
per 10 points	0.99 (0.97-1.01)	0.40	-	-
Hospital admission	0.98 (0.96-1.00)	0.04	0.96 (0.93-0.99)	0.01
Start CRRT	0.98 (0.96-0.99)	0.01	0.96 (0.94-0.99)	0.003
Days of ICU stay	0.96 (0.88-1.04)	0.31	0.94 (0.83-1.05	0.28
Year of treatment				

CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; ICU = intensive care unit; SOFA = sequential organ failure assessment. *Score available in 50 cases

Survival after hospital discharge

In total, 475 patients left the hospital alive of which 54 had no comorbidity. Median follow-up time was 4.4 years (2.1-8.0). In general, the percentage of survival at 1, 5 and 10 years in those that survived hospitalization was 87.2%, 64.7% and 50.4%, respectively. Stratified by presence of comorbidity survival rates were 85.7%, 61.1% and 45.0% compared to 96.3%, 91,6% and 86.0% in patients with and without comorbidity, respectively (Table 3).

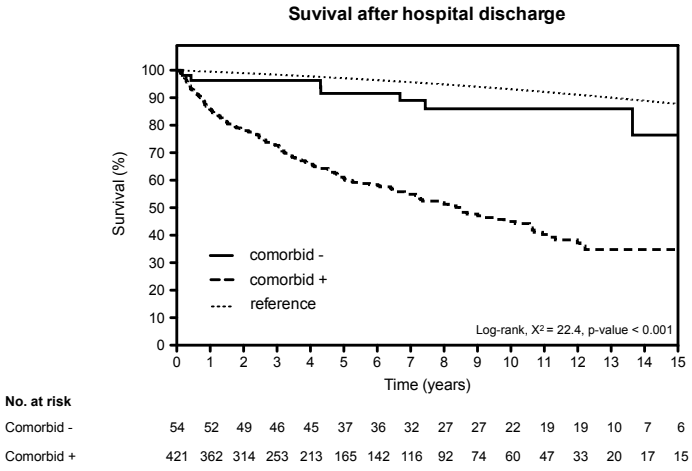
Table 3 Overall and renal survival of patients that survived hospital admission

	Overall survival (%)			Renal survival (%)		
	1 yr	5 yr	10 yr	1 yr	5 yr	10 yr
Comorbid +	85.7	61.1	45.0	85.8	82.9	76.0
Comorbid -	96.3	91.6	86.0	96.3	96.3	92.9

Data are given as percentage of cumulative overall survival and renal survival at 1, 5 and 10 years stratified by the presence of comorbidity.

Survival curves are presented in Figure 2 and log-rank test comparing both groups showed a crude significant difference in survival (P < 0.001). Adjusted for age, sex and year of treatment, patients without comorbidity had a significant better survival rate (Hazard-ratio [HR] = 0.28, 95%-CI = 0.14-0.58). Compared to the predicted survival in the Dutch population patients without comorbidity had a similar mortality risk (SMR = 1.6, 95%-CI = 0.7-3.2), while this risk was significantly increased in patients with comorbidity (SMR = 4.8, 95%-CI = 4.1-5.5) (Table 4). A reference curve, shown in Figure 2, represents the predicted survival in the Dutch population matched for age, sex and calendar period to patients without comorbidity.

Figure 2 Kaplan-Meier curves for overall survival after hospital discharge stratified by comorbidity



The reference curve represents the predicted survival in the Dutch population matched for age, sex and calendar period to patients without comorbidity.

Table 4 Standardized mortality ratio analysis in patients that survived hospital admission

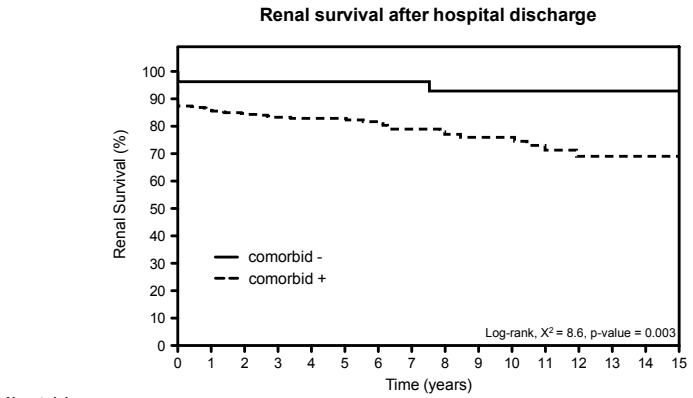
	Sex	No. in group	No. of deaths	Person years	SMR (95%-CI)	P-value
Comorbid +	Male	286	133	1441.8	4.3 (3.6-5.6)	<0.001
	Female	135	59	691.8	6.5 (4.9-8.4)	<0.001
	Overall	**421**	**192**	**2133.6**	**4.8 (4.1-5.5)**	**<0.001**
Comorbid -	Male	29	6	255.6	1.7 (0.6-3.6)	0.15
	Female	25	2	206.9	1.5 (0.2-5.2)	0.40
	Overall	**54**	**8**	**462.4**	**1.6 (0.7-3.2)**	**0.10**

Renal function and renal survival after hospital discharge

At time of hospital discharge 55 (11.6%) of all patients were dialysis dependent of which 53 (12.6%) and 2 (3.7%) with and without comorbidity, respectively (P = 0.07). Renal survival rates at 1, 5 and 10 years were, respectively, 85.8%, 82.9% and 76.0% versus 96.3%, 96.3% and 92.9% in patients with and without comorbidity (Table 3).

Renal survival curves stratified by comorbidity are presented in Figure 3 and log-rank test comparing both groups showed a crude significant difference in renal survival (P = 0.003). Adjusted for age, sex and year of treatment patients without comorbidity had a significant better renal survival rate (HR = 0.24, 95%-CI = 0.07-0.76). At hospital discharge, grouped by eGFR, 28 (51.9%) patients without comorbidity had an eGFR ≥ 90, 9 (16.7%) an eGFR = 60-89, 9 (16.7%) an eGFR = 30-59, 3 (5.6%) an eGFR = 15-29 and 5 (9.3%) patients left the hospital with an eGFR < 15 ml/min/1.73m^2.

Figure 3 Kaplan-Meier curves for renal survival stratified by comorbidity



No. at risk																
Comorbid -	54	50	47	45	44	37	36	32	26	26	21	19	19	10	7	6
Comorbid +	421	315	274	219	184	143	123	103	80	63	53	41	31	19	16	14

Defined as years after discharge until chronic replacement therapy is initiated, censored for death.

Discussion

To the best of our knowledge this is the first study to describe overall and renal survival in a group of critically ill patients with AKI necessitating RRT stratified by the presence of comorbid conditions. We demonstrated that patients without comorbidity constitute a minority of the ICU population, as only 9% of all ICU patients treated with RRT were not burdened with relevant pre-existing diseases. Although, hospital mortality in this group was still high, the overall and renal survival after hospital discharge was relatively good with 10-year survival rates of 86% and 93%, respectively. In particular the fact that

we could not identify a difference in long-term mortality risk compared to the predicted mortality in the Dutch population is of interest.

Hospital mortality and associated risk factors

In the overall study population the hospital mortality rate was 55.5%, which is in accordance with the results of previous studies [3]. We demonstrated that patients without comorbidity had a crude decreased risk for mortality, but contrary to what we expected, no significant difference was found after adjusting for age, sex and year of treatment. Given the fact that a trend towards better survival persisted, it is possible that the lack of statistical significance is due to the small population of patients without comorbidity. For instance, a recent study by *Ostermann and Chang* [28] evaluating a large cohort of patients (n = 1847) treated with RRT in the ICU, reported that the presence of one or more comorbidities was associated with increased ICU mortality. In spite of these results the risk for mortality during hospital admission in the critically ill patient without comorbidity remains excessively high. Multivariable analysis in patients without comorbidity revealed that serum creatinine at start of CRRT and length of ICU stay were associated with hospital mortality. Interestingly, a higher serum creatinine at start of RRT was associated with lower mortality. This finding is in accordance with previous studies, which demonstrated that an increase in RIFLE criteria was associated with higher mortality [29,30], while an absolute higher serum creatinine at time of diagnosis of AKI [29] or start of RRT [31,32] was associated with lower mortality. A hypothetical explanation for this observation is that low serum creatinine levels at start of RRT reflect poor clinical condition rather than better renal function as these patients may have had less muscle mass and/or could have been more fluid overloaded.

Long-term survival after hospitalization

The results on long-term survival presented in the overall study population are in accordance with the results of previous studies [33-38]. In contrast to hospital survival, we demonstrated that there was a great difference in survival after hospitalization in favor of those without comorbidity (adjusted HR = 0.28). Because this is the first study evaluating long-term mortality after AKI stratified by presence or absence of comorbidity it is not possible to directly compare these results to previous studies. Furthermore, studies that reported survival rates after for instance 5 or 10 years are scarce. Two studies that evaluated long-term mortality after AKI requiring RRT reported overall survival rates after 5 years of 15.5 to 35.5%, including those who died during hospitalization. These results are in accordance to the survival rate of 26.5% in the group with comorbidity in our study, including those who died during hospitalization. In patients without comorbidity this was 51.5%. Interestingly, patients without comorbidity had a similar long-term mortality risk as predicted in the Dutch population. However, a trend towards a higher mortality risk

was reported, and the lack of statistical significance could be the result small study size, which implies that future studies with a larger sample size are warranted.

Renal survival after hospitalization

At hospital discharge 11.6% of all patients were dependent on RRT, which is about average compared to results of previous studies that reported a percentage ranging from 0 to 32% [15,16,33,39,40]. Our result demonstrated that in patients without comorbidity only 3,7% patients left the hospital dependent on RRT, which is low compared to most of the aforementioned studies. However, *Schiffl et al.* reported that none of the 425 critically ill patients included in their study reached dialysis dependence at hospital discharge [39]. Interestingly, this is the only study that excluded all patients with a preliminary impaired renal function. These results suggest that in particular an impaired renal function prior AKI is an important risk factor for dialysis dependence thereafter. Furthermore, in a previous study of our research group we found that in the presence of chronic kidney disease no other comorbid condition was significantly associated with the need for RRT at hospital discharge in patients surviving AKI requiring RRT [16]. After hospital discharge only one more patient became chronic dialysis dependent after 7.5 years of follow-up. This 33-year-old male patient was admitted to the ICU after a severe trauma (motor accident) and left the hospital with an eGFR of 28 ml/min/1.73m^2, which slowly decreased towards ESRD necessitating dialysis. An explanation for the high renal survival rate reported in our study is the low number of patients that left the hospital with an impaired renal function, which is, as reported by *Stads et al.,* an important predictor for progression towards ESRD requiring RRT [38].

Limitations

There are certain limitations to our study that should be taken into consideration before interpretation of the results. First, the single center retrospective design has its inherent drawbacks and does not offer the possibility to establish causality and it is not known if the results can be generalized to other ICU populations. Second, the population of patients without comorbidity was rather small, which results in a lack of statistical power. Third, our study included patients over a period of 16 years and it is likely that patterns of referral to and treatment in the ICU have changed over time. Therefore, the year of therapy was included in all multivariable analyses to adjust for possible confounding. Third, it is possible that patients without comorbidity had chronic renal impairment before hospital admission, which could bias the results of our study. However, even if some patients with unknown chronic renal impairment were included it would strengthen our conclusion, because the long-term prognosis in patients without comorbidity would be even better. Fourth, it was not possible to collect information on progressive loss of renal function besides progression towards ESRD or renal function at time of hospital discharge. Thus, it is possible that besides the low number of patients that progressed towards ESRD

there actually was deterioration in renal function. Fifth, besides modality of CRRT, no further detailed information was available including type of dialysis access, type of anticoagulation regime, subsequent complications, etc. However, given these limitations, the results of this study are of interest as the presence or absence of comorbidity seems to have a substantial effect on the prognosis of the critically ill patient and this study offers an interesting perspective on such a complex syndrome as AKI.

Conclusions

The results of our study are indicative that the absence of comorbidity in critically ill patients with RRT-requiring AKI does not have a major impact on hospital mortality but is associated with a relatively good long-term survival rate and infrequent progression to ESRD. However, given the aforementioned limitations, future prospective studies with a large sample size are warranted before firm conclusions can be drawn.

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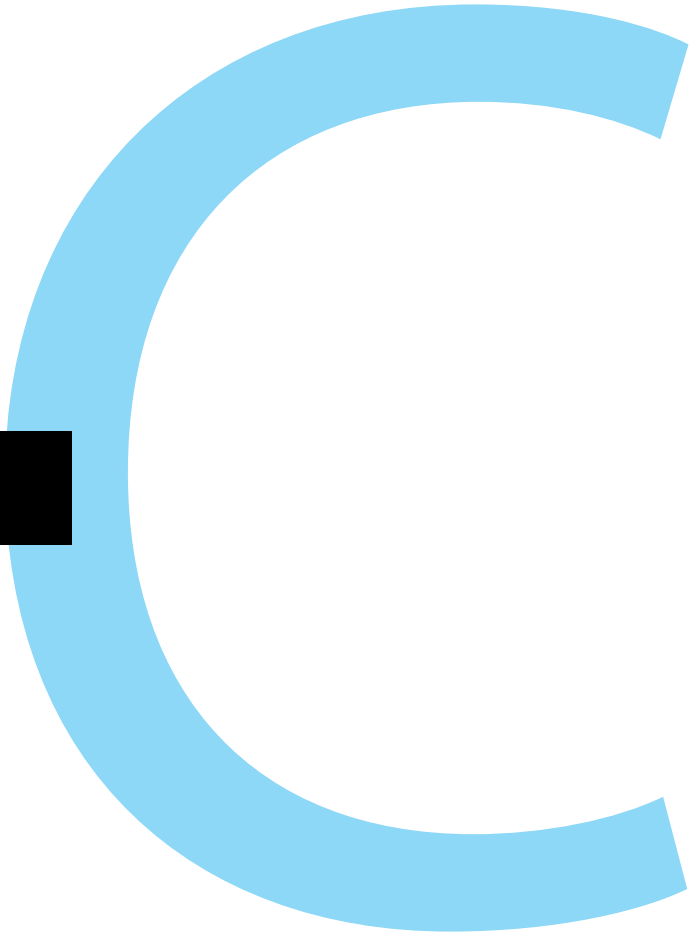
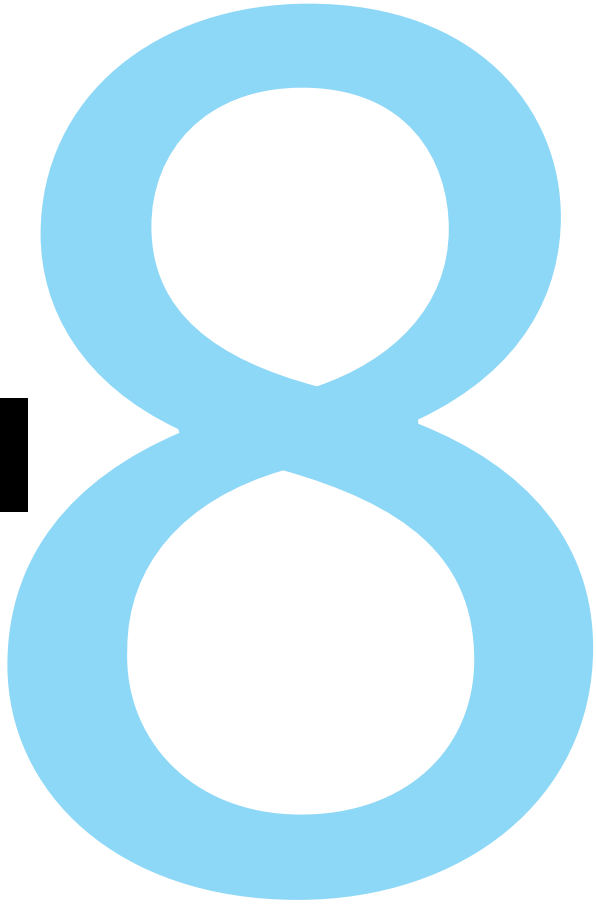
PART C



General discussion, summary and future perspectives

CHAPTER 8



General discussion, summary and future perspectives

Susanne Stads

General discussion, summary and future perspectives

Short-term outcome after AKI

In this thesis we evaluated determinants of short-term and long-term outcome after acute kidney injury (AKI). AKI is nowadays diagnosed by the ratio of the increased serum creatinine and baseline serum creatinine or by urine output as defined by the AKIN criteria. The AKIN criteria are widely used to define three stages of AKI and to compare outcome in studies according to the severity of AKI [1]. Recently the robustness of this definition is questioned by several authors, because the serum creatinine concentration is not only determined by renal excretory function but also by muscle mass and haemodilution caused by fluid overload [2, 3]. Endogenous creatinine generation occurs by turnover of muscle mass [4], therefore patients with lower muscle mass will have less creatinine generation and thereby an underestimation of severity of kidney injury. Accordingly, dilution of serum creatinine caused by fluid accumulation will result in a lower creatinine concentration and thereby also an underestimation of severity of kidney injury [3]. In **chapter two** we performed a post-hoc analysis on the multicentre data from the CASH trial, comparing citrate to heparin anticoagulation. No difference in outcome was found between groups. In 100 patients included in the CASH trial, we evaluated whether fluid balance-adjusted initiation creatinine was associated with 28-day mortality, independent of other markers of severity of AKI, surrogates of muscle mass (such as age, sex, race and body weight) and severity of disease (APACHE II (Acute physiology and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) score). We found that lower fluid balance-adjusted creatinine at continuous renal replacement therapy (CRRT) initiation (OR 0.996, p = 0.019) was independently associated with 28-day mortality, while unadjusted creatinine lost significance after covariate adjustment. Whether the association between lower fluid balance-adjusted creatinine at CRRT initiation and mortality represents earlier CRRT initiation or lower muscle mass remains uncertain, because only surrogates for muscle mass and fluid status were incorporated in the model. However, the study is hypothesis generating and suggests that future studies investigating timing of CRRT initiation using AKI stage, should take fluid balance and better markers for muscle mass into account.

Several studies evaluated predictors of outcome at initiation, and only a few did so after discontinuation of CRRT [5-16]. We performed a prospective multicentre observational study to evaluate predictors of short-term and long-term outcome *after* discontinuation of CRRT. In four hospitals, including an academic hospital, we included 92 patients alive and on the ICU at discontinuation of CRRT. In **chapter three** we found that 7-day successful discontinuation of CRRT can be predicted by better renal function at day 2 after discontinuation, determined by endogenous creatinine clearance (OR 1.066, p = 0.003) or creatinine ratio (day 2/day 0) (OR 0.149, p = 0.006) and non-renal SOFA score (OR 0.822, p = 0.045). Fluid balance contributed non-significantly to the final model. Urinary neutrophil

gelatinase-associated lipocalin (NGAL) lost significance after covariate adjustment. The optimal cut-off for creatinine clearance to predict 7-day successful discontinuation was 11 ml/min (95% CI 6 – 16 ml/min) and for incremental creatinine ratio 1.41 (95% CI 1.27 – 1.59). Unfortunately, despite screening a large group of patients starting CRRT, only a small group was included in our study, mainly because of mortality during CRRT (32%) or early discharge to the ward (22%). However, the rates of restart were similar in the excluded patients. There are no guidelines on discontinuation of CRRT yet, and in clinical practice CRRT is discontinued on an individual basis, based on bedside and logistic factors, for example when the circuit has to be replaced or the patient has to undergo a CT scan. With the results of this study we provide a practical bedside tool to support clinical decision making, when the incremental creatinine ratio is less than 1.4 or endogenous creatinine clearance is more than 16 ml/min, discontinuation of CRRT will likely be successful.

Decreased estimated glomerular filtration rate (eGFR) is associated with progression to chronic kidney disease and end-stage-renal disease [17, 18]. In **chapter four** we aimed to determine risk factors for an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge after an episode of AKI. We performed a retrospective single centre cohort study and analysed 353 patients alive at hospital discharge after RRT-requiring AKI between 1994 and 2010. Of this cohort, 64% of the patients left the hospital with an eGFR ≤ 60 ml/min/1.73m^2 and 8.2% were dialysis dependent at hospital discharge. We found an independent association between age (OR 1.051, $p < 0.001$) and an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge. Furthermore we found an association between pre-existing chronic kidney disease (CKD), defined by any documented impairment of renal function within the year before admission, or a baseline eGFR ≤ 60 ml/min/1.73m^2, and dialysis dependency at hospital discharge (OR 5.865, $P < 0.001$). Our results indicate that the elderly patient is at risk for an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge and patients with CKD are at risk for dialysis dependency at hospital discharge. Therefore these patients should be monitored closely to minimise further renal function deterioration after RRT-requiring AKI, for example by monitoring fluid status and urine output beyond ICU discharge and avoiding nephrotoxic or contrast agents [19]. This study has some limitations. The data were collected over a large timeframe, different CRRT modalities were used and baseline creatinine was available in only 34% of the patients, this might have caused selection bias. Furthermore the eGFR at hospital discharge is not a steady state and renal function might further recover after hospital discharge. However, because the majority of patients are at risk for an eGFR ≤ 60 ml/min/1.73m^2 at hospital discharge, nephrologist follow-up to prevent further renal function deterioration and to facilitate renal recovery seems warranted in these patients.

Long-term outcome after AKI

To further define the patients at risk for renal function deterioration after RRT-requiring AKI, we also evaluated predictors for restart of RRT within 90 days after initial discontinuation of CRRT for expected recovery of renal function. This analysis was performed in the prospective multicentre cohort including patients alive and still on the ICU at day 2 after discontinuation of CRRT. In **chapter five** we evaluated whether the renal function markers urine output and incremental creatinine ratio and the renal damage marker urinary NGAL at day 2 after CRRT discontinuation, predicted restart of RRT within 90 days adjusted for preadmission eGFR and non-renal SOFA score. We included 90 patients for this analysis, and 32 (36%) of these patients restarted RRT. In multivariate analysis only incremental creatinine ratio (OR 5.28, p = 0.012) remained independently associated with restarting RRT within 90 days. With an area under the receiver operating characteristic (AUROC) curve of 0.76 the prediction of incremental creatinine ratio for restart of RRT within 90 days was good. The optimal cut-off for creatinine ratio was 1.5, which is similar to the cut-off used to define AKI stage 1 according to the AKIN criteria for developing AKI [1]. Creatinine ratio after discontinuation of CRRT might be a new tool to identify patients at risk for renal function deterioration. An important limitation of this study was the large number of exclusions, because of early discharge or missing urinary NGAL. We therefore analysed the restart rate in the patients excluded because of early discharge or missing NGAL and found comparable rates. However, we cannot exclude that the high number of exclusions has caused selection bias.

In **chapter six** we questioned whether the degree of renal function impairment at hospital discharge was an independent risk factor for long-term renal survival and overall long-term mortality (1-17 years). In a large retrospective cohort of patients after RRT-requiring AKI, collected between 1994 and 2010, we divided the 475 included patients in categories according to their eGFR at hospital discharge. In multivariate analysis, evaluating the association with long-term mortality (1-17 years), we found an eGFR < 15 ml/min/1.73m^2 (OR 1.93, p = 0.004) and an eGFR between 15 -29 ml/min/1.73m^2 (OR 1.62, p = 0.04) at hospital discharge and age, date of intensive care unit (ICU) admission, nonsurgical admission and malignancy as independent predictors. In multivariate analysis, evaluating the association with long-term renal survival (1-17 years), we found an eGFR < 15 ml/min/1.73m^2 (OR 176.96, p < 0.001) and an eGFR between 15 -29 ml/min/1.73m^2 (OR 27.40, p = 0.04) and pre-existing CKD as independent predictors. The majority of the survivors after RRT-requiring AKI have renal function impairment at hospital discharge, and an eGFR < 30 ml/min/1.73m^2 is a strong and independent risk factor for long-term mortality and poor renal survival. Limitations of this study are the retrospective single centre design and large time span of our patient registry in which treatment modalities for RRT and treatment strategies for ICU patients had changed. To minimise these effects, date of ICU admission was added as confounder.

The predictors for worse long-term outcome after AKI in our previous study were decreased eGFR, but also co-morbid conditions such as CKD and malignancy. Whether these worse outcomes were caused by the renal insult itself or by the co-morbid conditions remained unclear. In **chapter seven** we evaluated this retrospective cohort for renal and overall survival stratified by the presence of comorbidities. For this analysis 1067 patients were included and patients with known chronic RRT or a kidney transplant were excluded. 96 (9%) patients of this cohort had no documented comorbidity. Hospital mortality was similar in the groups with and without comorbidity after adjustment for age, sex and year of admission. By contrast after hospital discharge, compared to patients with comorbidity, patients without comorbidity had a significant better overall (HR 0.28) and renal survival rate (HR 0.24) adjusted for age, sex and year of admission. The standardized mortality ratio (SMR) in AKI patients without comorbidity (SMR 1.6) was similar to the SMR in the overall Dutch population. Whereas the SMR in AKI patients with comorbidity (SMR 4.8), was significantly higher. Limitations to this study were the retrospective design and small number of patients without comorbidities. However despite the small number of patients without comorbidities, we found substantial differences in long-term survival between the groups. This might implicate that patients experiencing AKI without comorbidities have a long-term prognosis comparable to the Dutch population.

Biomarkers for AKI and renal recovery

Biomarkers of kidney injury, such as NGAL, kidney injury molecule-1 (KIM-1), interleukine-18 (IL-18) and liver-type fatty acid-binding protein (L-FABP) provide information about renal damage earlier than renal function markers [20]. To evaluate studies regarding the predictive ability of biomarkers it is important to consider when the samples are taken and whether they are used for the prediction of the diagnosis, staging or outcome of AKI [21]. Prior studies found that the renal damage marker urinary NGAL at ICU admission was a promising and early predictor of AKI and need of CRRT [22-28]. NGAL, KIM-1 and IL-18 also showed promising results in the prediction of 3-year mortality in AKI patients [29]. Of the known biomarkers, NGAL seemed to perform best in predicting AKI and outcome after AKI [24, 25]. In chapters three and five, we hypothesised that urinary NGAL after discontinuation of CRRT might be a marker for short-term successful discontinuation of CRRT, or restart of CRRT within 90 days. Unfortunately in both studies, urinary NGAL lost significance after adjustment for renal function markers and other confounders. However, NGAL concentrations were lower in groups without restart of RRT, therefore we cannot exclude that in a larger sample NGAL could still be predictive for restart of RRT. Nevertheless we found better prediction by the renal function markers creatinine clearance and creatinine ratio than the renal damage marker urinary NGAL for successful discontinuation or restart within 90 days. Accordingly, the more complex renal function marker kinetic eGFR showed better prediction of late major adverse kidney events

than urinary NGAL [14]. This might implicate that the remaining renal function is more important for outcome after AKI than renal damage.

NGAL is a 25 kDa protein secreted by distal tubular cells under stress, but also by neutrophils during bacterial infection as an innate immune response [30-32]. Recently, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth-factor binding protein 7 (IGFBP7) was discovered. Renal tubular cells in oxidative or inflammatory stress secrete these biomarkers. They induce G1 cell cycle arrest during the very early phases of cell injury and thereby avoid damaged tubular cells from dividing [33]. TIMP-2 and IGFBP7 showed superior performance compared to existing biomarkers (such as NGAL) in predicting AKI, major adverse kidney events at hospital discharge and renal recovery at hospital discharge after cardiac surgery associated AKI [33-35]. In the United States of America as well as in several European countries, the TIMP-2 * IGFBP7 test is approved for detection of AKI in high-risk patients. In the "PrevAKI" study in cardiac surgery patients the TIMP-2 * IGFBP7 test was used to identify patients at risk for high stage AKI and subsequently to prevent further damage to the kidneys by implementing a supportive care bundle according to the KDIGO guidelines. These authors found fewer occurrences of AKI and less severe AKI in the intervention group [36].
Whether the TIMP-2 * IGFBP7 test would be effective to identify patients at risk for high stage AKI or nonrecovery after AKI in the general ICU population needs to be investigated.

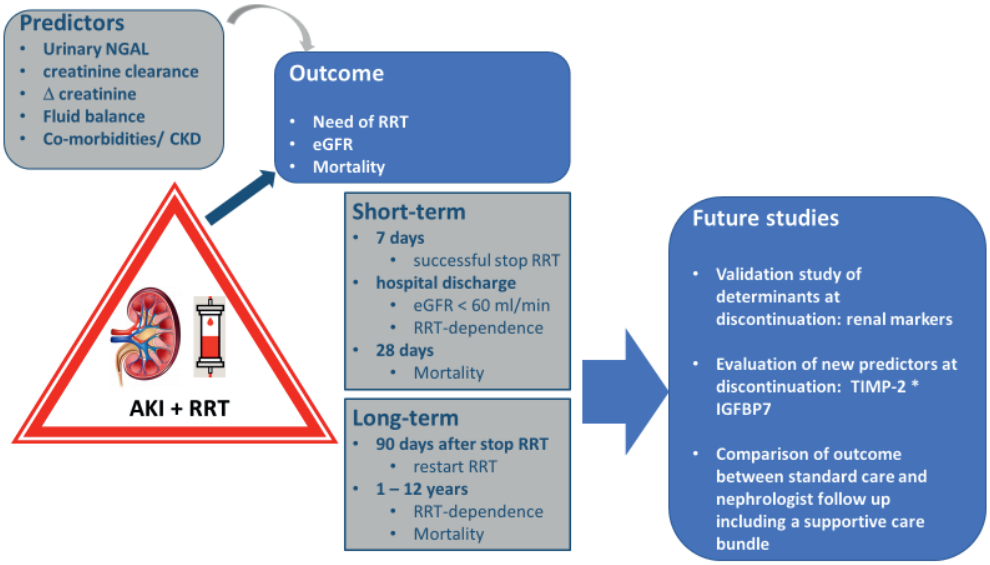
Future perspectives
As previously mentioned urinary TIMP-2 * IGFBP7 seems an interesting new biomarker for the early detection of AKI in selected populations. Compared to urinary NGAL, TIMP-2 * IGFBP7 showed superior performance in these selected populations [34-36]. However, up to now no studies tested TIMP-2* IGFBP7 after discontinuation of CRRT for the prediction of long-term outcome, such as renal recovery and survival. It would be interesting to test TIMP-2*IGFB7 after discontinuation of CRRT as a predictor for successful discontinuation and for restart of RRT within 90 days in our cohort. The decline in urinary biomarkers after cardiopulmonary bypass, especially urinary TIMP-2 * IGFBP7, has shown to be predictive for renal recovery at hospital discharge [34], it would be of interest to evaluate whether a decline in urinary TIMP-2 * IGFBP7 after discontinuation of CRRT in a large multicentre general ICU population can predict long-term renal survival and thereby provide tools to select patients who might benefit from close follow-up.
In accordance with results from the literature, mortality and renal survival after AKI seem strongly related to pre-existing CKD [18, 37]. However, also for patients not known with a history of CKD, the remaining renal function after AKI seems associated with outcome. According to our study, the majority of patients after RRT-requiring AKI have some degree of renal function impairment at hospital discharge. Therefore, further renal function deterioration should be minimised. The kidney disease: improving global outcomes

(KDIGO) guidelines on AKI recommend supportive measures in patients at high risk for AKI. Recommended supportive measures are: protocol-based hemodynamic and oxygenation management, glucose targeted insulin therapy, avoidance of nephrotoxic and radio-contrast agents whenever possible. And the KDIGO CKD guidelines recommend blood pressure and glucose control, dietary advice, encouragement of physical activities and if necessary dose adjustments for medication [19]. Furthermore early nephrologist follow-up may reduce the risk of further renal function decline and reduce mortality [38, 39]. Implementation of preventive measures for AKI has shown good short-term results in selected populations such as cardiac surgery patients [36]. However these studies need confirmation in larger prospective multicentre randomised controlled trials in more generalizable populations. For example the effect on long-term renal and overall survival of nephrological follow-up with implementation of preventive measures according to the KDIGO guidelines could be compared to standard care in patients with an eGFR < 60 ml/min/1.73m^2 at hospital discharge after RRT-requiring AKI.

Furthermore, we provided some tools to guide discontinuation of CRRT. When our results are taken into account, criteria for discontinuation could be an endogenous creatinine clearance of at least 16 ml/min at discontinuation or a creatinine ratio of less than 1.5 at day 2 after discontinuation. However these tools need confirmation in larger prospective trials. Future studies evaluating discontinuation of CRRT should focus on criteria at discontinuation of CRRT. Of interest would be a randomized controlled trial comparing renal and overall survival between patients receiving standard care and patients in whom CRRT is discontinued when predefined criteria are reached. The measurement of urinary TIMP-2 * IGFBP7 concentration at discontinuation would be interesting to add to this analysis, to evaluate whether this biomarker could improve the prediction of successful discontinuation of CRRT regarding short-term and long-term renal and overall survival.

In conclusion, guidelines for discontinuation of CRRT and nephrologist follow-up may improve patient outcome after RRT-requiring AKI. Randomised controlled trials are needed to validate criteria for successful discontinuation of CRRT and to define which patients should receive nephrologist follow up. This thesis provides practical tools to define criteria for future studies evaluating successful discontinuation and for studies evaluating which patients should receive nephrologist follow up.

Figure schematic presentation of predictors, outcome and future perspectives



NGAL, Neutrophil gelatinase-associated lipocalin; CKD, chronic kidney disease; AKI, acute kidney injury; RRT, renal replacement therapy; eGFR estimated glomerular filtration rate; TIMP-2 * IGFBP7, tissue inhibitor of metalloproteinases-2 * insulin-like growth-factor binding protein 7

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CHAPTER 9

Samenvatting, discussie en toekomstperspectieven

Samenvatting, discussie en toekomstperspectieven

Korte termijn uitkomsten na AKI

In dit proefschrift evalueerden we determinanten voor korte en lange termijn uitkomsten na acute nierinsufficiëntie (Acute Kidney Injury, AKI). AKI wordt tegenwoordig gediagnosticeerd door de ratio van het gestegen creatinine en het baseline creatinine of door urine productie zoals gedefinieerd in de AKIN criteria. De AKIN criteria worden veel gebruikt om drie stadia van AKI te definiëren en de uitkomsten in studies te vergelijken op basis van de ernst van AKI. Recent werd de robuustheid van deze definitie ter discussie gesteld door verschillende auteurs, omdat de serum creatinine concentratie niet alleen wordt bepaald door de renale excretoire functie, maar ook door spiermassa en hemodilutie veroorzaakt door overvulling.

Endogene creatinine generatie gebeurt door omzetting van spiermassa, daarom hebben patiënten met minder spiermassa, minder creatinine generatie. In beide gevallen kan dit leiden tot een onderschatting van de ernst van de nierinsufficiëntie. In **hoofdstuk twee** verrichtten we een post-hoc analyse op de multicenter data uit de CASH studie, welke citraat met heparine antistolling voor continue nierfunctievervangende therapie (CRRT) vergeleek. Er werd geen verschil in uitkomsten tussen de groepen gevonden. In 100 patiënten geïncludeerd in de CASH trial, evalueerden we of vochtbalans-gecorrigeerd creatinine bij start van CRRT geassocieerd was met 28 dagen mortaliteit, onafhankelijk van andere markers voor ernst van AKI, surrogaten voor spiermassa (zoals leeftijd, geslacht, ras en gewicht) en ernst van ziekte (APACHE II (Acute physiology and Chronic Health Evaluation) en SOFA (Sequential Organ Failure Assessment) score). Wij vonden dat een lager vochtbalans-gecorrigeerd creatinine ten tijde van start van de CRRT, geassocieerd was met 28 dagen mortaliteit (OR 0.996, $p = 0.019$), terwijl ongecorrigeerd creatinine significantie verloor na correctie voor covariaten. Of de associatie tussen lager vochtbalans-gecorrigeerd initiatie creatinine en mortaliteit staat voor eerdere CRRT start of lagere spiermassa blijft onduidelijk, omdat alleen surrogaten voor spiermassa en vocht status gebruikt zijn in het model. Maar deze studie is hypothese genererend en suggereert dat toekomstige studies die timing van CRRT initiatie op basis van AKI stadium onderzoeken, zouden moeten corrigeren voor vochtbalans en betere markers voor spiermassa.

Verschillende studies evalueerden voorspellers van uitkomsten ten tijde van start van CRRT, slechts enkelen deden dit na staken van CRRT. Wij deden een prospectieve multicenter observationele studie ter evaluatie van voorspellers voor korte en lange termijn uitkomsten na staken van CRRT. In vier ziekenhuizen, waaronder een academisch ziekenhuis, includeerden we 92 patiënten die nog in leven en nog opgenomen op de IC waren ten tijde van staken van CRRT. In **hoofdstuk drie** vonden we dat 7 dagen succesvol staken van CRRT kan worden voorspeld door een betere nierfunctie op dag 2

na staken, bepaald door endogene creatinine klaring (OR 1.066, p = 0.003) of creatinine ratio (dag 2/ dag 0) (OR 0.149, p = 0.006) en non-renale SOFA score (OR 0.822, p = 0.045). Vochtbalans droeg niet-significant bij aan het finale model. Urine neutrophil gelatinase-associated lipocalin (NGAL) verloor significantie na correctie voor covariaten. De optimale cut-off voor creatinine klaring als voorspeller voor 7 dagen succesvol staken van CRRT was 11 ml/min (95% CI 6 – 16 ml/min) en voor creatinine ratio 1.41 (95% CI 1.27 – 1.59). Ondanks screening van een grote groep patiënten die startten met CRRT, werd er maar een kleine groep geïncludeerd in onze studie, dit werd vooral veroorzaakt door overlijden tijdens CRRT (32%) of vroegtijdig ontslag naar de verpleegafdeling (22%). Desondanks was het percentage patiënten dat herstartte met CRRT vergelijkbaar in de geëxcludeerde groep. Er zijn nog geen richtlijnen omtrent het staken van CRRT en in de klinische praktijk wordt CRRT gestaakt op individuele basis, gebaseerd op patiënt-specifieke en logistieke factoren, bijvoorbeeld wanneer het systeem vervangen dient te worden of de patiënt een CT scan moet ondergaan. Met de resultaten van deze studie bieden we een praktisch handvat ter ondersteuning van de klinische besluitvorming, wanneer de creatinine ratio twee dagen na staken van CRRT minder is dan 1.4 of de endogene creatinine klaring is hoger dan 16 ml/min zal het staken waarschijnlijk succesvol zijn.

Een verlaagde eGFR (estimated glomerular filtration rate) is geassocieerd met progressie naar chronische nierinsufficiëntie en eindstadium nierfalen. In **hoofdstuk vier** was het doel om risicofactoren te vinden voor een eGFR ≤ 60 ml/min/1.73m^2 ten tijde van ziekenhuis ontslag na een episode van AKI. We deden een retrospectieve single center cohort studie en analyseerden 353 patiënten die nog in leven waren ten tijde van ziekenhuis ontslag na AKI waarvoor CRRT nodig was tussen 1994 en 2010. Van dit cohort verliet 64% het ziekenhuis met een eGFR ≤ 60 ml/min/1.73m^2, 8.2% was dialyse afhankelijk ten tijde van ziekenhuis ontslag. We vonden een onafhankelijke associatie tussen leeftijd (OR 1.051, p < 0.001) en een eGFR ≤ 60 ml/min/1.73m^2 ten tijde van ziekenhuis ontslag. Verder vonden we een associatie tussen pre-existente chronische nierinsufficiëntie, gedefinieerd als elke gedocumenteerde nierfunctiestoornis in het jaar voorafgaand aan de opname of een basis eGFR ≤ 60 ml/min/1.73m^2, en dialyse afhankelijkheid ten tijde van ziekenhuis ontslag (OR 5.865, P < 0.001). Onze resultaten impliceren dat oudere patiënten een verhoogd risico hebben op een eGFR ≤ 60 ml/min/1.73m^2 ten tijde van ziekenhuis ontslag en patiënten met chronische nierinsufficiëntie een verhoogd risico hebben om dialyse afhankelijk te zijn ten tijde van ziekenhuis ontslag. Daarom zouden deze patiënten goed gemonitord moeten worden, om verdere nierfunctie achteruitgang na AKI waarvoor CRRT nodig was te beperken, bijvoorbeeld door de vochtbalans en urine output na IC ontslag te monitoren en nefrotoxische medicatie en contrast te vermijden. Deze studie heeft enkele beperkingen. De gegevens zijn verzameld over een lange periode, verschillende CRRT modaliteiten werden gebruikt en een uitgangscreatinine was beschikbaar van slechts 34% van de patiënten, dit kan selectie bias hebben veroorzaakt. Verder verkeert de nierfunctie

op het moment van ziekenhuis ontslag nog niet in een steady state. De eGFR zou na ontslag uit het ziekenhuis verder kunnen herstellen. Niettemin loopt de meerderheid van de patiënten met een eGFR ≤ 60 ml/min/1.73m^2 bij ziekenhuis ontslag het risico op verdere achteruitgang van de nierfunctie. Daarom lijkt nefrologische follow-up ter preventie van nieuwe schade of verdere nierfunctie achteruitgang en ter bevordering van nierfunctie herstel aanbevolen.

Lange termijn uitkomsten na AKI

Om de patiënten met een verhoogd risico op verdere nierfunctie achteruitgang na AKI met CRRT beter te definiëren, evalueerden we ook voorspellers voor herstart van nierfunctie vervangende therapie binnen 90 dagen na initieel staken van CRRT vanwege verwacht herstel van nierfunctie. We verrichtten deze analyse op het prospectieve multicenter cohort bestaande uit patiënten in leven en op de IC op dag 2 na initieel staken van CRRT. In **hoofdstuk vijf** evalueerden we of de renale functie markers urine productie en creatinine ratio en de renale schade marker urine NGAL op dag 2 na staken van CRRT, herstart van nierfunctie vervangende therapie binnen 90 dagen voorspelden, gecorrigeerd voor eGFR voor opname en non-renale SOFA score. Voor deze analyse includeerden we 90 patiënten. Bij 32 van deze patiënten (36%) werd de nierfunctie vervangende therapie opnieuw gestart. In de multivariate analyse bleef alleen creatinine ratio op dag 2 (OR 5.28, p = 0.012) over als onafhankelijke voorspeller voor herstart van nierfunctie vervangende therapie binnen 90 dagen. Met een Area Under the Receiver Operating Characteristic curve (AUROC) van 0.76 was de voorspellende waarde van creatinine ratio voor herstart van nierfunctie vervangende therapie goed. De optimale cut-off van creatinine ratio was 1.5, welke gelijk is aan de cut-off die gebruikt wordt om AKI stadium 1 volgens de AKIN criteria voor ontwikkelende AKI te definiëren. Creatinine ratio na staken van CRRT zou een nieuwe tool kunnen zijn om patiënten met een verhoogd risico op verdere nierfunctie achteruitgang te definiëren. Een belangrijke beperking van deze studie was het grote aantal exclusies, vanwege vroegtijdig IC ontslag of ontbrekend urine NGAL. Daarom hebben we het percentage herstart in de geëxcludeerde groep vanwege vroegtijdig ontslag of ontbrekend NGAL ook geanalyseerd en vonden we vergelijkbare percentages van herstart. Desondanks kunnen we niet uitsluiten dat het grote aantal exclusies selectie bias heeft veroorzaakt.

In **hoofdstuk zes** vroegen we ons af of de mate van nierinsufficiëntie ten tijde van ziekenhuis ontslag een onafhankelijke voorspeller is voor lange termijn renale overleving en lange termijn mortaliteit (1-17 jaar). In een groot retrospectief cohort bestaande uit AKI patiënten na CRRT, verzameld tussen 1994 en 2010, stratificeerden we de 475 geïncludeerde patiënten in groepen volgens hun eGFR bij ziekenhuis ontslag. In de multivariate analyse, waarbij we keken naar de lange termijn mortaliteit (1-17 jaar), vonden we een eGFR < 15 ml/min/1.73m^2 (OR 1.93, p = 0.004) en een eGFR tussen 15

-29 ml/min/1.73m^2 (OR 1.62, p = 0.04) bij ziekenhuis ontslag en leeftijd, datum van IC opname, niet-chirurgische opname en maligniteit als onafhankelijke voorspellers. In de multivariate analyse waarbij we keken naar de associatie met 1-17 jaar renale overleving, vonden we een eGFR < 15 ml/min/1.73m^2 (OR 176.96, p < 0.001) en een eGFR tussen 15 -29 ml/min/1.73m^2 (OR 27.40, p = 0.04) en pre-existente chronische nierinsufficiëntie als onafhankelijke voorspellers. Het merendeel van de overlevenden van AKI na CRRT heeft een verminderde nierfunctie ten tijde van ziekenhuis ontslag, en een eGFR < 30 ml/min/1.73m^2 is een sterke en onafhankelijke voorspeller van lange termijn mortaliteit en beperkte renale overleving. Beperkingen van deze studie zijn de retrospectieve en single center opzet en de lange periode waarin patiënten geïncludeerd zijn waarin behandel modaliteiten voor nierfunctie vervangende therapie en de behandel strategieën van IC patiënten veranderd zijn. Om het effect van deze beperkingen te minimaliseren hebben we de datum van IC opname toegevoegd als confounder.

De voorspellers voor een slechte lange termijn uitkomst na AKI in de voorafgaande studie waren een verlaagde eGFR, maar ook comorbiditeit zoals chronische nierinsufficiëntie en maligniteit. Het was onduidelijk of deze slechte lange termijn uitkomsten veroorzaakt werden door de AKI of door de comorbiditeit. In **hoofdstuk zeven** hebben we renale en overall mortaliteit (na 1, 5 en 10 jaar) geanalyseerd in dit retrospectieve cohort, gestratificeerd naar de aanwezigheid van comobiditeit of niet. Voor deze analyse werden 1067 patiënten geïncludeerd, patiënten bekend met chronische nierinsufficiëntie of een niertransplantatie in de voorgeschiedenis werden geëxcludeerd. 96 patiënten (9%) in dit cohort hadden geen gedocumenteerde comorbiditeit. Ziekenhuis mortaliteit was gelijk in beide groepen na correctie voor leeftijd, geslacht en jaar van ziekenhuis opname. Maar vergeleken met patiënten met comorbiditeit, hadden patiënten zonder comorbiditeit na ziekenhuisontslag een betere overall (HR 0.28) en een betere renale overleving (HR 0.24), gecorrigeerd voor leeftijd, geslacht en jaar van ziekenhuis opname. De gestandaardiseerde mortaliteitsratio (SMR) voor patiënten zonder comorbiditeit (SMR 1.6) was vergelijkbaar met de SMR voor de overall Nederlandse populatie. De SMR voor patiënten met comorbiditeit (SMR 4.8) was daarentegen significant hoger. Beperkingen van deze studie waren de retrospectieve studie opzet en het kleine aantal patiënten zonder comorbiditeit. Maar ondanks het kleine aantal patiënten zonder comorbiditeit vonden we een substantieel verschil in lange termijn overleving tussen beide groepen. Dit zou kunnen betekenen dat AKI patiënten zonder comorbiditeit een lange termijn prognose hebben die vergelijkbaar is met de algemene Nederlandse populatie.

Biomarkers voor AKI en nierfunctie herstel

Biomarkers voor AKI zoals NGAL, kidney injury molecule-1 (KIM-1), interleukine-18 (IL-18) en liver-type fatty acid-binding protein (L-FABP) geven eerder informatie over nier schade dan renale functie markers. Om studies betreffende de voorspellende waarde van

biomarkers te vergelijken is het belangrijk om het tijdstip van afname in ogenschouw te nemen, maar ook of ze worden gebruikt om de diagnose, stadiëring of uitkomst van AKI te voorspellen. Eerdere studies vonden dat de nier schade marker NGAL een veelbelovende en vroege voorspeller was voor de diagnose AKI en de noodzaak voor CRRT. NGAL, KIM-1 en IL-18 waren ook veelbelovend als voorspellers voor 3-jaar mortaliteit na AKI. Van de bekende biomarkers leek NGAL het beste in het voorspellen van AKI en de uitkomsten van AKI. In de hoofdstukken drie en vijf hypothetiseerden wij dat urine NGAL na het staken van CRRT een voorspeller zou kunnen zijn voor 7 dagen succesvol staken van CRRT en voor herstart van nierfunctie vervangende therapie binnen 90 dagen na staken van CRRT. Urine NGAL was weliswaar hoger in de groep bij wie herstart van nierfunctie vervangende therapie nodig was, maar urine NGAL verloor significantie in beide studies na correctie voor renale functie markers en andere confounders. Gezien het verschil in de univariate analyses, kunnen we niet uitsluiten dat in een groter cohort NGAL wel voorspellend zou kunnen zijn voor herstart van RRT. Anderzijds vonden we een betere voorspellende waarde voor de renale functie markers creatinine klaring en creatinine ratio dan voor de renale schade marker urine NGAL voor succesvol staken of herstart van RRT binnen 90 dagen. In een andere studie, voorspelde de complexere renale functie marker kinetische eGFR ook beter de late "major adverse kidney events" dan urine NGAL. Dit kan betekenen dat resterende nierfunctie belangrijker is voor de uitkomst dan renale schade.

NGAL is een eiwit van 25 kDa dat uitgescheiden wordt door distale tubulus cellen in stress, maar ook door neutrofielen tijdens een bacteriële infectie als aangeboren immuunrespons. Recent zijn tissue inhibitor of metalloproteinases-2 (TIMP-2) en insulin-like growth-factor binding protein 7 (IGFBP7) ontdekt. Renale tubulus cellen in oxidatieve of inflammatoire stress scheiden deze biomarkers uit. Ze induceren een G1 celcyclus arrest tijdens de zeer vroege fasen van cel schade en voorkomen daarmee dat beschadigde tubuluscellen zich delen. Vergeleken met bestaande biomarkers (zoals NGAL) lieten TIMP-2 en IGFBP7 superieure resultaten zien voor de voorspelling van AKI, "major adverse kidney events" bij ziekenhuis ontslag en nierfunctie herstel bij ziekenhuisontslag bij patiënten met AKI na cardiale chirurgie. In de Verenigde Staten, maar ook in sommigen Europese landen is de TIMP-2* IGFBP7 test goedgekeurd voor de detectie van AKI in hoog risico patiënten. In de "prevAKI" studie in patiënten na cardiale chirurgie werd de TIMP-2 * IGFBP7 test gebruikt om patiënten met een verhoogd risico op AKI te identificeren en om daarna verdere nier schade te voorkomen door implementatie van een 'supportive care' bundel gebaseerd op de KDIGO richtlijn. De auteurs vonden minder AKI en minder ernstig AKI in de interventie groep.
Of TIMP-2 * IGFBP7 ook effectief is om patiënten te identificeren met een verhoogd risico op een hoog AKI stadium of op het uitblijven van herstel van nierfunctie na AKI in de algemene IC populatie en of een positieve uitslag en de daaraan gekoppelde interventies de klinisch uitkomst van de patiënt verbeteren dient nog onderzocht te worden.

Toekomstperspectieven

Zoals eerder genoemd lijkt TIMP-2 * IGFBP7 een interessante nieuwe biomarker voor de vroege detectie van AKI in specifieke populaties. Vergeleken met NGAL, liet TIMP-2 * IGFB7 betere resultaten zien in specifieke populaties. Maar tot op heden heeft geen enkele studie TIMP-2 * IGFBP7 getest *na* staken van CRRT als voorspeller voor lange termijn uitkomsten zoals herstel van nierfunctie en overleving. Het zou interessant zijn om TIMP-2 * IGFBP7 na staken van CRRT te testen als voorspeller voor succesvol staken van CRRT of herstart van RRT binnen 90 dagen in ons cohort. De daling van urine biomarkers na cardiopulmonale bypass, in het bijzonder van TIMP-2 * IGFBP7, bleek voorspellend te zijn voor nierfunctie herstel bij ziekenhuis ontslag. Het zou interessant zijn te evalueren of een daling van TIMP-2 * IGFBP7 na staken van CRRT in een grote multicenter algemene IC populatie voorspellend zou kunnen zijn voor lange termijn renale overleving en daardoor handvatten kan opleveren om patiënten te selecteren die baat kunnen hebben bij nefrologische follow-up.

Wij vonden net als in de literatuur dat mortaliteit en renale overleving na AKI sterk gerelateerd zijn aan pre-existente chronische nierinsufficiëntie. Maar ook bij patiënten zonder chronische nierinsufficiëntie in de voorgeschiedenis, lijkt de resterende nierfunctie na AKI geassocieerd te zijn met uitkomsten. Volgens onze studie heeft de meerderheid van de patiënten bij ziekenhuis ontslag een verminderde nierfunctie na AKI waarvoor zij CRRT hebben gehad. Daarom zou verdere nierfunctie achteruitgang beperkt moeten worden. De kidney disease improving global outcomes (KDIGO) richtlijnen voor AKI bevelen ondersteunende maatregelen aan voor patiënten met een verhoogd risico op AKI. Tot deze aanbevolen maatregelen horen: geprotocolleerd hemodynamisch en zuurstof management, insuline therapie gericht op specifieke glucose targets, vermijden van nefrotoxische medicatie en contrast middelen indien mogelijk. Aanbevolen maatregelen volgens de KDIGO richtlijn voor chronische nierinsufficiëntie zijn: bloeddruk en glucose controle, dieet adviezen, aanmoedigen van fysieke activiteiten en zo nodig dosis aanpassingen van medicatie. Daarnaast kan vroegtijdige nefrologische follow-up waarschijnlijk verdere nierfunctie achteruitgang beperken en mortaliteit verlagen. Implementatie van preventieve maatregelen voor AKI heeft goede korte termijn uitkomsten laten zien in geselecteerde populaties, zoals cardiale chirurgie patiënten. Maar deze studies moeten bevestigd worden in grotere prospectieve multicenter gerandomiseerde trials in de algemene IC populatie. Bijvoorbeeld, een gerandomiseerde studie in patiënten met een eGFR < 60 ml/min/1.73m^2 bij ziekenhuis ontslag na AKI waarin het behoud van nierfunctie en overleving worden vergeleken tussen patiënten die standaard behandeling krijgen en patiënten die nefrologische follow-up en maatregelen volgens een 'supportive care' bundel volgens de KDIGO richtlijn krijgen.

Wij hebben ondersteunende handvatten gevonden die gebruikt kunnen worden om succesvol staken van CRRT te voorspellen. Volgens onze resultaten, kunnen voorspellers

voor succesvol staken van CRRT zijn: een endogene creatinine klaring van ten minste 16 ml/min, of een creatinine ratio kleiner dan 1.5 op dag 2 na staken van CRRT. Maar deze bevindingen hebben nog bevestiging nodig in grotere multicenter studies. Toekomstige studies naar staken van CRRT zouden zich moeten concentreren op criteria ten tijde van stop van CRRT. Het zou interessant zijn een gerandomiseerde gecontroleerde studie te doen waarin renale en overall overleving vergeleken wordt van patiënten die standaard behandeling krijgen met patiënten waarbij CRRT gestaakt wordt als vooraf gedefinieerde voorspellende criteria voor succesvol staken van CRRT behaald zijn. Het zou interessant zijn om bepaling van de TIMP-2 * IGFBP7 concentratie ten tijde van staken van CRRT toe te voegen aan deze analyse, om te evalueren of dit de voorspelling van succesvol staken van CRRT betreffende korte en lange termijn renale en overall overleving kan verbeteren.

Concluderend zouden richtlijnen voor staken van CRRT en nefrologische follow-up de uitkomsten van patiënten na een zodanig ernstig AKI dat CRRT nodig was, kunnen verbeteren. Gerandomiseerde gecontroleerde trials zijn nodig om criteria voor succesvol staken van CRRT te valideren en om verder te specificeren welke patiënten baat kunnen hebben bij nefrologische follow-up. Dit proefschrift heeft praktische handvatten gegeven om criteria te definiëren voor toekomstige studies die succesvol staken van CRRT evalueren en studies die evalueren welke patiënten nefrologische follow-up zouden moeten krijgen.

PART D

Appendices

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Publications

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- Fortrie G, **Stads S**, de Geus HR, Groeneveld AB, Zietse R, Betjes MG. Determinants of renal function at hospital discharge of patients treated with renal replacement therapy in the intensive care unit. J Crit Care 2013 Apr;28(2):126-32
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PhD Portfolio

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Research School: COEUR
PhD period: 2013 – 2019
Promotor: prof. dr. H.M. Oudemans – van Straaten
prof. dr. D. Gommers

1. PhD training	Year	Workload (ECTS)
General courses		
- Basisregelgeving onderzoek (BROK)	2013	1.5
- Survival analysis	2013	1.5
- Biomedical English writing and communication	2016	3
- Good Clinical Practice (GCP)	2019	0.3
In-depth courses		
- Intensive care research (COEUR)	2013 - 2018	2.0
- Training MDS/ NICE	2014	0.3
Specific courses		
- circulatiedagen NVIC	2013	0.6
- Advanced Life Support Houten	2018	1.5
- JCI Dutch Academy – persoonlijk leiderschap incl insights discovery	2018	1.5
- Workshop social media voor medisch specialisten	2015	0.1
Didactic skills		
- Teach the teacher	2016	0.3
- Entrustable Professional Activities (EPA's)	2019	0.1
National Conferences – participation and presentation		
25e Nederlandse Internistendagen (NIV)	2013	0.6
Nederlandse Intensivistendagen (NVIC)	2016- 2018	1.2
Nederlandse Intensivistendagen (NVIC) – Rotterdam	2019	0.8
Poster presentation		

International Conferences – Participation and presentations		
- ESICM 2013, Paris, France	2013	0.9
- ESICM 2014, Barcelona, Spain	2014	0.9
- ISICEM 2016, Brussels, Belgium, *poster presentation*	2016	1.4
- ESICM 2016, Milan, Italy	2016	0.9
- ISICEM 2017, Brussels, Belgium	2017	1.2
- ESICM 2018, Paris, France	2018	0.9
Seminars and workshops		
- Various intensive Care (evening) symposia	2013 - 2015	2.0
- Internal Medicine evening symposium	2013	0.1
- Intensive Care research Meetings (weekly)	2013 - 2016	2.0
- Journal Club intensive Care (weekly)	2013 - 2016	2.0

2. Teaching activities	**Year**	**Workload (ECTS)**
Presentation Coeur research seminar – Impaired kidney function at hospital discharge has a major impact on long-term renal survival and mortality of critically ill patients	2013	0.5
Supervision of research students		
Temporary supervision of G. Fortrie	2013	0.3
Temporary supervision of B. Kazemi	2013 - 2015	0.6
Temporary supervision of V. Van Broekhoven	2015 - 2017	0.6
Temporary supervision of F. Yousufzai	2015 - 2016	0.6

ECTS: European Credit Transfer and Accumulation System
1 ECTS credit represents 28 hours
COEUR: Cardiovascular research school Erasmus University Rotterdam
ESICM: Annual congress of the European Society of Intensive Care Medicine
ISICEM: International Symposium on Intensive Care and Emergency Medicine

Curriculum Vitae

Susanne Stads was born on the 26th of August 1980 in Goirle, the Netherlands. After graduating from secondary school at the Theresia lyceum Tilburg in 1998, she studied medicine at Utrecht University from 1998 until 2005. After graduation, she started as a junior doctor at the department of Internal Medicine of the IJsselland hospital in Capelle aan den IJssel. In January 2007 she started her specialty training in Internal Medicine at the IJsselland hospital, under supervision of dr. H.R.A. Fischer and later of dr. H.E. van der Wiel. In 2009 she continued her specialty training in Internal Medicine in the Erasmus Medical Centre Rotterdam. In 2011 she started her specialty training in Intensive Care Medicine at the Department of Intensive Care, Erasmus Medical Centre, Rotterdam, under supervision of Prof. dr. J. Bakker and later of Prof. dr. D. Gommers. In 2012 she finished her specialty training and successfully passed the written European Intensive Care examination. In 2013 she also passed the oral European Intensive Care examination and received the European Diploma in Intensive Care.

She started working as an internist-intensivist for six months at Meander Medisch Centrum, Amersfoort and as an intensivist for the Mobile Intensive Care Unit (MICU). In 2013 she started working as an internist-intensivist, with special focus on critical care nephrology, at Ikazia Hospital Rotterdam, where she still works with great pleasure.
In the final year of her Intensive Care training she started a research project on outcome after acute kidney injury, which was the basis for her PhD trajectory. She started her PhD trajectory under supervision of prof. dr. A.B.J. Groeneveld and later of prof. dr. H. M. Oudemans-van Straaten.
For local impact and personal development she joined Junior Chamber International Breda, where she is the president of 2019. Susanne lives in Breda, together with Jeroen, his sons Stan and Jack, and their son Teun.

Dankwoord

Eindelijk is het klaar! Voor je ligt het resultaat van ruim 6 jaar onderzoek; mijn proefschrift en ik ben er trots op! Velen hebben mij geholpen in dit traject. Graag wil ik iedereen bedanken voor alle steun, hulp en interesse en zeker ook voor de ontspanning en gezelligheid op z'n tijd. Een aantal mensen wil ik graag in het bijzonder bedanken.

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En natuurlijk ook alle IC-verpleegkundigen, leerlingen, arts-assistenten, ondersteunend personeel en lab-medewerkers Ikazia, heel erg bedankt voor jullie hulp, steun en interesse de afgelopen tijd.

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Outcome after acute kidney injury in ICU patients

Susanne Stads

Stellingen behorende bij dit proefschrift

1. The change in serum creatinine, is not only determined by renal excretory function, but also by creatinine generation by muscle mass and haemodilution. (AS Levey, Kidney international 1990; 38; 167-184)

2. Future studies investigating timing of CRRT initiation using AKI stage, should take fluid balance and better markers for muscle mass into account. (this thesis)

3. Creatinine ratio can predict short-term and long-term need for restart of RRT after initial discontinuation of CRRT. (this thesis)

4. The remaining renal function seems more important to predict whether the kidney will recover than the renal damage marker NGAL. (this thesis)

5. The majority of survivors after RRT-requiring AKI have renal function impairment at hospital discharge. (this thesis)

6. An eGFR < 30 ml/min/1.73m^2 is a strong and independent risk factor for long-term mortality and poor renal survival. (this thesis)

7. Intensive Care physicians are more likely to be oliguric than their patients. (AW Solomon, BMJ 2010; 341; c6761)

8. Implementation of a supportive care bundle could improve outcome for AKI patients – KDIGO 2012

9. Curiosity keeps leading us down new paths – Walt Disney

10. It always seems impossible until it's done – Nelson Mandela

11. Everything will be okay in the end, if it's not okay, it's not the end – John Lennon