Long term end-stage renal disease and death following acute renal replacement therapy in the ICU

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Introduction: In ICU the need for acute renal replacement therapy (RRT) associates with high mortality and risk of end-stage renal disease (ESRD), but there are limited long-term data. We investigated these outcomes and their risk factors.
Methods: Retrospective analysis of all adult patients admitted to a general, university hospital ICU 2005–2012, excluding chronic dialysis patients. ESRD was defined as need of RRT > 90 days or kidney transplant.
Results: Of 5766 patients included, 1004 (16%) received acute RRT; their 30-day mortality was 42% vs. 16% for those not requiring acute RRT (adjusted hazard ratio (HR) 1.13 (0.96–1.32)). The 90-day mortality was 55% for patients receiving acute RRT vs. 22% for those who did not (adjusted HR 1.32 (1.15–1.51)) and 1-year mortality was 63% vs. 30%, respectively, (adjusted HR 1.31 (1.16–1.48)). The 7-year risk of ESRD for ICU patients surviving 90 days was 10% for patients who received acute RRT vs. 0.5% among those who did not (adjusted HR 5.9 (2.9–12.4)). Independent risk factors for ESRD included pre-existing kidney disease, pre-existing peripheral vascular disease and use of acute RRT in ICU.
Conclusions: The need of acute RRT was associated with markedly increased long term risk of death and ESRD; in contrast its use was not associated with 30-day mortality. In addition to acute RRT, decreased kidney function and peripheral vascular disease before ICU admission were risk factors for ESRD. It seems warranted offering medical follow-up to patients after acute RRT in ICU.

Editorial comment: what this article tells us
Patients requiring acute renal replacement therapy in the ICU have higher long-term risks for death and dialysis need. This study showed that the 30 day mortality risk for these patients was not increased, suggesting that the post-ICU period is also important for these outcomes.

The incidence of acute kidney injury (AKI) in patients admitted to the ICU is high,[1–6] and AKI is associated with increased short term[5–7] and long term mortality.[1,2,8] Severe AKI with need of acute renal replacement therapy (RRT) occurs in up to 9% of all ICU patients,[1,3,8–11] and is associated with even higher short and long term mortality rates,[1,11–13] and increased risk of

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end-stage renal disease (ESRD) of up to 12% after 90 days.[12,14–17] The underlying pathophysiology of AKI and how this affects patient mortality is not yet fully understood.[18–20]

Only few single center studies have been published with large homogenously selected patient populations needing acute RRT in ICU describing the risk of death and ESRD beyond one year.[21]

We describe the long term (up to 7 years) risk of death and ESRD in patients requiring acute RRT in a large general ICU population. We also investigate characteristics of those patients surviving acute RRT compared to those who do not and whether long term outcome after acute RRT is associated with specific risk factors. Further we investigate which risk factors in acute RRT patients can lead to developing ESRD.

Material and methods

Patients

We included all patients admitted to the general ICU at Rigshospitalet, University of Copenhagen, Denmark, from January 1st 2005 to December 31st 2012. The hospital runs separate ICUs for cardiothoracic, cardiac, hepatologic, neurosurgical and neurologic patients, so we did not include patients with admission diagnoses within these specialties. We excluded patients under the age of 18 years, postoperative patients with expected stay of less than 24 h, patients without permanent residency in Denmark and all patients registered in the Danish Society of Nephrology database as receiving chronic dialysis at the time of ICU admission. Patients were allocated to the acute RRT group if they received acute RRT at any time during their ICU stay; otherwise they were counted as non-RRT patients. We excluded all readmissions, unless non-RRT patients received acute RRT during a later admission, in which case they were moved from the non-RRT group at the time of readmission and added to the acute RRT group with delayed entry. Therefore, a patient could count in both groups but only appear in one group at any given time. Acute RRT was available in the ICU around the clock, and was initiated at clinical indications according to KDIGO Clinical Practice Guidelines for Acute Kidney Injury which include fluid overload, electrolytes imbalance, acid/base disturbances, trends in blood urea nitrogen or creatinine rather than single thresholds alone or intoxications.[22] Indications for acute RRT did not change during the study period. The routine practice for acute RRT in our department was to use continuous renal replacement therapy (CRRT) in hemodynamically unstable patients and change modality to intermittent hemodialysis (IHD) when the patients were hemodynamically stable. Follow up for all patients was until October 10th 2013.

The study was approved by the Danish Data Protection Agency (record number 2013-41-1981) and by the Danish Health and Medicines Authority with waiver of patient consent (record number 3-3013-361/1). The use of data in our study did not require the approval of the National Committee on Health Research Ethics (record number H-4-2013-027-FSP).

Data collection

Patients' data were retrieved from the Rigshospital ICU database, 'Critical Information System' (CIS, Daintel ApS, Copenhagen) in which use of acute RRT was coded by the ICU clinicians. We utilized the civil registration number, which is assigned to all Danish residents by the Danish Civil Registration System and links all Danish registries.[23] Variables from CIS included date of ICU admission and discharge, gender, age, Simplified Acute Physiology Score 2 (SAPS 2), Sepsis-related Organ Failure Assessment score (SOFA), and ICU treatments such as vasopressors and mechanical ventilation. The reliability of data from CIS has previously been found to be high.[24] We did a quality control of the data to ensure the accuracy of acute RRT registration in the database. This was done by manually going through the notes of all patients admitted to the ICU during the months of October and November in 2007 and 2012, to find potential discrepancies between the notes and coding of acute RRT. The accuracy was above 95%. To identify preexisting comorbidity data from the Danish National Registry of Patients (DNRP) was used. Diagnoses from the DNRP have been coded according to the International Classification of Diseases 10th revision (ICD-10)

since 1994, and include all hospital admission diagnoses since 1977, and all emergency room and outpatient clinic visit diagnoses since 1995.[25] The primary diagnoses for hospitalizations and outpatient clinic visits of minimum one year, up to 8 years before the current ICU admission were used to group comorbidities.[14] The validity of ICU admission data from the DNRP has previously been established.[26] The DNRP was also used for to obtain the mortality data. Finally, data on preexisting chronic dialysis were taken from the Danish Society of Nephrology (DNS) database, where every patient receiving chronic dialysis in Denmark is registered and monitored through their civil registration number.[27] Data from the DNS database were also used to determine which patients would develop ESRD, which by the database definition was the need of RRT for more than 90 days or kidney transplant.

Statistical analysis

Patient characteristics were presented in tables as absolute numbers and medians with interquartile ranges (IQR), or percentages with 95% confidence intervals (CI). Groups were compared using the Wilcoxon–Mann–Whitney test for continuous data and the χ^2-test for categorical data. Cumulative mortality plots with 95% confidence intervals (CI) were made using Greenwood's formula for the survival of non-RRT patients and acute RRT patients. Patients were followed until death or the end of the 7-year study period on October 1st, 2013, whichever came first. The survival was similarly calculated at 30, 90 and 365 days after admission for the groups. A cumulative incidence curve for the risk of ESRD after admission with mortality as competing risk was made, comparing non-RRT patients with acute RRT patients. Patients were followed until ESRD, death or the end of the 7-year study period, whichever came first. The Cox proportional hazards regression model with acute RRT as time dependent covariate was used to calculate the differences in survival between the groups as hazard ratios (HR). In this way we could include patients initially not receiving RRT who would be readmitted and receive acute RRT without omitting the follow up period of either. HR were adjusted for age, gender, SAPS 2, chronic kidney disease, hypertension, diabetes, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, malignant neoplasm, ischemic heart disease and chronic obstructive pulmonary disease. Patients with missing data were omitted from the Cox proportional hazards regression. *P* values less than 0.05 and a HR not including 1 in the 95% CI were considered significant.

The data was analyzed using MATLAB release 2014b (MathWorks, Natick, MA, USA) and R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

We included 5766 adults admitted to the ICU from January 1st 2005 to December 31st 2012 (Fig. 1). The total follow-up time was 14,525 person-years with a median duration of 4.1 years (IQR 2.3–6.4). Nine-hundred and thirty-one of the 5766 patients received acute RRT (16.1% (95% CI 15.2–17.1)) at their first admission. Seventy-three patients (1.3% (1.0–1.6) received acute RRT only during a subsequent ICU admission. Of the 4762 patients not receiving RRT, 249 (5.2%) died within the first 24 h. The patients receiving acute RRT in the ICU were older and more acutely and chronically ill, had a longer ICU stay and required more life support than those not receiving acute RRT (Table 1).

Mortality

Mortality rates at 30-, 90- and 365-days and the cumulative 7-year mortality were markedly higher in patients receiving acute RRT as compared to those who did not (Fig. 2). The adjusted HR was significantly higher for acute RRT patients for 90 and 365-day mortality, but this was not the case for 30-day mortality (Table 2).

The median age was 61 years (IQR: 49–68) for acute RRT 90-day survivors compared to 65 years (55–73) for non-survivors. The median SAPS 2 score was 53 (43–64) acute RRT 90-day

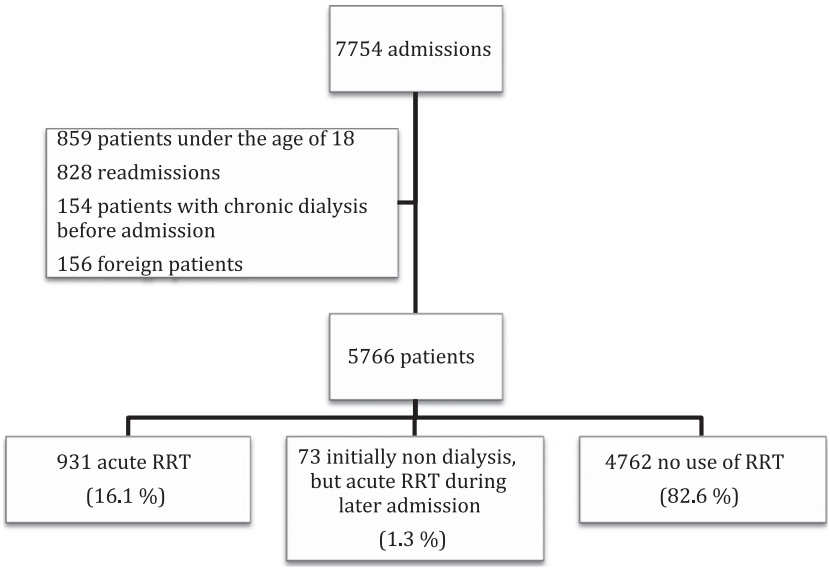

Fig. 1. Study population flow chart: Admissions to the ICU 2005–2012, exclusions and study groups based on use of acute renal replacement therapy (RRT) in ICU.

survivors and 61 (49–74) for non-survivors ($P < 0.001$). Acute RRT 90-day survivors compared to non-survivors less often needed vasopressor treatment (72.6% vs. 84.2% ($P < 0.001$)) had a lower incidence of preexisting congestive heart failure (9.7% vs. 16.5% ($P = 0.007$)) and had a lower incidence of preexisting malignant neoplasm (21.5% vs. 41.5% ($P < 0.001$)). Otherwise there were no significant differences in comorbidities.

Risk of ESRD

The cumulative 7-year incidence of ESRD for patients surviving 90 days after ICU admission was 10.1% (7.3–13.8%) for patients who had received acute RRT vs. 0.53% (0.32–0.85%) for those who had not (adjusted HR 5.93 (2.85–12.36), Fig. 3).

The main difference between acute RRT 90-day survivors developing ESRD and those not developing ESRD was the rate of chronic kidney disease prior to ICU admission (Table 3).

Independent risk factors for ESRD among all 90-day survivors, both non-RRT patients and acute RRT patients, are presented in Table 4. In addition to acute RRT, preexisting kidney disease and peripheral vascular disease were independent risk factors for developing ESRD.

Discussion

The rate of acute RRT after admittance to the general ICU at Rigshospitalet was 16%. Acute RRT patients were older, more often male and more severely ill at admission and during their ICU stay. The 30-day mortality of acute RRT patients was 42%, more than double compared to non-RRT patients, with acute RRT patients having more preexisting comorbidities. After adjustment for confounders we found that acute RRT patients had no significant increased 30-day mortality. A possible explanation for this finding could be that the acute RRT patients simply were more severely ill and that acute RRT can be seen as a marker for disease burden. Also, dividing patients into groups based on the need of acute RRT at any time during their stay in the ICU might have affected this. Consequently, patients with severe AKI but without the need of acute RRT were included in the non-RRT group. In addition, some patients could have died before they would receive acute RRT. Still, it could be argued that the excess mortality in the first 30 days is not due to the absence of kidney function defined by need of acute RRT. Rather it may seem to be a result of patients being more severely ill, or be dependent on the presence of severe AKI without the

Table 1 Characteristics of ICU patients by the use of acute RRT during ICU admission.

	Data available	No use of RRT (n = 4835)	Acute RRT (n = 1004)	P
Age (years), median (IQR)	5839	60 (45–70)	63 (52–71)	< 0.01
Gender (male)	5839	3022 (62.5%)	671 (66.8%)	0.04
Days in the ICU, median (IQR)	5839	1.8 (0.8–4.8)	9.0 (3.7–18.4)	< 0.01
ICU scores				
SAPS 2 (points), median (IQR)	3990	38 (29–48)	57 (46–70)	< 0.01
First SOFA (points), median (IQR)	3776	6 (4–9)	12 (9–15)	< 0.01
MAX SOFA (points), median (IQR)	3782	7 (5–10)	14 (12–17)	< 0.01
ICU treatment				
Vasopressor treatment	5839	1707 (35.3%)	794 (79.1%)	< 0.01
Mechanical ventilation	5839	3608 (74.6%)	930 (92.6%)	< 0.01
Mechanical ventilation (days), median (IQR)	5839	1.4 (0.5–4.3)	7.4 (2.6–15.4)	< 0.01
Preexisting comorbidity				
Chronic kidney disease (non-RRT)	5839	294 (6.1%)	254 (25.3%)	< 0.01
Hypertension	5839	1169 (24.2%)	299 (29.8%)	< 0.01
Diabetes	5839	497 (10.3%)	168 (16.7%)	< 0.01
Congestive heart failure	5839	407 (8.4%)	136 (13.5%)	< 0.01
Myocardial infarction	5839	193 (4.0%)	50 (5.0%)	0.36
Peripheral vascular disease	5839	792 (16.4%)	234 (23.3%)	< 0.01
Cerebrovascular disease	5839	521 (10.8%)	103 (10.3%)	0.89
Malignant neoplasm	5839	1447 (29.9%)	328 (32.7%)	0.23
Ischemic heart disease	5839	296 (6.1%)	77 (7.7%)	0.19
Chronic obstructive pulmonary disease	5839	618 (12.8%)	145 (14.4%)	0.37
Primary diagnosis at ICU admission				
Sepsis	5839	402 (8.3%)	306 (30.5%)	< 0.01
Other infectious diseases	5839	303 (6.3%)	59 (5.9%)	0.90
Cancer	5839	5 (0.1%)	2 (0.2%)	0.73
Endocrinological diseases	5839	25 (0.5%)	4 (0.4%)	0.89
Cardiovascular diseases	5839	454 (9.4%)	118 (11.8%)	0.07
Respiratory diseases	5839	1326 (27.4%)	201 (20.0%)	< 0.01
Gastrointestinal or liver diseases	5839	148 (3.1%)	43 (4.3%)	0.14
Trauma or poisoning	5839	963 (19.9%)	65 (6.5%)	< 0.01
Other	5839	1209 (25.0%)	206 (20.5%)	0.01

Results are presented as number (percent) or as median (IQR). MAX SOFA is the highest SOFA score recorded during the ICU stay. RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment score.

need for acute RRT which we could not evaluate from our data. Conversely, the long term mortality beyond 30 days was significantly higher even after adjustment and hence not only due to differences in severity of illness and comorbidities. It may be speculated that a severe kidney insult (AKI requiring acute RRT) is followed by a decrease in kidney function and thus increased long term mortality, which is a well-established relation in the general population.[2,12,22]

Acute RRT patients not surviving more than 90 days from admission were older and more severely ill during the course of their ICU stay compared to those that did survive, but were similar in terms of preexisting comorbidity. Acute RRT 90-day survivors had a 10.1% long term risk of developing ESRD compared to non-RRT patients (0.5%). This corresponded to an HR of 5.9 for acute RRT patients when adjusting for confounders. In comparison, the cumulative incidence of ESRD in Denmark in the entire 6 year period from 2008 to 2013 was 0.07%.[27] Acute RRT patients surviving 90 days and developing ESRD had a higher incidence of pre-existing chronic kidney disease compared to those that did not develop ESRD. Thus patients with preexisting decreased renal function are the most vulnerable patients in the ICU in terms of risk of losing renal function if surviving. The risk of ESRD was higher for acute RRT patients, even several years following the initial

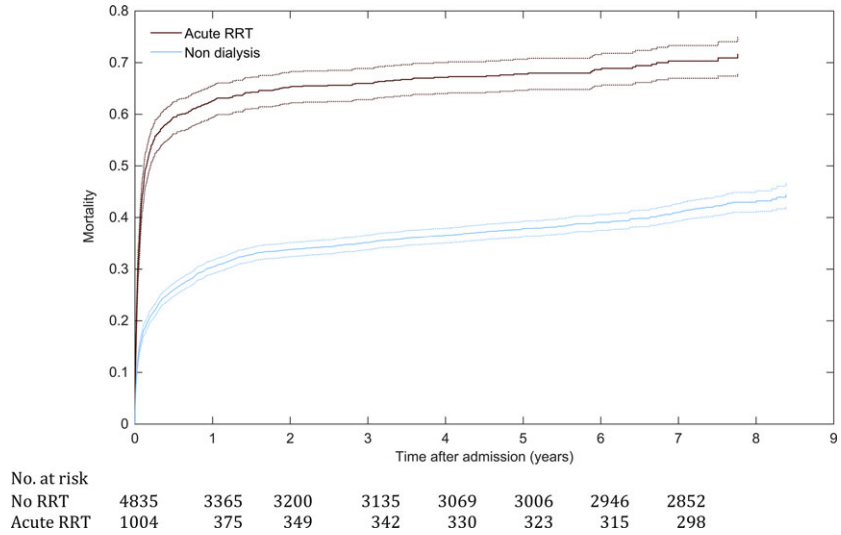

Fig. 2. Cumulative 7-year mortality after ICU admission. 95% confidence interval shown as broken lines. RRT, renal replacement therapy.

Table 2 Mortality rates after ICU admission.

	No use of RRT (n = 4835) (95% CI)	Acute RRT (n = 1004) (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
30-day mortality	16.3% (15.2–17.4)	41.9% (38.6–44.9)	2.95 (2.62–3.33)	1.13 (0.96–1.32)
90-day mortality	21.9% (20.7–23.1)	55.0% (51.7–58.1)	3.14 (2.83–3.49)	1.32 (1.15–1.51)
365-day mortality	30.4% (29.1–31.7)	62.6% (59.4–65.6)	2.78 (2.53–3.06)	1.31 (1.16–1.48)

*Adjusted for age, gender, SAPS2, chronic kidney disease (without RRT), hypertension, diabetes, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, malignant neoplasm, ischemic heart disease, and chronic obstructive pulmonary disease. RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval.

admission, emphasizing the importance of the KDIGO recommendations to follow patients after AKI as they are at increased risk for chronic kidney disease (recommendation 2.3.4).[22] It seems warranted offering nephrological follow-up to patients after acute RRT according to international guidelines[22,28] to manage metabolic complications associated with loss of kidney function, to institute medical treatment with the aim of slowing of progression to end state kidney disease and to prepare for dialysis, transplantation or conservative uremia management in time.[2] Further studies on the effectiveness and benefits of such follow up are necessary.

Concerning comparison with previous studies, our study is one of the largest single center studies with a large homogenously selected patient population evaluating the mortality and risk of ESRD between non-RRT and acute RRT patients, with a median follow up of 4.1 years.

The frequency of acute RRT in our study (16.1%) was generally higher than in other similar studies. Other previous studies found a frequency of acute RRT between 4% and 9%[1,3,8–11]; of which all were multi-center studies with more diverse patient populations. In contrast, in our study there were no neurological and uncomplicated post-operative patients, groups who rarely need acute RRT. Also, RRT was readily available and might have been started on different indications. However, a recent multicenter study by the FINNAKI-study group found frequencies of acute RRT in septic shock

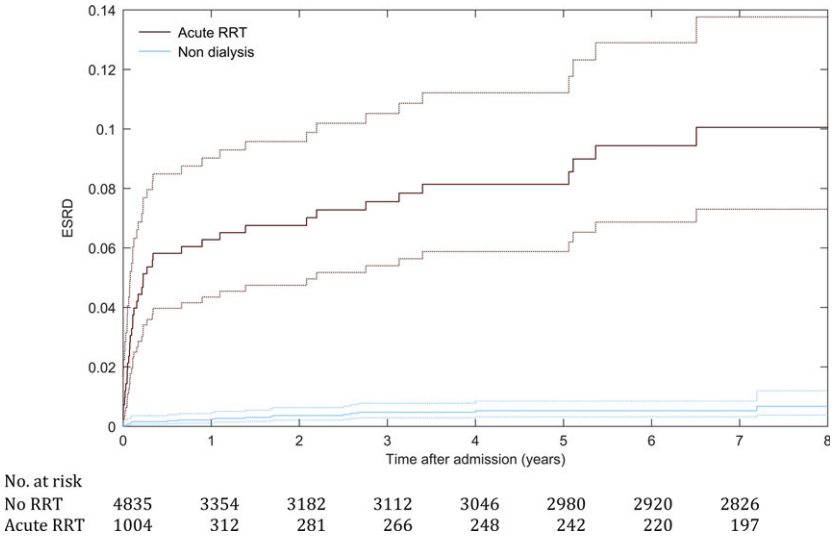

Fig. 3. Cumulative 7-year incidence of end-stage renal disease (ESRD) in 90-day survivors after ICU admission. 95% confidence interval shown as broken lines.

patients varying from 3% to 36% in different centers with a total of 18% of patients with septic shock receiving acute RRT.[29] This indicates that the use of acute RRT varies greatly between centers, and that multicenter studies may have lower frequency than that observed in highly specialized centers. Severity of illness scores in our population were generally higher compared to other studies.[1,3,9,11,29]

The 90-day mortality of acute RRT patients (55%) found in our study is comparable to studies by Triverio et al.,[12] and Bagshaw et al.[9] Several other studies had no long-term data but reported hospital mortalities between 60% and 63%.[3,10,11] In a multicenter study by Nisula et al.[1] the reported 90-day mortality was lower (39%) than in our study, but the variability in mortality between different centers was large.

Few other studies have investigated a comparable long-term risk of ESRD. We found a 10% long-term risk of ESRD in acute RRT 90-day survivors. This is comparable to other studies reporting a long term risk of ESRD between 10% and 12% among acute RRT ICU patients.[12,14,21] In our cohort, the risk of developing ESRD in the first half a year after leaving the ICU was comparable to the risk after half a year, suggesting that the risk is sustained over time. Similar results were found in a nationwide study by Gammelager et al.,[14] and a study by Wald et al.[17] investigating acute RRT patients from all hospital wards.

We found that acute RRT, preexisting kidney disease and peripheral vascular disease were independent risk factors for developing ESRD. This is comparable to a nationwide study by Riemes-Stigare et al.[2] who found that both acute kidney injury patients and chronic kidney disease patients had an increased risk of ESRD.

The main strengths of our study are the single center design, a large homogenous patient population, a long follow-up period and high quality data. Furthermore, our study focuses on acute RRT instead of AKI stages because the risk profile of acute RRT patients is of high significance to clinicians. Our study has some limitations as well. There are missing results on SAPS 2 scores, which led to omitting patients from the Cox proportional hazards model. These patients were generally from the group not receiving RRT and where generally younger and had less comorbidities, but where otherwise comparable to patients not receiving RRT. Therefore, the remaining patients should be representative. Alternatively, this would create type two error increasing the difference in mortality. Furthermore, as already mentioned patients

Table 3 Characteristics of acute RRT 90-day survivors developing ESRD and those who did not.

	Data available	90-day survivors developing ESRD (n = 38)	90-day survivors not developing ESRD (n = 404)	P
Age (years), median (IQR)	442	61 (52.0–70.0)	61 (49–68)	0.55
Gender (male)	442	25 (65.8%)	271 (67.1%)	1.00
Days in the ICU, median (IQR)	442	7.2 (3.6–15.6)	10.9 (5.7–20.9)	0.02
ICU scores				
SAPS 2 score (points), median (IQR)	427	56 (41–68)	53 (43–64)	0.72
First SOFA (points), median (IQR)	417	11 (8–15)	12 (9–14)	0.91
MAX SOFA (points), median (IQR)	418	12 (9–15)	13 (11–16)	0.34
ICU treatment				
Vasopressor treatment	442	24 (63.2%)	297 (73.5%)	0.28
Mechanical ventilation	442	30 (78.9%)	371 (91.8%)	0.04
Mechanical ventilation (days), median (IQR)	442	7.0 (2.0–12.8)	8.6 (4.2–16.8)	0.13
Preexisting comorbidity				
Chronic kidney disease (non-RRT)	442	23 (60.5%)	90 (22.3%)	< 0.01
Hypertension	442	14 (36.8%)	119 (29.5%)	0.51
Diabetes	442	6 (15.8%)	56 (13.9%)	0.78
Congestive heart failure	442	4 (10.5%)	39 (9.7%)	0.99
Myocardial infarction	442	2 (5.3%)	16 (4.0%)	0.94
Peripheral vascular disease	442	9 (23.7%)	82 (20.3%)	0.73
Cerebrovascular disease	442	3 (7.9%)	36 (8.9%)	0.97
Malignant neoplasm	442	12 (31.6%)	83 (20.5%)	0.18
Ischemic heart disease	442	4 (10.5%)	29 (7.2%)	0.78
Chronic obstructive pulmonary disease	442	4 (10.5%)	50 (12.4%)	0.93
Primary diagnosis at ICU admission				
Sepsis	442	7 (18.4%)	112 (27.7%)	0.47
Other infectious diseases	442	6 (15.8%)	20 (5.0%)	0.03
Cancer	442	(0.0%)	1 (0.2%)	0.95
Endocrinological diseases	442	(0.0%)	3 (0.7%)	0.87
Cardiovascular diseases	442	3 (7.9%)	43 (10.6%)	0.87
Respiratory diseases	442	9 (23.7%)	66 (16.3%)	0.51
Gastrointestinal or liver diseases	442	2 (5.3%)	11 (2.7%)	0.68
Trauma or poisoning	442	4 (10.5%)	38 (9.4%)	0.98
Other	442	7 (18.4%)	110 (27.2%)	0.50

Results are presented as number (percent) or as median (IQR). MAX SOFA is the highest SOFA score recorded during the ICU stay. ESRD, end-stage renal disease; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment score.

with severe AKI but without the need of acute RRT were not included in the acute RRT group but rather in the non-RRT group. Thus, we cannot address the impact of AKI in terms of AKI stages. However, AKI stages at the moment of decision in the clinical setting are subtle because changes in creatinine and urine output are dependent on hydration status, rehydration strategy, and use of diuretics. This study aims at describing the outcomes of patients with a lack of kidney function as defined by need of aRRT. We therefore focused on patients where the clinician finds overall indication for acute RRT instead of changes of a single parameter alone. Also, we might have missed patients who died in the ICU, but would otherwise have developed the need for acute RRT. This could potentially have increased the difference in mortality between the two groups. However, this would only have made the difference more significant and not have changed the conclusion. Finally, due to the retrospective design of this study there is a certain risk of selection bias and unmeasured confounding. Although we adjusted for confounders in groups, we cannot make any definitive statements on causality. However, our data can still identify acute RRT patients as an especially high risk population,

Table 4 Independent risk factors for ESRD in all 90-day survivors.

	Adjusted* HR (95% CI)
aRRT	5.93 (2.85–12.36)
Gender (Male)	0.97 (0.52–1.80)
Age	1.02 (0.99–1.04)
SAPS 2	1.02 (1.00–1.04)
Chronic kidney disease (non-RRT)	8.18 (4.37–15.31)
Hypertension	1.00 (0.52–1.95)
Diabetes	0.90 (0.41–1.98)
Congestive heart failure	1.04 (0.40–2.69)
Myocardial infarction	0.71 (0.18–2.74)
Peripheral vascular disease	2.13 (1.02–4.42)
Cerebrovascular disease	0.87 (0.33–2.31)
Malignant neoplasm	0.88 (0.30–2.55)
Ischemic heart disease	1.25 (0.63–2.48)
Chronic obstructive pulmonary disease	0.83 (0.33–2.05)

*Adjusted for each of the other variables. HR, hazard ratio; CI, confidence interval; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score.

and our conclusion should therefore still be valid.

In summary, we found that the need of acute RRT did not have an independent impact on 30-day mortality after adjustment for confounders. This might be due to the group allocation, but it may be that the lack of renal function in itself is not associated with short-term mortality. However, the need of acute RRT was associated with long-term mortality and this might be due to decreased kidney function following AKI. Patients known to have decreased kidney function before admission to the ICU were identified to be a vulnerable population in terms of developing ESRD after acute RRT. We conclude that offering patients nephrological or medical follow-up after acute RRT in an ICU setting seems warranted.

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References

1. Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R, Laurila JJ, Tenhunen J, Reinikainen M, Ala-Kokko T, Ruokonen E, Kuitunen A, Pettila V, Group FS. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013; 39: 420–8.
2. Rimes-Stigare C, Frumento P, Bottai M, Martensson J, Martling CR, Bell M. Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. Crit Care 2015; 19: 383.
3. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35: 1837–43; quiz 52.
4. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant 2008; 23: 1203–10.
5. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10: R73.
6. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009; 35: 1692–702.
7. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34: 1913–7.
8. Gammelager H, Christiansen CF, Johansen MB, Tonnesen E, Jespersen B, Sorensen HT. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. Crit Care 2012; 16: R124.
9. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005; 9: R700–9.
10. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C. Beginning, ending supportive therapy for the kidney I. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813–8.
11. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W. Effect of acute renal failure requiring renal replacement therapy

on outcome in critically ill patients. Crit Care Med 2002; 30: 2051–8.
12. Triverio PA, Martin PY, Romand J, Pugin J, Perneger T, Saudan P. Long-term prognosis after acute kidney injury requiring renal replacement therapy. Nephrol Dial Transplant 2009; 24: 2186–9.
13. Renal Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361: 1627–38.
14. Gammelager H, Christiansen CF, Johansen MB, Tonnesen E, Jespersen B, Sorensen HT. Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study. Crit Care 2013; 17: R145.
15. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012; 380: 756–66.
16. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 53: 961–73.
17. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JG; University of Toronto Acute Kidney Injury Research G. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009; 302: 1179–85.
18. Bonventre JV. Pathophysiology of AKI: injury and normal and abnormal repair. Contrib Nephrol 2010; 165: 9–17.
19. Wen X, Murugan R, Peng Z, Kellum JA. Pathophysiology of acute kidney injury: a new perspective. Contrib Nephrol 2010; 165: 39–45.
20. Moore EM, Bellomo R, Nichol AD. The meaning of acute kidney injury and its relevance to intensive care and anaesthesia. Anaesth Intensive Care 2012; 40: 929–48.
21. Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH. Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. Am J Kidney Dis 2002; 40: 275–9.
22. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Inter Suppl 2012; 2: 1–138.
23. Pedersen CB. The Danish civil registration system. Scand J Public Health 2011; 39: 22–5.
24. Gronlykke L, Brandstrup SL, Perner A. Data from clinical database on septic shock are valid. Dan Med J 2012; 59: A4522.
25. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46: 263–8.
26. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Norgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report. Clin Epidemiol 2013; 5: 9–12.
27. The Danish Society of Nephrology (DNS). Annual Report 2013. 2014 edn. http://www.nephrology.dk: Danish Nephrology Registry (DNR), 2014: 23.
28. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter Suppl 2013; 3: 1–150.
29. Poukkanen M, Koskenkari J, Vaara ST, Pettila V, Karlsson S, Korhonen AM, Laurila JJ, Kaukonen KM, Lund V, Ala-Kokko TI, Group FS. Variation in the use of renal replacement therapy in patients with septic shock: a substudy of the prospective multicenter observational FINNAKI study. Crit Care 2014; 18: R26.