FACULTY OF HEALTH, AARHUS UNIVERSITY

Timing of renal replacement therapy and long-term risk of chronic kidney disease and death in intensive care patients with acute kidney injury

Research year report

Søren Christiansen
Department of Clinical Epidemiology, Aarhus University Hospital

Supervisors and collaborators

Christian Fynbo Christiansen, MD, PhD, Associate professor (Main supervisor)
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Steffen Christensen, MD, PhD, Associate professor (Co-supervisor)
Department of Anesthesiology and Intensive Care, Aarhus University Hospital

Henrik Gammelager, MD, PhD, Associate professor (Co-supervisor)
Department of Anesthesiology and Intensive Care, Aarhus University Hospital
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Lars Pedersen, PhD, Professor (Co-supervisor)
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Bradley Layton, PhD, Research assistant professor (Collaborator)
Gillings School of Global Public Health, University of North Carolina

Alan Brookhart, PhD, Associate professor (Collaborator)
Gillings School of Global Public Health, University of North Carolina

Preface

The present report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital.

First of all, I would like to express my deepest gratitude to my main supervisor, Christian Fynbo Christiansen, who has introduced me to scientific research and the field of clinical epidemiology. Throughout the project he has motivated me, shown never-ending engagement and guided me with constructive feedback.
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Abbreviations

AKI	Acute kidney injury
BUN	Blood urea nitrogen
CI	Confidence interval
CIS	Clinical information system
CKD	Chronic kidney disease
CPR	Civil registration number
DNPR	Danish National Patient Registry
ECMO	Extra corporal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HR	Hazard ratio
ICU	Intensive care unit
IQI	Interquartile interval
KDIGO	Kidney Disease Improving Global Outcomes
MDRD	Modification of diet in renal disease
OR	Odds ratio
P	Plasma
RCT	Randomized controlled trial
RRT	Renal replacement therapy
SD	Standard deviation
SMD	Standard mean difference
RR	Relative risk

Table of contents

ABSTRACT **1**

DANSK RESUMÉ **1**

INTRODUCTION **1**

METHODS **1**

STUDY POPULATION AND SETTING 1

TIMING OF RENAL REPLACEMENT THERAPY 2

CHRONIC KIDNEY DISEASE, END-STAGE RENAL DISEASE AND MORTALITY 3

COVARIATES 3

STATISTICAL ANALYSIS 4

RESULTS **5**

DESCRIPTIVE RESULTS 5

CHRONIC KIDNEY DISEASE 6

END-STAGE RENAL DISEASE 6

MORTALITY 6

DISCUSSION **7**

EXISTING STUDIES 7

STRENGTHS AND LIMITATIONS 8

CONCLUSION 9

SUPPLEMENTARY **10**

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS 10

Study Design *10*

Immortal time *10*

Information bias *11*

Selection bias *11*

Confounding *12*

Generalizability *12*

STATISTICAL METHODS AND ADDITIONAL RESULTS 12

Propensity scores *12*

Stratification *13*

Matching *13*

Weighting *14*

Results *16*

Discussion of the additional results *17*

Abstract

Background

The long-term effects of different initiation strategies of renal replacement therapy (RRT) treatment in intensive care unit (ICU) patients with acute kidney injury (AKI) is unknown. We examined the impact of early RRT initiation on the risk of chronic kidney disease (CKD), end-stage renal disease (ESRD), and death.

Methods

All adult patients receiving RRT in the ICU at Aarhus University Hospital, Skejby, Denmark in the period 2005-2015 were included. Data were obtained from a clinical information system and population-based registries. Early initiation was defined as initiation of RRT at AKI stage 2 or below and late initiation as initiation of RRT at stage 3. Inverse probability of treatment weights (IPTW) were computed from propensity scores. After a 5^{th} percentile asymmetrical trim, the cumulative risk of CKD (eGFR<60 ml/min/1.73 m^2), ESRD, and death was estimated in the IPTW weighted cohort and compared using a Cox regression.

Results

RRT was initiated early in 621 and late in 592 patients. The 5-year risk of CKD was 39.1% (95 % CI, 28.4%-49.5%) in the early group and 44.6% (95% CI, 34.7%-54.0%) in the late group, corresponding to a hazard ratio (HR) of 0.81 (95% CI, 0.41-1.21) in early compared to late. The 5-year risk of ESRD was 14.9% (95% CI, 10.0%-20.8%) in the early group and 15.5% (95% CI, 10.8%-21.0%) in the late group, corresponding to a HR of 0.94 (95% CI, 0.39-1.50). The 90-day mortality in the early group was 52.3% (95% CI, 47.5%-56.8%) compared to 46.9% (95% CI, 42.0%-51.6%) in the late group, corresponding to a HR of 1.18 (95% CI, 0.93-1.43). The 90-day to 5-year mortality was 38.9% (95% CI, 31.6%-46.1%) and 41.7% (95% CI, 34.2%-49.1%) in the early and late, respectively, with a 90-day to 5 year HR of 0.99 (95% CI, 0.65-1.33).

Conclusion

Early RRT may be associated with a reduced 5-year risk of CKD, but estimates were statistically imprecise. While 90-day mortality may be increased in early RRT, we found no difference in mortality beyond 90 days or risk of ESRD.

Dansk resumé

Baggrund

Det optimale tidspunkt for initiering af dialysebehandling af intensivpatienter med akut nyresvigt (AKI) er ukendt. Vi undersøgte risikoen for udvikling af kronisk nyresygdom, kronisk dialysekrævende nyresygdom og død efter tidlig initiering af dialyse.

Metoder

Alle patienter over 15 år og behandlet med dialyse fra 2005 til 2015 blev identificeret i et klinisk informationssystem og koblet til sundhedsregistre vha. deres CPR-nummer. Tidlig initiering af dialyse blev defineret som AKI stadie 2 og derunder, mens sen initiering blev defineret som AKI stadie 3. Fra patientkarakteristika ved initiering af dialyse beregnede vi inverse probability of treatment weights (IPTW) ud fra propensity scores. I IPTW-vægtede kohorter beregnede vi den kumulative risiko samt en hazard ratio (HR) for kronisk nyresygdom (eGFR < 60 ml/min/1.73 m^2), kronisk dialysekrævende nyresygdom og død efter en 5-percentil asymmetrisk trimming.

Resultater

Dialyse blev initieret tidligt og sent i henholdsvis 621 og 592 patienter. Den 5-årige risiko for kronisk nyresygdom var 39.1% (95 % CI, 28.4%-49.5%) i den tidlige gruppe sammenlignet med 44.6% (95% CI, 34.7%-54.0%) i den sene gruppe. Det svarer til en HR på 0.81 (95% CI, 0.41-1.21) i den tidlige gruppe i forhold til den sene. Den 5-årige risiko for kronisk dialysekrævende nyresygdom var 14.9% (95% CI, 10.0%-20.8%) i den tidlige gruppe sammenlignet med 15.5% (95% CI, 10.8%-21.0%) i den sene gruppe, svarende til en HR på 0.94 (95% CI, 0.39-1.50). Dødeligheden efter 90 dage i den tidlige gruppe var 52.3% (95% CI, 47.5%-56.8%), mens den i den sene gruppe var 46.9% (95% CI, 42.0%-52.6%), svarende til en HR på 1.18 (95% CI, 0.93-1.43). For patienter der overlevede de første 90 dage, var 5-års-dødeligheden 38.9% (95% CI, 31.6-46.1) i den tidlige gruppe sammenlignet med 41.7% (95% CI, 34.2-49.1) i den sene gruppe, svarende til en HR på 0.99 (95% CI, 0.65-1.33).

Konklusion:

Tidlig dialysering af intensivpatienter nedsætter muligvis risikoen for udvikling af kronisk nyresygdom og øger måske dødeligheden i de første 90 dage, men der er stor usikkerhed i resultaterne. Vi fandt ingen forskel i dødelighed for patienter, der overlevede de første 90 dage, eller i risikoen for at udvikle kronisk dialysekrævende nyresygdom.

Introduction

Acute kidney injury (AKI) occurs in approximately 39%-57% of intensive care unit (ICU) patients and 6%-14% require renal replacement therapy (RRT) [1-4]. Patients with AKI who require RRT have a 90-day mortality of 50%-60% and a 5-year risk of end-stage renal disease (ESRD) of more than 10% [5-8]. The optimal time to initiate RRT remains unclear [9]. There is a theoretical rationale for early initiation of RRT, such as improved control of fluid balance, electrolytes and acid-base status. However, a treatment strategy of earlier initiation is accompanied by the risk of exposing patients, who might have recovered without RRT, to RRT and treatment-related complications [10].

A meta-analysis of mainly observational studies found early RRT initiation to be associated with reduced mortality compared with late RRT initiation [11]. However, the majority of these had methodological limitations such as small samples sizes and inadequate control of bias. Six randomized controlled trials (RCT), including between 24 and 619 patients ICU patients with AKI, have examined the impact of timing and [12-17]. Results from these RCTs are conflicting regarding short-term mortality, but after pooling the data a meta-analysis found no difference in short-term mortality and RRT dependence [18]. To our knowledge, only two small observational studies have assessed mortality beyond day 90, and none have examined the impact on chronic kidney disease (CKD) and ESRD [19, 20]. Therefore, we conducted a cohort study to examine the impact of early RRT on 5-year risk of ESRD, CKD and death.

Methods

Study population and setting

We conducted a cohort study using prospectively collected data from all patients aged 15 or older, who required continuous RRT in the 13-bed ICU at Aarhus University Hospital, Skejby from January 1st 2005 to January 1st 2015. Patients are admitted from departments of infectious diseases, cardiology, nephrology, urology, gynecology, thoracic, and vascular surgery. The patients were identified in a clinical information system (CIS) database used in the ICU (Picis, Picis Inc., Wakefield, MA). The CIS database contains detailed electronically registered data on vasopressor and inotropy treatment, mechanical ventilation, mean arterial pressure and ECMO. Additionally, it contains manually registered data on weight and urine output.

The Danish health care system is tax-funded and provides free and universal health care for all Danish citizens. Every citizen has a unique civil registration (CPR) number assigned at birth or immigration [21]. Through the CPR number, unambiguous individual-level linkage between clinical and administrative databases is possible. To ensure information on preadmission morbidity and follow-up, we only included patients with a Danish CPR number and who had residency in Denmark [21]. We only considered patients with newly developed severe renal impairment and therefore excluded patients with prior ESRD.

Timing of renal replacement therapy

The AKI stage was assessed by using the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria on plasma creatinine (P-creatinine) and urine output (volume in ml/min/kg) (whichever gave them the highest stage) (table 1) [22]. The P-creatinine measurements were obtained from a laboratory database [23]. The database contains information on every blood test taken during in- and outpatient visits to public or private hospitals or submitted by general practitioners in the Central and Northern regions of Denmark, except point of care tests. The information is stored using the international NPU codes (supplementary table 4). The P-creatinine ratio was calculated using the latest P-creatinine measurement within 24 hours before RRT initiation divided by the baseline P-creatinine. Baseline P-creatinine was estimated as the mean of all P-creatinine measurements from outpatient visits or visits to the general practitioner from 1 year to 7 days before ICU admission [24]. For patients without outpatient P-creatinine measurements, the baseline was imputed with the Modification of Diet in Renal Disease (MDRD) equation (assuming eGFR is 75 ml/min/1.73 m^2 and Caucasian race) as suggested by the KDIGO AKI guideline [22].
The urine output was obtained from the CIS, requiring at least 6 hours of observation time in accordance with the KDIGO AKI criteria. To compute urine output per kilogram bodyweight, we used the average weight of the ICU stay. Patients who could not be evaluated for their urine output due to less than 6 hours of observation time, absent diuresis measurements in the specified time period before RRT, or had no recorded weight, were assigned an AKI stage based on their P-creatinine measurements only.
Timing of RRT was defined as early if treatment was initiated at AKI stage 2 or below, including patients not meeting the AKI criteria. Late initiation of RRT was defined as AKI stage 3.

Chronic kidney disease, end-stage renal disease and mortality

Time of CKD was defined as the first date after at least two estimated glomerular filtration rates (eGFR) below 60 ml/min per 1.73 m^2 separated by more than 90 days [25]. The eGFR was estimated from P-creatinine measurements using the four-variable MDRD-equation (assuming Caucasian race) including only outpatient blood samples to avoid inclusion of P-creatinine measurements performed during hospitalization with acute illness.

Time of ESRD was defined as date of initiation of chronic RRT or kidney transplantation at least 90 days after initiation of RRT in the ICU and was obtained from the Danish National Patient Registry (DNPR) [26]. The DNPR contains information on all non-psychiatric admissions since 1977 and outpatient and emergency visits since 1995. The data include the type of admission (elective or acute), procedures performed, and up to 20 diagnoses given by the physician at discharge, using the 10^{th} edition of International Classification of Diseases since 1994. Patients who initially recovered without RRT, but eventually needed regular RRT as well as patients without initial recovery, were included.

Time of death was obtained from the Danish Civil Registration system. The registry is updated daily and contains complete information since 1968 on vital status, emigration and residency [21].

Covariates

Information on preadmission morbidity 10 years before ICU admission was obtained from the DNPR and included diagnoses assigned after an in- or outpatient visit, except visits to the emergency department to increase validity. We thus included previous diagnoses of renal disease, diabetes (type 1 and 2), congestive heart failure, myocardial infarction, cerebrovascular disease, chronic pulmonary disease, liver disease, periphery vascular disease, malignant solid tumors, lymphoma, leukemia and metastatic solid tumors, all of which are considered valid [26]. Using the DNPR, patients were categorized as non-surgical, elective non-cardiac surgical, acute non-cardiac surgical, elective cardiac surgical, and acute cardiac surgical dependent on their type of admission and surgery performed within a period from 24 hours before ICU admission until RRT initiation [27]. Information on mechanical ventilation initiation 24 hours before RRT was obtained from the DNPR. From the laboratory database and the CIS, we computed the patients' sequential organ failure assessment (SOFA) score based on the worst values 24 hours before initiation of RRT, not considering Glasgow Coma Score [28]. Missing values on parameters included in the SOFA score

were considered normal. The latest potassium and sodium measurements 24 hours before RRT initiation were obtained from the laboratory database [23].

Statistical analysis

The patient's characteristics, including demography, other ICU treatments, laboratory values, and time of treatment, were tabulated for the early group and late group. Continuous variables are presented as means with standard deviations (SD) or medians with interquartile intervals, as appropriate. Categorical variables are presented with frequencies and percentages. We followed patients until outcome of interest, emigration, five years from RRT initiation or censoring January 1st 2016, whichever came first. Due to restrictions in follow-up and outcome definitions, we performed an analysis for each outcome: CKD, ESRD and death. By definition, chronic renal impairment should last for at least 90 days. Therefore, we only considered patients who survived until day 90 when we examined the impact on CKD and ESRD. Furthermore, to examine the impact of early RRT on risk of CKD, we only included patients having residency in a Danish region covered by the laboratory database and had no evidence of prior renal disease. Prior renal disease was defined as at least two outpatient eGFR measurements below 60 ml/min/1.73 m^2 at least 90 days apart during the year before ICU admission, or a diagnosis of renal disease before admission [23]. With death as the outcome of interest, we included all patients initiating RRT.

To adjust for potential confounders, propensity scores were estimated using a multivariable logistics regression model including all the pre-specified characteristics presented for each cohort. The included variables are presented in table 2 for the mortality analysis, with the CKD and ESRD analyses presented in the supplementary. The propensity score is the probability of treatment given measured covariates [29]. Continuous variables were included in the model a with restricted cubic spline function with 4 knots. From the propensity scores, we computed inverse probability of treatment weights (IPTW); when these weights are applied to a population, they create a pseudo population in which exposure status is independent of measured baseline covariates [30, 31]. The covariate balance in the full and weighted cohorts was evaluated with standard mean differences (SMD) [30]. To remove the potential influence of unmeasured confounding in the tails of the propensity score distributions, we performed an asymmetrical 5th percentile trim [32].

We used a weighted Kaplan-Meier method to compute the cumulative incidence. With ESRD and CKD as outcomes of interests, we accounted for death as a competing risk. The hazard ratios (HR)

were estimated using a weighted Cox proportional hazards regression. The assumption of proportional hazards was checked graphically by log(-log) plots and found appropriate. To estimate the 95% confidence interval of the HR, we used a bootstrap method with 200 samples [33].

Analyses were performed using the statistical software package Stata version 14.1 (StataCorp LP, College Station; TX, USA). The study was approved by the Danish Data Protection Agency (record number: 2014-14-3658).

Results

Descriptive results

In the 10-year study period, 1372 patients required RRT. We excluded 69 patients with previous ESRD, 31 with residency outside Denmark, 14 who could not be linked to the DNPR and 3 below 15 years of age. We had to exclude 42 patients due to missing information on covariates. This gave us a study population of 1213 patients (figure 1). The total follow-up time was 1994 years. The median (interquartile interval) time from ICU admission to RRT initiation was 18.9 (8.3-35.2) hours in the early group compared to 32.8 (7.8-79.8) hours in the late group. Characteristics for the full and weighted cohort after trimming are presented in table 2. In the full cohort, early and late RRT was initiated in 621 (51.2%) and 592 (48.8%) patients, respectively. Patients who initiated RRT early were less frequently non-surgical, but more often initiated with mechanical ventilation 24 hours before RRT. The early and late group had similar preadmission morbidities, except congestive heart failure which was more frequent in the early group. A higher proportion of patients in the late group were treated in the beginning of the study period (2005-2008). In the weighted cohort and after trimming, 436 (51.6%) and 409 (48.4%) patients initiated RRT early and late, respectively. Demographic characteristics, other ICU treatments, laboratory values, and time of treatment were equally distributed between the early group and late group. The mean age was 65.9 years, 594 (70.2%) patients were male and the mean SOFA score was 8.2. The most frequent preadmission morbidities were renal disease, vascular disease and congestive heart failure.

Baseline P-creatinine was available in 829 (68.3%) patients. Patients without baseline P-creatinine were equally distributed between both treatment groups and they were younger and had less

preadmission morbidity than those with baseline P-creatinine (supplementary table 3). It was possible to assess AKI stage according to the urine output criteria in 682 (56.2%) patients, with the remaining only being staged according to their P-creatinine.

Chronic kidney disease

The analysis with CKD as outcome of interest was limited to 303 patients. Of the 141 patients who initiated RRT early, 119 (84.4%) had two or more outpatient creatinine measurements after hospital discharge compared to 146 (90.1%) out of the 162 patients who initiated RRT late. After trimming, we included 204 patients. Patient's characteristics were equally distributed between the early group and late group (supplementary table 1). The 5-year risk of CKD for the early group was 39.1% (95% CI, 28.4%-49.5%) compared to 44.6% (95% CI, 34.7%-54.0%) for the late group (figure 2b). We estimated a 90-day to 5-year HR of 0.81 (95% CI, 0.41-1.21) for early RRT compared to late RRT.

End-stage renal disease

The analysis with ESRD as outcome of interest was limited to 617 patients. After trimming, we included 401 patients. The patients' characteristics were equally distributed between the early and late groups (supplementary table 2). The 5-year risk of ESRD was 14.9% (95% CI, 10.0%-20.8%) compared to 15.5% (10.8%-21.0%) in the early and late groups (figure 2c), respectively, corresponding to a 90-day to 5-year HR of 0.94 (95% CI, 0.39-1.50) early compared to late.

Mortality

The 90-day mortality was 52.3% (95% CI, 47.5%-56.8%) in the early group compared to 46.9% (95% CI, 42.0%-51.6%) in the late group (figure 2a). The corresponding 0 to 90-day HR was estimated to 1.18 (95% CI, 0.93-1.43) in the early group compared to the late group. The 90-day to 5-year mortality was 38.9% (95% CI, 31.6%-46.1%) in the early group compared to 41.7% (95% CI, 34.2%-49.1%) in the late group. The 90-day to 5-year HR was 0.99 (0.65-1.33) for early compared to late RRT treatment. The 0 to 5-year cumulative mortality was 70.8% (95% CI, 66.1-75.1) and 69.0% (95% CI, 63.9-73.6) in the early and late groups, respectively.

Discussion

We used prospectively data collected from high-quality clinical and administrative registries to examine the association between early and late RRT in ICU patients and clinical outcomes. Early RRT may be associated with a reduced long-term risk of CKD and might be associated with higher mortality during the first 90 days, but estimates were statistically imprecise. We observed no impact of early initiation on the risk of ESRD or mortality in patients surviving beyond day 90. To our knowledge, this is the first study examining the impact of early RRT on the risk of CKD, ESRD and long-term risk of death using the consensus AKI criteria [22].

Existing studies

Our results on short-term mortality are in contrast to a meta-analysis by Wierstra et al. [11]. The authors categorized studies according to their level of quality and observed that low quality studies (mainly observational studies) favored early initiation (odds ratio [OR] 0.47 [95% CI, 0.34-0.65] early compared to late). However, in high quality studies (mainly RCTs), early RRT was associated with a weaker reduction mortality (OR 0.67 [95% CI, 0.38-1.15]) [11]. A meta-analysis of six trials by Xu et al, including two recent RCTs, the authors observed no impact on short-term mortality with early initiation of RRT (relative risk [RR] 0.93 [95% CI, 0.68-1.26] early compared to late) and only minor impact on RRT dependence (RR 0.88 [95% CI, 0.48-1.62]) [18].

Our results on short-term mortality are in line with a multicenter RCT, including 619 ICU patients with AKI stage 3, who required mechanical ventilation, catecholamine infusion, or both [15]. Early RRT was initiated immediately after randomization while late RRT was withheld until one of the following indications occurred: hyperkalemia, pulmonary edema, metabolic acidosis, blood urea nitrogen (BUN) higher than 112 mg/dL (> 40 mmol/L), oliguria for more than 72 hours. The authors observed no difference in 60-day mortality or RRT dependence.

The present study are in contrast to a single center RCT including 231 patients with AKI stage 2 and plasma neutrophil gelatinase-associated lipocalin > 150 ng/ml to continuous RRT [16]. Early was defined as RRT treatment immediately after randomization and late RRT at AKI stage 3, or if critical indications developed. The authors observed a reduction in 90-day mortality with a HR of 0.66 (95% CI, 0.45-0.97) early compared to late, but found no difference in RRT dependence.

We identified two observational studies with long-term follow-up, but none of these examined the impact on CKD and ESRD [19, 20]. Park et al. classified 607 patients as early and late initiators based on the median 6-hour urine output [19]. In contrast to the present study, the authors found that late initiation was associated with a higher mortality. The authors adjusted for a limited set of confounders and restricted to elderly patients. Carl et al. defined non-surgical 147 ICU patients as early and late initiators if their BUN was below or above 100 mg/dL (35 mmol/L), respectively [20]. Also in contrast to the present study, they observed a reduced mortality with early initiation.

Strengths and limitations

Our study has some limitations. First, baseline P-creatinine was available in 68.2% of the patients with the remaining being estimated with the MDRD equation. This method may lead to a slight over- and underestimation of the AKI stage [34-36]. However, since the proportion of patients without available baseline P-creatinine were equally distributed between early and late RRT, any misclassification will most likely bias the estimates towards no difference. Examination of patients with missing baseline creatinine showed that they were younger and had fewer comorbidities. Therefore, we found an imputation using the MDRD equation reasonable. Second, we were able to obtain information on urine output in 56.2% of the patients with the remaining only being staged according to their creatinine ratio. This may have led to some misclassification of the early and late groups and biased the estimates towards no difference. Third, since CKD can be present without symptoms our outcome is dependent upon patients having an outpatient blood sample with creatinine taken. A large proportion of the patients included in the CKD analysis had two or more outpatient measurements. Therefore, we find it plausible that we have identified the vast majority of patients with CKD. Furthermore, we observed a small difference in the proportion of patients with two or more outpatient measurements in the two groups. This may have contributed to the difference observed; however, it is possible that the difference simply indicates improved renal recovery at hospital discharge or at first outpatient measurement. We have no reason to believe that AKI at initiation of RRT would impact health care vigilance after discharge. Lastly, despite being able to adjust for demographic characteristics, other ICU treatments and laboratory values at initiation of RRT, there still is a risk of residual confounding.

Conclusion

In conclusion, we found that early initiation of RRT in ICU patients with AKI may be associated with a lowered risk of CKD and may be associated with an increased mortality during the first 90 days of follow-up, although estimates were statistically imprecise. We observed no difference in risk of developing ESRD or mortality beyond day 90. More trials with long-term follow-up are needed to confirm these findings. Currently, two trials on timing of RRT in ICU patients are ongoing, but none of these are following patients longer than 90 days [37, 38].

Supplementary

In the supplementary part of this report, methodological considerations are discussed, including the design of the study and potential bias. Furthermore, additional propensity score analyses are presented and discussed.

Methodological considerations and limitations

Study Design

Our study design was an observational historical cohort study with an accrual period from January 1st 2005 to January 1st 2015. It included all adult patients requiring renal replacement therapy (RRT) at the intensive care unit (ICU), Aarhus University Hospital, Skejby, Denmark. Patients were followed from initiation of RRT until 5 years, emigration, January 1st 2016 or outcome of interest. The exposure of interest was severity of acute kidney injury (AKI) prior to initiation of RRT. We defined early initiation of RRT as AKI stage 2 or below and late initiation of RRT as AKI stage 3. Stages are defined according to the consensus criteria including both the urine output and the creatinine criteria [22]. We examined whether early initiation had impact on the subsequent risk of chronic kidney disease (CKD, defined as an estimated glomerular filtration below 60 ml/min/1.73 m^2 in more than 90 days), end-stage renal disease (ESRD, defined as initiation of regular RRT or a kidney transplant) and death [25].

Based on the available literature at study initiation, we hypothesized that early initiation of RRT would reduce the risk of CKD, ESRD and mortality [39].

Immortal time

According to the Kidney Disease Improving Global Outcomes CKD guideline, renal impairment should be present for at least 90 days to meet the CKD criteria. Therefore, we initiated follow-up at day 90 to minimize immortal time in the CKD and ESRD analyses (supplementary figure 1) [25]. Immortal time is a span of cohort follow-up during which the outcome can not occur [40]. In the CKD analysis the outcome was defined as two outpatient eGFR measurements below 60 ml/min/1.73 m^2 at least 90 days apart. Since it is only possible to have an outpatient blood sample taken after hospital discharge, the earliest CKD event can occur at day 90 plus the time from RRT initiation to hospital discharge. No bias will occur if the time from RRT initiation to hospital discharge is the same. We were not able to obtain valid estimates on the time of hospital

discharge for every patient, but meta-analyses of timing studies have found that length of hospital admission was not affected by treatment strategy [11].

Information bias

Information bias is a systematic error that occur when the information on the study participants is erroneous [40]. Information bias can be defined as either *non-differential* if the error is unrelated to other study variables or *differential* if the error is related to other study variables. Non-differential misclassification will bias towards the null (no difference) if the exposure if dichotomous, but differential misclassification could both under- and overestimate the treatment effect.

A potential source of information bias is the classification of early and late RRT. Patients were staged according to their urine output and creatinine level (whichever gave them the highest stage), but we were only able to estimate an AKI stage by urine output in 58% of the patients. Patients who were only staged according to their creatinine level and with mild AKI (stage 1 and 2), could be misclassified due to missing information on their urine output [41]. This potential misclassification would bias the effect towards the null (no difference).

CKD can be asymptomatic and since our outcome is dependent on patients visiting their general practitioner or an outpatient clinic and have a blood sample taken and analyzed for creatinine, patients who visit their general practitioner more often and have more blood samples taken are more likely to have a CKD event. Bias could occur if the surveillance after discharge were different in the early group and late group. However, we find it unlikely that the level of vigilance should be impacted be the AKI stage at initiation of RRT. When we examined the proportion of patients with two or more outpatient creatinine measurements this was very similar in the two exposure groups (84% and 90% in the early and late group, respectively).

Selection bias

Selection bias occurs when patients included in a study are systematically different from patients not included in the study [40]. The bias occurs if the association between participants are different from non-participants and thereby the target population. We included every patient who required RRT at the ICU from a Clinical Information System (CIS). We have no information on the sensitivity

in the database regarding RRT treatment; however, since the RRT machine settings are monitored through the CIS system, we find it unlikely that any patients should be excluded.

Confounding

Confounding occurs when the effect of the exposure on the outcome is affected by a third variable (supplementary figure 2) [42]. By definition, a confounder is related to the exposure, the outcome, and not a part of the causal chain from exposure to the outcome. An example of a potential confounder in our study could be hyperkalemia, which influences the decision to initiate RRT and could lead to death through cardiac arrhythmia. We identified potential confounders and risk factors [43] from existing literature and clinical knowledge, but we were not able to obtain information on possible confounders such as cumulative fluid balance and sepsis. Therefore unmeasured confounding may have altered our results.

Confounders can be eliminated through the design of the study (e.g. randomization) or in with statistical methods (e.g. multivariable models). We used inverse probability of treatment weights computed using propensity scores. The use of propensity scores to avoid potential confounders will be explained in the following.

Generalizability

The generalizability or extern validity of our results was affected by the exclusion of several patients in our analysis to limit the influence of potential unmeasured confounding in tails of the propensity score. The exclusion of patients treated contrary to their prediction increases the intern validity; however, comes at the cost of limited generalizability [32].

Statistical methods and additional results

Propensity scores

In 1983 Rubin and Rosenbaum showed that, conditional on propensity score, the characteristics will on average be equally distributed and allow the researcher to estimate causal effects if the assumptions the propensity scores rely on are satisfied [44]. A propensity score is the probability of treatment assignment given the measured patients characteristics. This is also denoted $Pr(Z = 1 \mid X)$, where treatment status is denoted Z, and X are the patients' characteristics. The propensity score relies on four assumptions: consistency, exchangeability, positivity and no miss-specification

of the propensity score model [30, 31]. Consistency means that the outcome of the subject is also the outcome that is actually observed. Exchangeability (or ignorable treatment assignment or assumption of no unmeasured confounding) implies that treatment groups are comparable and have the same chance of potential outcomes. The positivity assumption requires exposure variation within each confounder stratum [31, 45]. Miss-specification of the propensity score model can be difficult to assess; however, Austin et al. argues that the covariate balance achieved with the model is the main priority [30]. There are different methods of implementing propensity scores in the analysis and the methods can give very different results [46].

In the following, I will briefly go over different methods of using propensity scores to adjust for baseline characteristics. Finally, I will present the results obtained when these methods applied to the current study. We will not go into detail with variable selection, balancing diagnostics, impact of remaining imbalances, evaluation of assumptions, trimming or evaluation of the distribution of continuous variables, but these are also important aspects of a propensity score analysis.

Stratification

Stratification on propensity score allows one to examine treatment heterogeneity or effect modification by the propensity score. We separated the patients in quintiles of the propensity score. By the property of the propensity score, the patient's characteristics within each stratum are roughly the same. A higher number of strata would have resulted in a better balance between the groups until matching is reached. A treatment effect can be estimated directly within each stratum, or an overall treatment effect can be obtained by a weighted average of each stratum's treatment estimate. A separation into five strata is expected to remove more than 90% of the bias [47]. Treatment heterogeneity by the propensity score can be caused by real differences in treatment effect or unmeasured confounding, and the impact of the latter can be reduced by trimming and is especially important when using inverse probability of treatment weights (IPTW) [32].

Matching

Matching is the most commonly used method for controlling for imbalances in baseline characteristics with propensity scores. Treated and untreated patients are matched based on their propensity scores. In the matched cohort, patients will on average have similar a distribution of

covariates [48]. If every treated patient is matched, it allows the researcher to estimate the average treatment effect in the treated (ATT) [29]. Matching excludes patients in the non-overlapping regions of the propensity score where a treatment effect cannot be measured without making assumptions about treatment effect similarity compared the rest of the patients and violating the positivity assumption. There are different matching algorithms; however, 1:1 matching within a specified caliper seems to be the most common. There is no consensus as to the most efficient caliper. When choosing a caliper, there is a tradeoff between confounding due to imbalanced matches and number of matches available for the analysis. A caliper of 0.2 times the standard deviation of the logit of the propensity seems to result in an acceptable reduction in bias and number of matches, at least when the model includes continuous variables [49]. The rationale for matching on the logit transformed propensity score is that the propensity score is more likely to have a normal distribution [49]. Compared to other propensity score methods, matching makes it possible to make a direct comparison between the treated and untreated groups, and it is efficient in reducing bias from unmeasured confounding in the tails of the propensity score [32, 50]. However, it comes at the cost of a reduction in sample size (in the current study the study population was reduced from 1213 to 750 after matching in the mortality analysis).

Weighting

Weighting is being increasingly used with propensity scores to adjust for measured imbalances in baseline characteristics [30]. Generally, two types of weights are used: inverse probability of treatment weights (IPTW) and standardized mortality ratio weights (SMRW) [29]. IPTW weighting creates a pseudo population with no association between measured baseline characteristics and the treatment status, and it allows the researcher to estimate the average treatment effect (ATE) [29]. The ATE can be interpreted as the effect of moving the whole study population to the treated group and is similar to the interpretation of randomized controlled trials [51]. The weights are estimated as:

$$\text{IPTW} = \frac{Z}{p} + \frac{1-Z}{1-p}$$

where Z denotes the treatment status (1 denotes treated [early RRT], 0 denotes controls [late RRT]) and p denotes the propensity score. From the formula, we see that each patient's weight is equal to the inverse of the probability of receiving the treatment that the patient received. Very

high weights can increase uncertainty of the estimate. This can be handled by using stabilized weights or excluding patients with weights that exceed a specified threshold (weight truncation) [30]. Stabilized weights increase the precision of the estimate without any impact on the bias [29]. In the following analyses stabilized weights are used.

Standardized mortality ratio weight (SMRW) creates an untreated group that have a distribution of baseline covariates similar to the treated group. Therefore, the estimate obtained is the ATT and can be interpreted as the effect in the treated patients had they not been treated. The weights are estimated as:

$$SMRW = Z + \frac{p * (1 - Z)}{1 - p}$$

where Z denotes treatment status (1 denotes treatment [early RRT], 0 denotes control [late RRT]) and p denotes the propensity score. From the formula, we see that patients treated with early RRT receive a weight of 1, to which the controls are standardized. Unlike matching, this allows one to keep the full study population in the analysis, while still making it possible to estimate the ATT.
For both types of weights, the use of robust variance estimators is advised. A recent Monte Carlo simulation study by Austin et al., suggested that a bootstrap method for estimating variance in weighted Cox models performed better than a robust variance estimator [33]. The bootstrap method more accurately estimated the sample variance and coverage of confidence intervals regardless of the type of weights used (stabilized IPTW, IPTW, SMRW). Depending on the treatment effect and prevalence, a robust variance estimator overestimated the standard error of the HR with more than 20%, but with the bootstrap method the standard error was under- and overestimated by no more than 5% [33].

In the absence of treatment effect heterogeneity, both types of weights give the same effect estimate. In the presence of treatment effect heterogeneity, the SMRW and IPTW weighting can give very different estimates. Kurth et al found odds ratios ranging from 1.1 estimated with SMRW weights to 10.7 estimates with IPTW weights [46].

Results

The distribution of patients by the propensity score for the full cohort is visualized in a kernel plot (supplementary figure 3). The highest density of patients in the late group and early group is in the lower and upper part of the propensity score, respectively. This indicates some distinction regarding the baseline characteristics between the two treatment groups. The overlapping regions of the curves allow for estimation of a treatment effect, but in the tails of the propensity only one of the treatment groups is represented (non-overlap) and no valid estimates can be obtained.

The stratified analysis is visualized in supplementary figure 4, with a hazard ratio (HR) estimated for each quintile. The stratified analysis showed considerably treatment heterogeneity with a high HR in quintile 1, but with rather stable treatment effect measures from quintile 2 to 5. This could be due to a real difference in treatment effect or due to unmeasured confounding in the lower tail of the propensity score. We have no reason to believe that these patients in the lower end of the propensity score should have a different effect of early RRT than the rest. Therefore, we find it more likely that this treatment effect heterogeneity is caused by unmeasured confounding. If early RRT is initiated in patients with a low probability of actually receiving early RRT (treated contrary to their prediction), treatment could have been initiated as a “last resort” attempt to save patients with a high frailty. If we are not able to adjust for this frailty, the HR will increase in the first quintile. To avoid this problem of unmeasured confounding in the tails of the propensity score, we examined the effect of various trims.

The results from each propensity score method are presented in supplementary table 5 for each outcome as HRs and with the number of patients included in each analysis. Furthermore, each weighting analysis was performed with a robust variance estimator and a bootstrap method with 200 samples.

The number of patients included in the analysis is different in different analyses, depending on trimming and matching. In the 0- to 90-day mortality analysis, the number of patients included ranged from 1213 in the crude analysis to 750 in the matched analysis.

In the 0- to 90-day mortality analysis, the HRs ranged from 1.31 (95% CI, 1.08-1.59, robust) with IPTW weighting trimmed to the propensity score area with common support to 1.17 (95% CI, 0.95-

1.42, robust) with IPTW weighting after a 5th percentile trim. In the crude analysis, the HR was 1.24 (95% CI, 1.06-1.46). Higher discrepancy was observed in the 90-day to 5-year mortality analysis, were HRs ranged from 0.83 (95% CI, 0.58) with the SMRW weighting trimmed to the area with overlapping propensity scores to 1.14 (95% CI, 0.84-1.58) with IPTW weighting trimmed to 2.5th percentile. In the crude analysis, the HR was 0.89 (95% CI, 0.68-1.17.)

In the CKD analysis, the HRs ranged from 0.64 (95% CI, 0.41 to 1.01, robust) with IPTW weighting and a 1st percentile trim to 0.84 (95% CI, 0.52-1.34) with IPTW weighting after a 5th percentile trim. In the crude analysis, the HR was 0.95 (95% CI, 0.67-1.34).

In the ESRD analysis, HRs ranged from 0.71 (95% CI, 0.42-1.20, robust) with IPTW weighting trimmed to the area with overlapping propensity scores to 0.94 (95% CI, 0.55-1.62, robust) with IPTW weighting after a 5th percentile trim. In the crude analysis, the HR was 0.96 (95% CI, 0.62-1.48, robust).

Discussion of the additional results

There are several reasons for the differences in the results. First of all, the composition of the population for which the propensity score methods are applied can potentially vary depending on trimming and matching. For example, in the IPTW weighting the number of patients included decreased from 1193 to 845 depending on the extent of the trimming. If the association between early RRT and outcome of interest varies by the difference in composition of patient characteristics in the cohort, this could potentially explain some of the differences observed. As a matter of fact, the only analyses performed on the same cohort are the IPTW and SMRW weighting trimmed to the area with overlapping propensity scores and including 1193 patients; however, we still observe a difference between the two analyses. It is probably of higher importance that the obtained results by the SMRW weighting and matching should be interpreted as the ATT, while the IPTW weighting should be interpreted as the ATE. Depending on the method used, the treatment effect is estimated in different parts of the propensity score (e.g. the SMRW weighting primarily measures the effect in the upper part of the propensity score, since the majority of treated patients are located here). This can drastically change the effect estimate in the presence of treatment heterogeneity [46].

Finally, we examined a robust variance estimator and compared it with a bootstrap method with 200 samples. We observed only minor differences in the 95% CI and their coverage.

Tables

Table 1: Stages of acute kidney injury			
Group	Stage	Creatinine	Urine output
Early		Patients not meeting AKI criteria	
	1	1.5-1.9 times baseline or ≥ 26.5 5 µmol/l (0.3 mg/dl) increase in creatinine within 48 hours	< 0.5 ml/kg/h for 6-12 hours
	2	2.0-2.9 times baseline	< 0.5 ml/kg/h for > 12 hours
Late	3	3.0 times baseline or creatinine ≥ 354 µmol/l (4.0 mg/dl)[a]	< 0.3 ml/kg/h for > 24 hours or anuria for ≥ 12 hours
[a] And satisfies AKI criteria			

	Full cohort			After trimming		
	Early	Late	SMD	Early	Late	SMD
N	621	592		436	409	
Demography						
Age, median (IQI)	67.7 (58.5-75.3)	69.0 (59.3-75.8)	-0.09	67.9 (59.5-76.2)	69.4 (58.8-75.4)	-0.04
Male, n (%)	419 (65.5)	419 (70.8)	-0.11	306 (70.1)	288 (70.3)	-0.00
Surgical status, n (%)						
Non-surgical	229 (36.9)	281 (47.5)	-0.22	178 (40.9)	174 (42.5)	-0.04
Non-cardiac surgery, elective	37 (6.0)	47 (7.9)	-0.08	30 (6.8)	25 (6.2)	0.03
Non-cardiac surgery, acute	67 (10.8)	66 (11.1)	-0.01	53 (12.2)	43 (10.4)	0.05
Cardiac surgery, elective	100 (16.1)	66 (11.1)	0.14	58 (13.4)	57 (13.9)	-0.02
Cardiac surgery, acute	188 (30.3)	132 (22.3)	0.18	117 (26.7)	110 (27.0)	-0.01
SOFA score, mean	8.1 (2.7)	8.2 (2.6)	-0.04	8.2 (2.7)	8.2 (2.7)	0.02
ICU treatments, n (%)						
Vasopressor of inotropy	555 (89.4)	491 (82.9)	0.19	386 (88.4)	356 (87.0)	0.05
Mechanical ventilation[a]	318 (51.2)	177 (29.9)	0.44	175 (40.2)	165 (40.3)	-0.00
Extracorporeal membrane oxygenation	84 (13.5)	40 (6.8)	0.23	40 (9.1)	39 (9.4)	-0.01
Laboratory values						
Creatinine, baseline, µmol/L, median (IQI)	94.9 (82.0-117.0)	90.7 (73.7-102.2)	0.19	94.0 (78.7-116.0)	93.3 (80.0-112.0)	-0.00
Potassium, mmol/l, median (IQI)	4.4 (3.9- 5.0)	4.5 (4.1- 5.1)	-0.17	4.5 (4.1-5.0)	4.5 (4.0-5.0)	0.02
Sodium, mmol/L, mean (SD)	139.3 (7.0)	138.8 (7.2)	0.06	138.9 (7.3)	139.1 (7.1)	-0.02
Preadmission morbidity, n (%)						
Renal disease	178 (28.7)	208 (35.1)	-0.14	132 (30.2)	129 (31.5)	-0.03
Diabetes	101 (16.3)	107 (18.1)	-0.05	77 (17.6)	71 (17.3)	0.01
Congestive heart disease	180 (29.0)	120 (20.3)	0.20	109 (25.0)	103 (25.2)	-0.00
Myocardial infarction	154 (24.8)	136 (23.0)	0.04	108 (24.7)	97 (23.7)	0.02
Cerebrovascular disease	80 (12.9)	86 (14.5)	-0.05	60 (13.7)	62 (15.2)	-0.04
Chronic pulmonary disease	113 (18.2)	90 (15.2)	0.08	69 (15.8)	73 (18.0)	-0.06
Liver disease	21 (3.4)	23 (3.9)	-0.03	15 (3.4)	12 (2.9)	0.03
Vascular disease	172 (27.7)	161 (27.2)	0.01	135 (31.0)	124 (30.4)	0.01
Tumor	68 (11.0)	95 (16.0)	-0.15	53 (12.1)	48 (11.7)	0.01
Lymphoma	9 (1.4)	6 (1.0)	0.04	7 (1.6)	6 (1.4)	0.02
Leukemia	7 (1.1)	5 (0.8)	0.03	4 (1.0)	2 (0.4)	0.07
Metastasis	16 (2.6)	17 (2.9)	-0.02	12 (2.6)	10 (2.4)	0.01
Year of treatment, n (%)						
2005-2006	95 (15.3)	149 (25.2)	-0.25	90 (20.6)	84 (20.5)	-0.00
2007-2008	101 (16.3)	120 (20.3)	-0.10	79 (18.1)	75 (18.2)	-0.00
2009-2010	141 (22.7)	93 (15.7)	0.18	84 (19.2)	79 (19.3)	-0.00
2011-2012	158 (25.4)	94 (15.9)	0.24	84 (19.3)	83 (20.3)	-0.03
2013-2014	126 (20.3)	136 (23.0)	-0.07	99 (22.8)	88 (21.6)	0.03

Table 2: Baseline characteristics for the full and weighted cohort after trimming with death as outcome of interest.
[a] Initiated 24 hours before RRT
ICU: intensive care unit, IQI: interquartile interval, N: number, RRT: Renal replacement therapy, SD: Standard deviation, SMD: Standard mean difference, SOFA: sequential organ assessment score

	Early	Late	Hazard ratio (95% CI)
Mortality, % (95% CI)		N = 845	
0 to 90 days	52.3 (47.5-56.8)	46.9 (42.0-51.6)	1.18 (0.93-1.43)
90 days to 5 years	38.9 (31.6-46.1)	41.7 (34.2-49.1)	0.99 (0.65-1.33)
0 to 5 years	70.8 (66.1-75.1)	69.0 (63.9-73.6)	NA
CKD, % (95% CI)		N = 203	
90 days to 5 years	39.1 (28.4-49.5)	44.6 (34.7-54.0)	0.81 (0.41-1.21)
ESRD, % (95% CI)		N = 401	
90 days to 5 years	14.9 (10.0-20.8)	15.5 (10.8-21.0)	0.94 (0.39-1.50)

Table 3: Cumulative risk and hazard ratios in the weighted and trimmed cohorts.
CI: Confidence interval, CKD: Chronic kidney disease, ESRD: End-stage renal disease, NA: Not Applicable (due to non-proportional hazards)

	Full CKD cohort			CKD cohort after trimming		
	Early	Late	SMD	Early	Late	SMD
N	141	162		95	108	
Demography						
Age, median (IQI)	66.2 (56.4-73.2)	66.8 (52.8-72.6)	0.03	66.9 (57.7-73.2)	67.0 (57.0-73.4)	-0.00
Male, n (%)	88 (62.4)	122 (75.3)	-0.28	72 (76.0)	78 (72.2)	0.08
Surgical status, n (%)						
Non-surgical	43 (30.5)	59 (36.4)	-0.13	32 (33.9)	38 (35.4)	-0.03
Non-cardiac surgery, elective	15 (10.6)	15 (9.3)	0.05	13 (13.4)	12 (11.0)	0.08
Non-cardiac surgery, acute	10 (7.1)	27 (16.7)	-0.30	9 (9.3)	10 (8.9)	0.02
Cardiac surgery, elective	28 (19.9)	21 (13.0)	0.19	11 (11.3)	17 (15.5)	-0.12
Cardiac surgery, acute	45 (31.9)	40 (24.7)	0.16	30 (32.1)	32 (29.2)	0.06
SOFA score, mean (SD)	8.5 (2.6)	8.2 (2.6)	0.11	8.6 (2.4)	8.4 (2.5)	0.09
ICU treatments, n (%)						
Vasopressor or inotropy	135 (95.7)	136 (84.0)	0.40	92 (96.3)	100 (92.9)	0.15
Mechanical ventilation[a]	65 (46.1)	51 (31.5)	0.30	40 (41.8)	44 (40.9)	0.02
Extra corporal membrane oxygenation	21 (14.9)	10 (6.2)	0.29	7 (7.6)	8 (7.4)	0.01
Laboratory values						
Creatinine, baseline, µmol/L, median (IQI)	90.3 (74.5-98.0)	85.3 (73.5-96.0)	0.17	88.0 (73.4-96.5)	89.5 (73.5-98.7)	-0.00
Preadmission morbidities, n (%)						
Diabetes	14 (9.9)	31 (19.1)	-0.26	12 (13.1)	14 (13.1)	-0.00
Cardiovascular disease[b]	79 (56.0)	97 (59.9)	-0.08	61 (64.4)	65 (60.6)	0.08
Neoplasm[c]	15 (10.6)	29 (17.9)	-0.21	15 (16.2)	15 (13.5)	0.08
Year of treatment, n (%)						
2005-2006	16 (11.3)	29 (17.9)	-0.19	12 (13.0)	15 (14.0)	-0.03
2007-2008	24 (17.0)	25 (15.4)	0.04	17 (18.0)	20 (18.9)	-0.02
2009-2010	36 (25.5)	24 (14.8)	0.27	16 (17.1)	21 (19.3)	-0.06
2011-2012	34 (24.1)	31 (19.1)	0.12	23 (24.0)	25 (22.8)	0.03
2013-2014	31 (22.0)	53 (32.7)	-0.24	27 (27.9)	27 (25.1)	0.06

Supplementary table 1: Baseline characteristics for the CKD and weighted cohort after trimming with CKD as outcome of interest. Only patients surviving until day 90, having residency in a region covered by the laboratory database and no history of prior kidney disease were included.

[a]Initiated 24 hours before RRT

[b]Myocardial infarction, congestive heart disease, cerebrovascular disease, vascular disease.

[c]Tumor, leukemia, lymphoma, metastasis

ICU: intensive care unit, IQI: interquartile interval, N: number, SD: Standard deviation, SMD: Standard mean difference, SOFA: sequential organ assessment score

	Full ESRD cohort			ESRD cohort after trimming		
	Early	Late	SMD	Early	Late	SMD
N	295	322		187	214	
Demography						
Age, median (IQI)	63.9 (53.4-72.5)	66.8 (55.8-73.4)	-0.10	64.7 (53.4-72.7)	67.0 (56.8-73.4)	-0.12
Male, n (%)	231 (65.4)	231 (71.7)	-0.14	132 (70.5)	147 (68.8)	0.04
Surgical status, n (%)						
Non-surgical	99 (33.6)	151 (46.9)	-0.27	79 (42.4)	89 (41.6)	-0.01
Non-cardiac surgery, elective	21 (7.1)	26 (8.1)	-0.04	15 (7.9)	17 (8.1)	-0.01
Non-cardiac surgery, acute	21 (7.1)	37 (11.5)	-0.15	18 (9.4)	13 (6.0)	0.13
Cardiac surgery, elective	59 (20.0)	41 (12.7)	0.20	27 (14.4)	38 (17.7)	-0.09
Cardiac surgery, acute	95 (32.2)	67 (20.8)	0.26	49 (26.0)	57 (26.6)	-0.01
SOFA score, mean	8.1 (2.7)	8.0 (2.6)	0.02	8.0 (2.6)	8.0 (2.6)	0.01
ICU treatments, n (%)						
Vasopressor of inotropy	263 (89.2)	254 (78.9)	0.28	160 (85.5)	186 (86.9)	-0.04
Mechanical ventilation[a]	146 (49.5)	93 (28.9)	0.43	74 (39.3)	80 (37.6)	0.04
Extracorporeal membrane oxygenation	47 (15.9)	23 (7.1)	0.28	17 (8.9)	18 (8.6)	0.01
Laboratory values						
Creatinine, baseline, µmol/L, median (IQI)	95.0 (80.5-116.0)	91.4 (74.0-102.6)	0.19	94.0 (78.7-111.5)	93.3 (77.0-108.0)	0.06
Potassium, mmol/l, median (IQI)	4.4 (4.0- 5.0)	4.5 (4.1- 5.0)	-0.20	4.5 (4.1-5.0)	4.5 (4.1-5.0)	0.04
Sodium, mmol/L, mean (SD)	139.2 (6.5)	138.1 (7.3)	0.16	138.3 (6.9)	138.6 (7.0)	-0.05
Preadmission morbidity, n (%)						
Renal disease	86 (29.2)	122 (37.9)	-0.19	61 (32.5)	69 (32.1)	0.01
Diabetes	41 (13.9)	59 (18.3)	-0.12	29 (15.3)	37 (17.3)	-0.05
Congestive heart disease	79 (26.8)	59 (18.3)	0.20	47 (25.1)	52 (24.2)	0.02
Myocardial infarction	59 (20.0)	58 (18.0)	0.05	39 (20.9)	43 (20.3)	0.01
Cerebrovascular disease	28 (9.5)	42 (13.0)	-0.11	19 (10.3)	25 (11.6)	-0.04
Chronic pulmonary disease	40 (13.6)	41 (12.7)	0.02	23 (12.4)	30 (14.1)	-0.05
Liver disease	5 (1.7)	14 (4.3)	-0.16	1 (0.7)	4 (1.9)	-0.09
Vascular disease	72 (24.4)	91 (28.3)	-0.09	53 (28.3)	62 (29.1)	-0.02
Neoplasm[b]	30 (10.2)	54 (16.8)	-0.19	24 (12.6)	31 (14.7)	-0.06
Year of treatment, n (%)						
2005-2006	37 (12.5)	72 (22.4)	-0.26	34 (18.1)	36 (17.0)	0.01
2007-2008	43 (14.6)	58 (18.0)	-0.09	31 (16.4)	28 (13.3)	0.09
2009-2010	79 (26.8)	54 (16.8)	0.24	38 (20.4)	49 (23.0)	-0.06
2011-2012	76 (25.8)	55 (17.1)	0.21	37 (19.7)	50 (23.4)	-0.09
2013-2014	60 (20.3)	83 (25.8)	-0.13	48 (25.5)	50 (23.3)	0.05

Supplementary table 2: Baseline characteristics for the full and weighted cohort after trimming with ESRD as outcome of interest. Only patients surviving until day 90 were included.

[a] Initiated 24 hours before RRT

[b] Tumor, leukemia, lymphoma, metastasis

ESRD: End-stage renal disease, ICU: intensive care unit, IQI: interquartile interval, N: number, SD: Standard deviation, SMD: Standard mean difference, SOFA: sequential organ assessment score

	Not missing	Missing
N (%)	829 (68.3)	384 (31.7)
Early renal replacement therapy, n (%)	423 (68.1)	198 (31.9)
Late renal replacement therapy, n (%)	406 (68.6)	186 (31.4)
Demography		
Age, median (IQI)	69.0 (59.3-75.8)	67.7 (58.5-75.3)
Male, n (%)	551 (70.8)	275 (65.5)
Patient category, n (%)		
Non-surgical	375 (45.2)	135 (35.2)
Non-cardiac surgery, elective	79 (9.5)	5 (1.3)
Non-cardiac surgery, acute	88 (10.6)	45 (11.7)
Cardiac surgery, elective	121 (14.6)	45 (11.7)
Cardiac surgery, acute	166 (20.0)	154 (40.1)
SOFA score, men (SD)	8.1 (2.6)	8.2 (2.8)
ICU treatments, n (%)		
Vasopressor or inotropy treatment	715 (86.2)	331 (86.2)
Mechanical ventilation[a]	335 (40.4)	160 (41.7)
Extracorporeal membrane oxygenation	44 (5.3)	80 (20.8)
Laboratory values		
Potassium, mmol/l, median (IQI)	4.5 (4.0- 5.0)	4.4 (4.0- 5.0)
Sodium, mmol/L, mean (SD)	138.7 (6.9)	139.9 (7.5)
Preadmission morbidity, n (%)		
Renal disease	285 (34.4)	101 (26.3)
Diabetes	179 (21.6)	29 (7.6)
Congestive heart disease	245 (29.6)	55 (14.3)
Myocardial infarction	210 (25.3)	80 (20.8)
Cerebrovascular disease	127 (15.3)	39 (10.2)
Chronic pulmonary disease	167 (20.1)	36 (9.4)
Liver disease	32 (3.9)	12 (3.1)
Vascular disease	244 (29.4)	89 (23.2)
Tumor	141 (17.0)	22 (5.7)
Lymphoma	12 (1.4)	3 (0.8)
Leukemia	8 (1.0)	4 (1.0)
Metastasis	28 (3.4)	5 (1.3)
Year of treatment, n (%)		
2005-2006	139 (16.8)	105 (27.3)
2007-2008	155 (18.7)	66 (17.2)
2009-2010	162 (19.5)	72 (18.8)
2011-2012	185 (22.3)	67 (17.4)
2013-2014	188 (22.7)	74 (19.3)

Supplementary table 3: Description of patients with missing baseline P-creatinine. N: Number IQI: Interquartile interval

[a] Initiated 24 hours before RRT

ICU: intensive care unit, IQI: interquartile interval, N: number, SD: Standard deviation, SOFA: sequential organ assessment score

Supplementary table 4: Relevant codes used in current study	
Description	**Codes**
Preadmission morbidity (ICD-10)	
Myocardial infarction	I21, I22, I23
Congestive heart failure	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	I70, I71, I72, I73, I74, I77
Chronic pulmonary disease	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Diabetes	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Renal disease	I12, I13, N00-N05, N07, N11, N14, N18-N19, Q61
Any tumor	C00-C75
Leukemia	C81-C85, C88, C90, C96
Lymphoma	C81-C85, C88, C90, C96
Metastatic solid tumor	C76-C80
Liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85 B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Treatment (Nordic surgical codes and Danish procedure codes)	
Non-cardiac surgery	KA, KB, KC, KD, KE, KG, KH, KJ, KK, KL, KM, KN, KP, KQ, KX, KY
Cardiac surgery	KF
Mechanical ventilation	BGDA0
Outcomes (ESRD)	
Chronic renal replacement therapy	BKFD2
Kidney transplant	KKAS
Laboratory measurements (NPU codes and local analysis numbers)	
Creatinine	NPU26918, NPU04998, NPU01807, NPU18016, NPU17559, NPU09101, NPU18105, ASS00354, ASS00355, ASS00356, 110266, 111016, 1311235, 1411235, 1511235, 1511236, 1511237, 1610154, 1610296, 1611807, 1710301, 1710552, 1711807, 1811807, 1817156, 1817428, 18016, 1155, 38927, 4998
Potassium	NPU03230, ASS00102, ASS00255, 110262, 111262, 1311140, 1411140, 1511140 , 1610147, 1613230, 1710304, 1713230, 1813230, 1817159
Sodium	NPU03429, ASS00101, ASS00256, 110261, 1311170, 1411170, 1511170, 1610146, 1713429, 1813429
Bilirubin	NPU01370, NPU01366, 110270, 1311218 , 1411218 , 1511218 , 1610191, 1711370, 1811370, 110476, 1522032, 1722032, 1822032
Platelets	NPU03568, NPU17586, AAA00946, 122576, 122587, 122676, 1313160, 1413160 , 1523077, 1610113, 1813568, 1510899, 1710946
Pa-O2	NPU08977, NPU03009, NPU14104, 111029, 122063, 1324064, 1424064, 1622196, 1622286 , 1722184, 1722663, 1817282, 1817514, 1822184, 1524074

Supplementary table 5: Summary of propensity score methods and results presented with hazard ratios and 95% Cis and the number of patients included in the analysis				
Method	Mortality, 0 to 90 days HR (95% CI) (n)	Mortality, 90 days to 5 years HR (95% CI) (n)	Chronic kidney disease HR (95% CI) (n)	End-stage renal disease HR (95% CI) (n)
Crude	1.24 (1.06-1.46) (1213)	0.89 (0.68-1.17) (617)	0.95 (0.67-1.34) (303)	0.96 (0.62-1.48) (617)
Matching	1.25 (1.02-1.54) (750)	0.91 (0.64-1.29) (397)	0.68 (0.43-1.07) (190)	0.85 (0.49-1.47) (370)
IPTW	1.31 (1.08-1.59) (1193)	0.92 (0.67-1.25) (606)	0.65 (0.41-1.02) (303)	0.71 (0.42-1.20) (599)
IPTW, 1st centile trim	1.29 (1.07-1.56) (1092)	1.05 (0.76-1.43) (558)	0.64 (0.41-1.01) (256)	0.79 (0.48-1.31) (520)
IPTW, 2.5th centile trim	1.21 (1.00-1.46) (990)	1.14 (0.83-1.58) (508)	0.75 (0.48-1.18) (233)	0.87 (0.51-1.48) (446)
IPTW, 5th centile trim	1.17 (0.95-1.42) (845)	0.97 (0.69-1.37) (427)	0.84 (0.52-1.34) (196)	0.94 (0.55-1.62) (446)
SMRW	1.21 (0.97-1.51) (1193)	0.83 (0.58-1.17) (606)	0.79 (0.50-1.23) (269)	0.73 (0.38-1.37) (599)
IPTW, bootstrap	1.31 (1.08-1.54) (1193)	0.92 (0.61-1.23) (606)	0.65 (0.35-0.94) (269)	0.71 (0.30-1.11) (599)
IPTW, 1st centile trim, bootstrap	1.29 (1.06-1.53) (1092)	1.05 (0.69-1.40) (558)	0.64 (0.33-0.95) (256)	0.79 (0.39-1.19) (520)
IPTW, 2.5th centile trim, bootstrap	1.21 (0.98-1.43) (990)	1.14 (0.81-1.47) (508)	0.75 (0.38-1.12) (233)	0.87 (0.38-1.36) (446)
IPTW, 5th centile trim, bootstrap	1.17 (0.93-1.40) (845)	0.97 (0.62-1.33) (427)	0.83 (0.44-1.23) (204)	0.94 (0.35-1.54) (401)
SMRW, bootstrap	1.21 (0.93-1.49) (1213)	0.83 (0.52-1.13) (617)	0.79 (0.41-1.16) (269)	0.73 (0.20-1.26) (599)
95% CI estimated with a robust variance estimator, unless otherwise specified. CI: Confidence interval, HR: Hazard ratio, IPTW: Inverse probability of treatment weighting, SMRW: Standard mortality ratio weighting, n: number				

Figures

Figure 1: Flow chart of eligible patients and included in the analyses

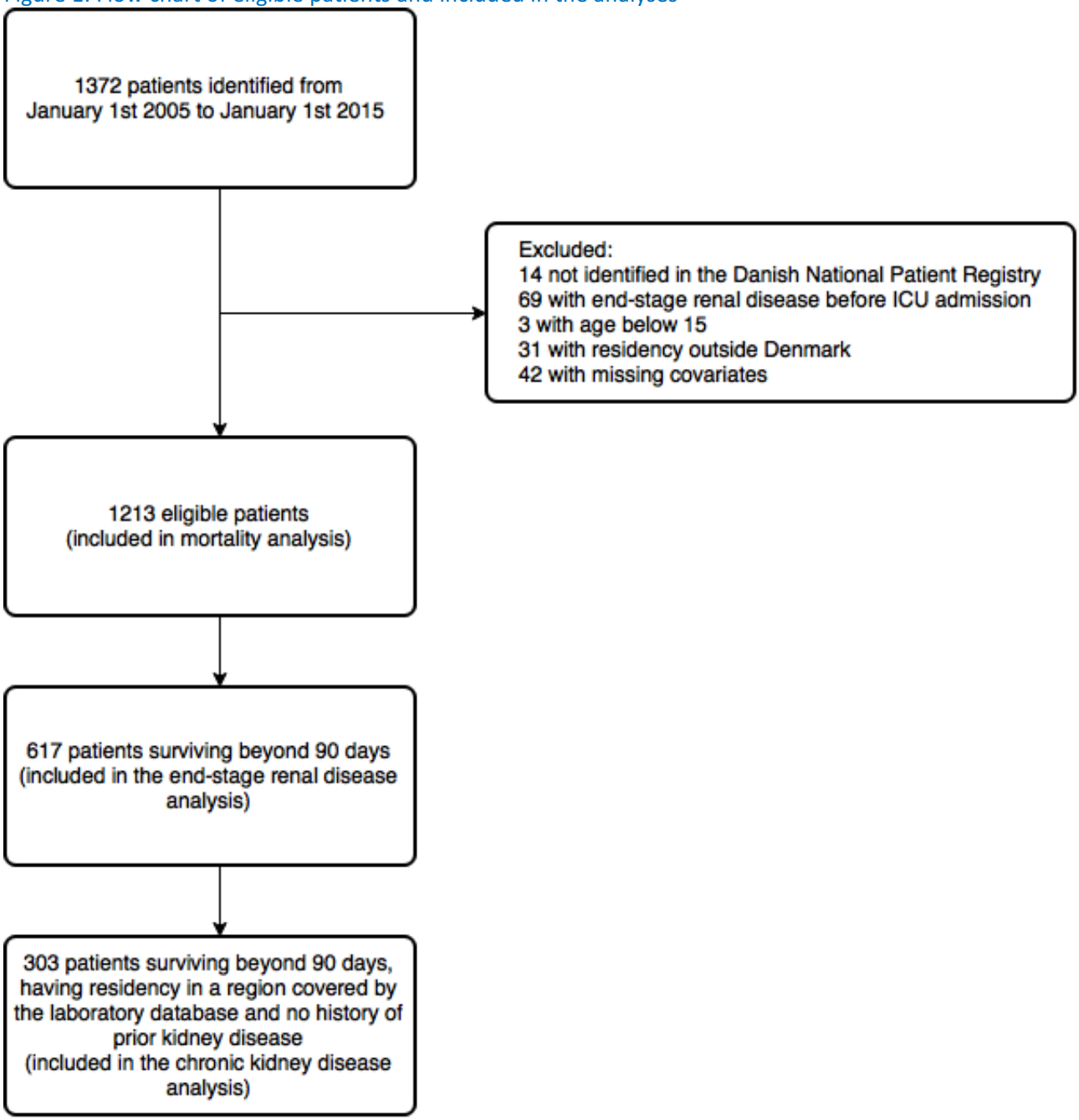


Figure 2a: Cumulative mortality

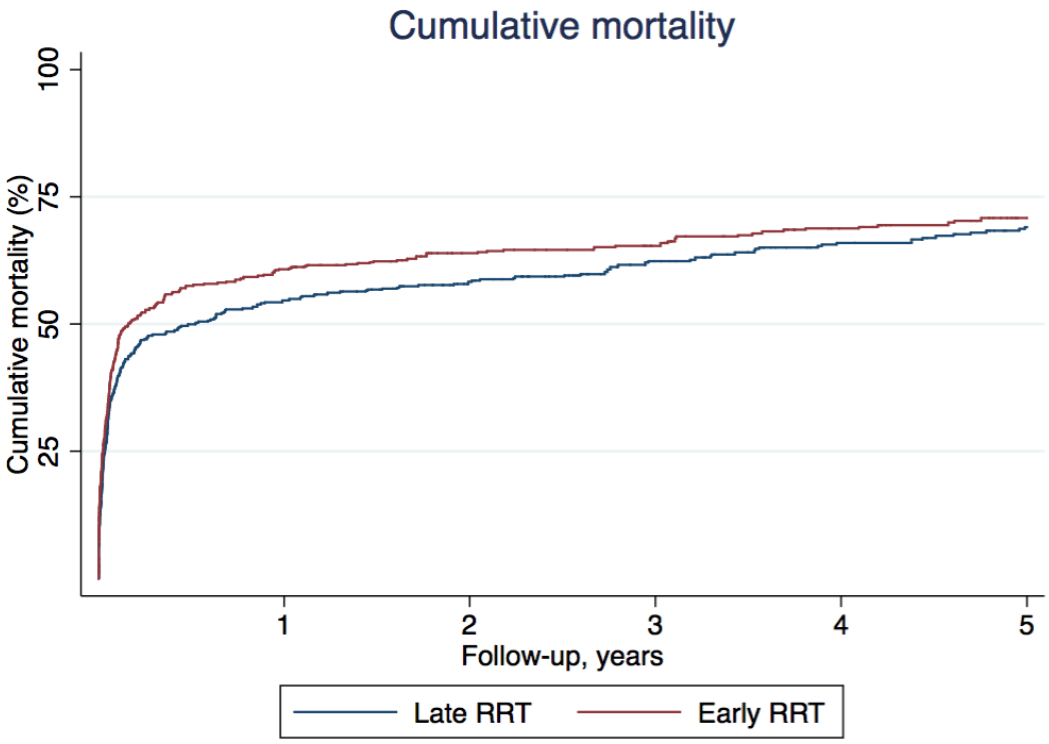


Figure 2b: Cumulative risk of chronic kidney disease

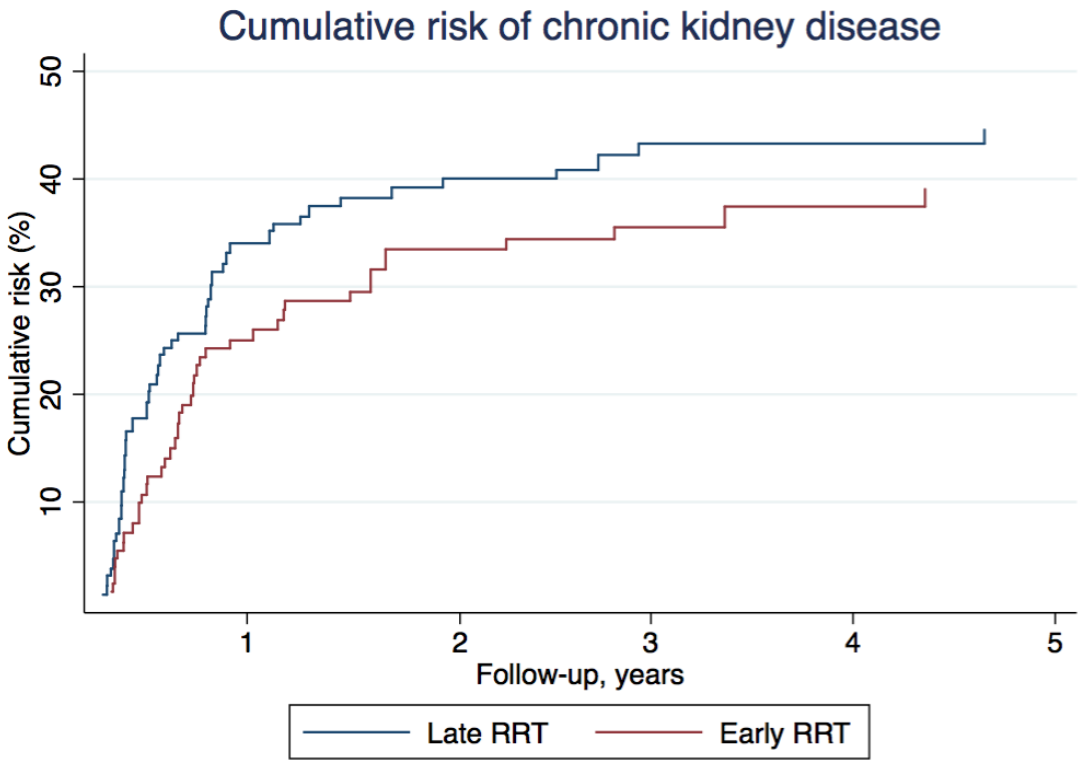
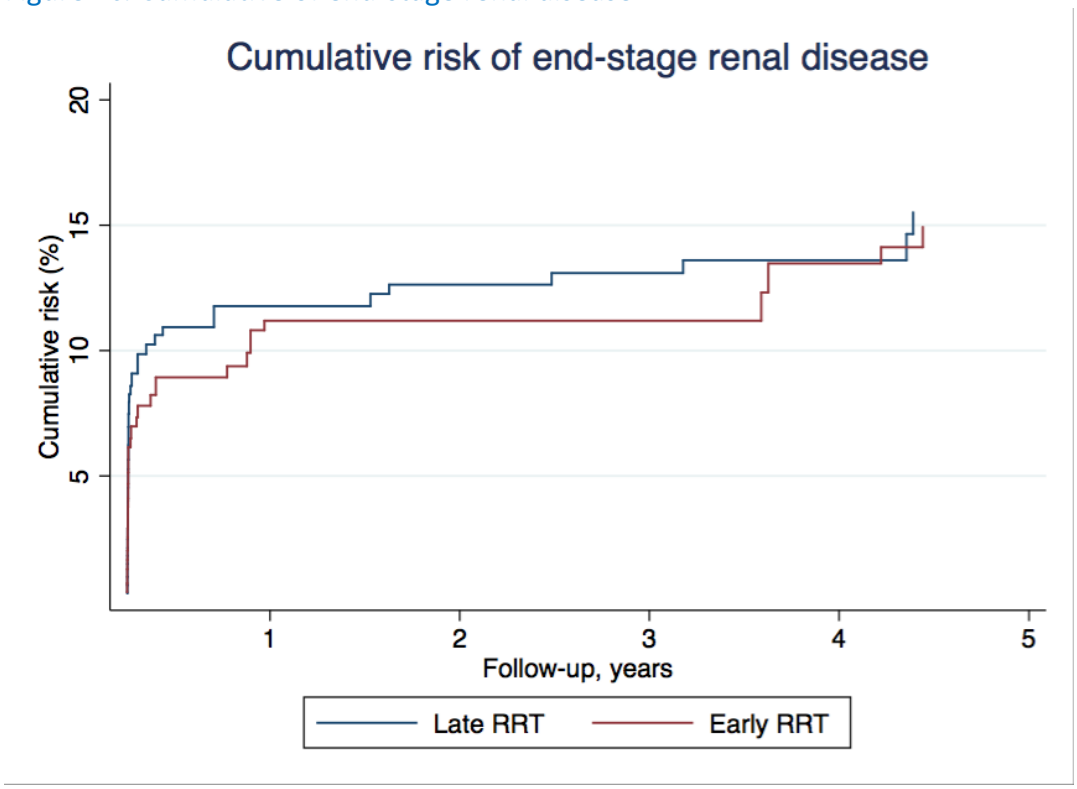
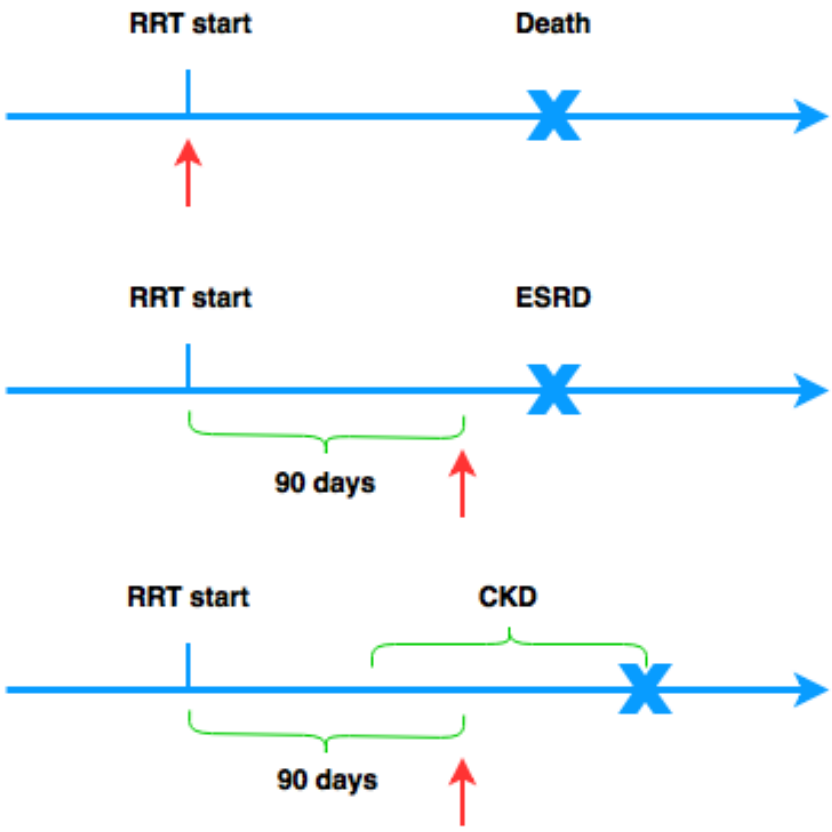


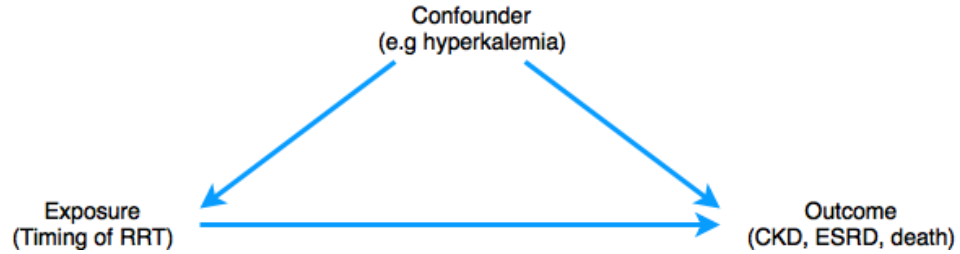
Figure 2c: Cumulative of end-stage renal disease



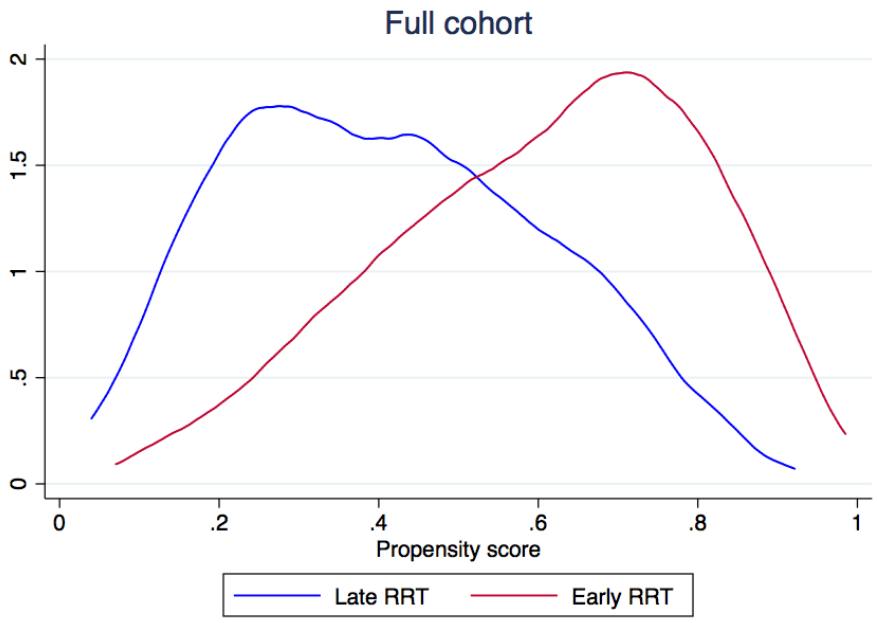
Supplementary figure 1: Description of outcomes. Start of follow-up indicated by red arrows. CKD: Chronic kidney disease, ESRD: End-stage renal disease, RRT: Renal replacement therapy



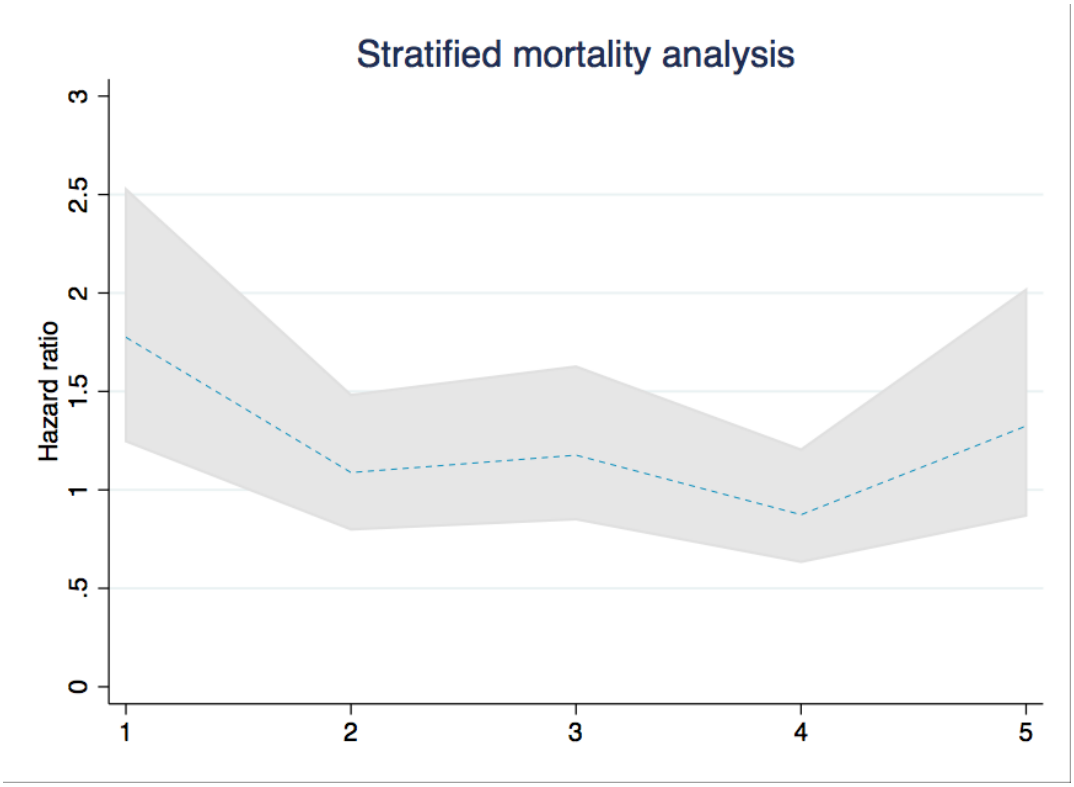
Supplementary Figure 2: Definition of a confounder. CKD: Chronic kidney disease, End-stage renal disease, RRT: Renal placement therapy



Supplementary figure 3: Kernel plot of propensity scores in early and late treatment group



Supplementary figure 4: Stratified mortality analysis with hazard ratios and 95% confidence intervals for each quintile



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