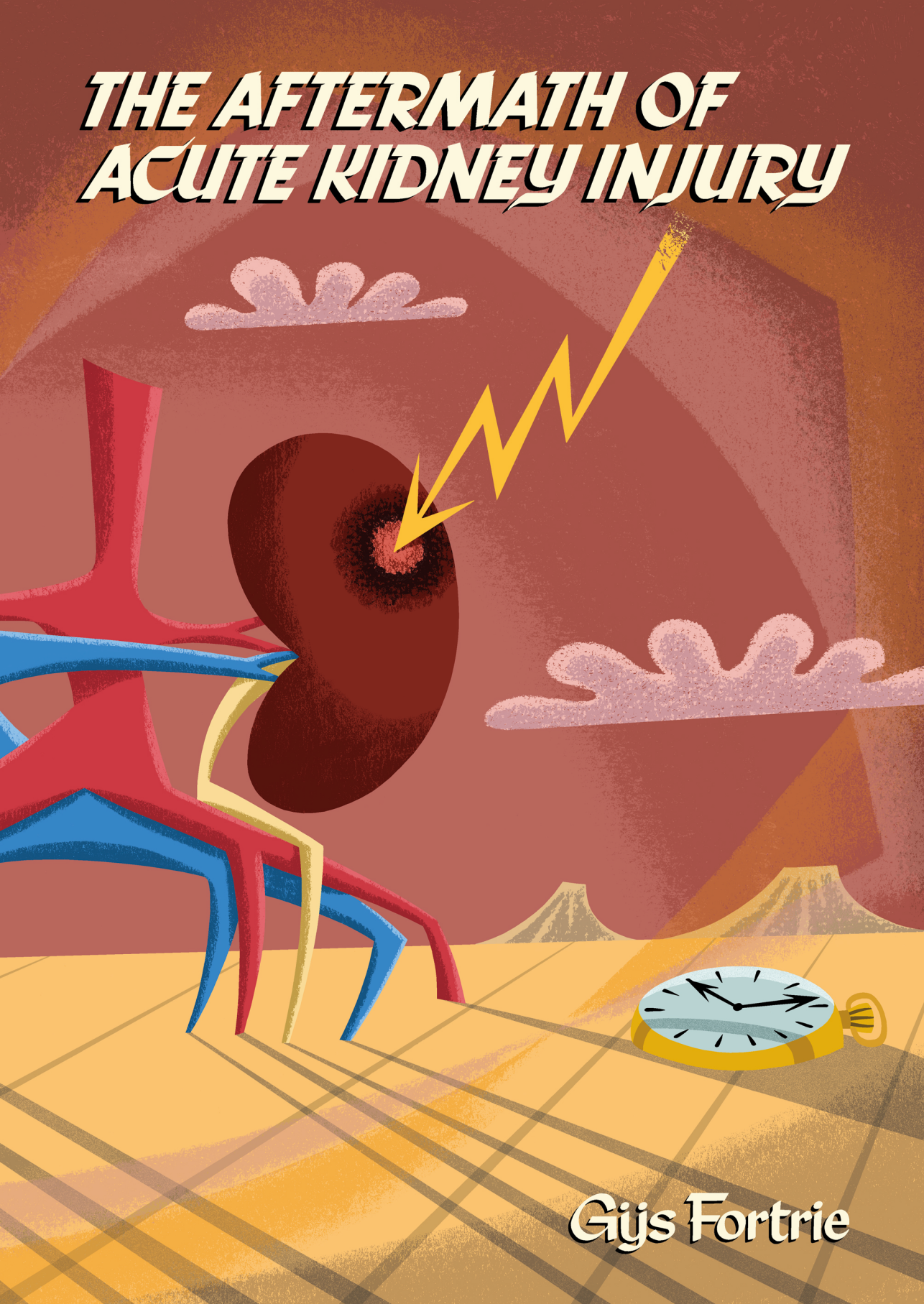
THE AFTERMATH OF ACUTE KIDNEY INJURY



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Printing of this thesis is supported by
Erasmus University Rotterdam, ChipSoft BV,
ABN-AMRO, Vifor Pharma, Chiesi Pharmaceuticals BV,
Astellas Pharma BV, stichting T.T.I.

The publication of this thesis is supported by
the Dutch Heart Foundation and the support is
gratefully acknowledged.

The publication of this thesis is supported by
the Dutch Kidney Foundation and the support is
gratefully acknowledged.

cover design P.M. Dorrenboom
layout M.C. de Wilde
printed by Ridderprint BV

ISBN 978-94-6375-630-3

The aftermath of acute kidney injury

De nasleep van acuut nierfalen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 13 november 2019 om 11:30 uur
door

Gijs Fortrie

geboren te Heinkenszand

Erasmus University Rotterdam

promotiecommissie

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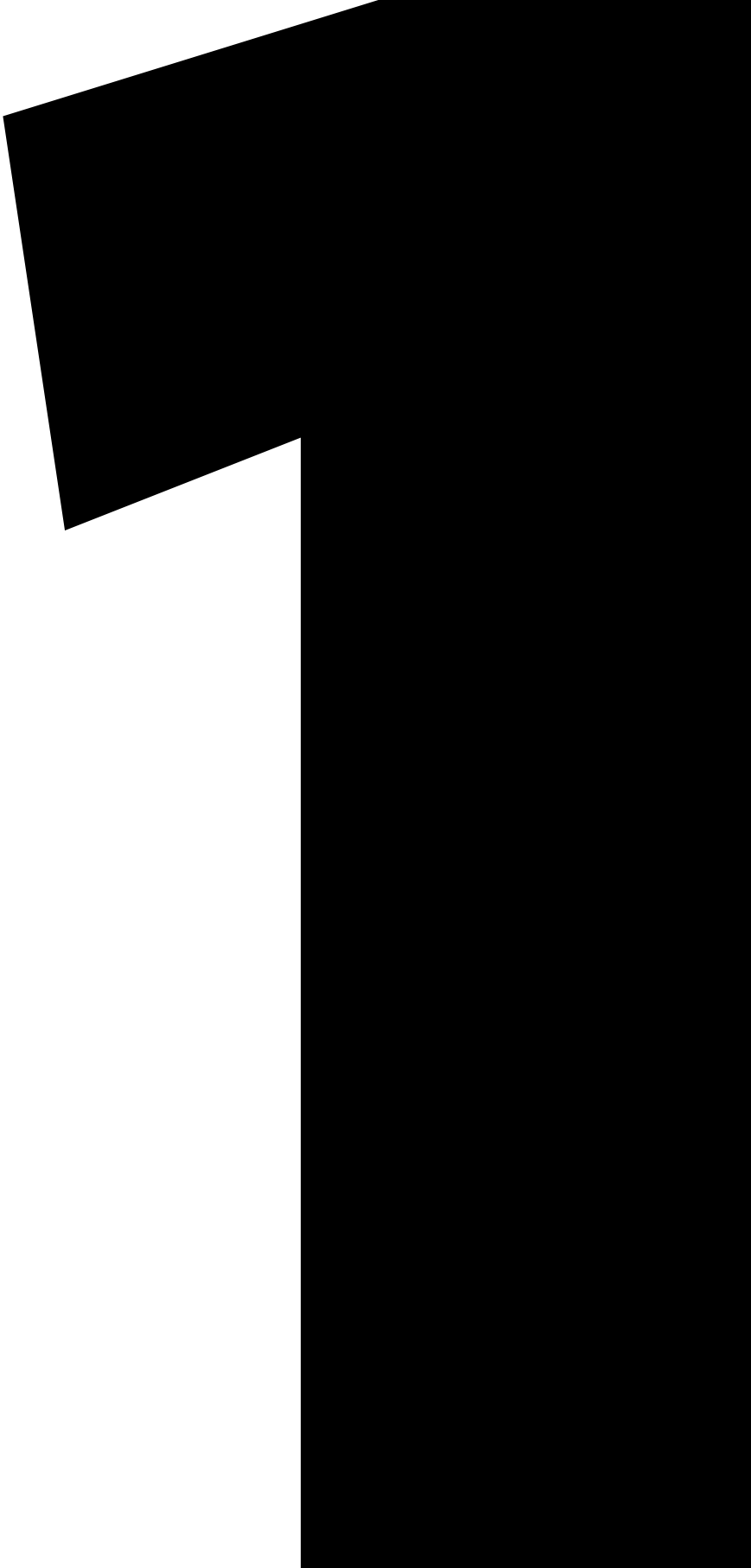
CONTENTS



Introduction

The aftermath of acute kidney injury: a narrative review of long-term mortality and renal function

G. Fortrie, H.R.H. de Geus, M.G.H. Betjes

Critical Care (2019) 23: e-publication

ABSTRACT

Acute kidney injury (AKI) is a frequent complication of hospitalization and is associated with an increased risk of chronic kidney disease (CKD), end-stage renal disease (ESRD) and mortality. While AKI is a known risk factor for short-term adverse outcomes, more recent data suggest that the risk of mortality and renal dysfunction extends far beyond hospital discharge. However, determining whether this risk applies to all patients who experience an episode of AKI is difficult. The magnitude of this risk seems highly dependent on the presence of comorbid conditions, including cardiovascular disease, hypertension, diabetes mellitus, pre-existing CKD, and renal recovery. Furthermore, these comorbidities themselves lead to structural renal damage due to multiple pathophysiological changes, including glomeruloscleroses and tubulointerstitial fibrosis, which can lead to the loss of residual capacity, glomerular hyperfiltration and continued deterioration of renal function. AKI seems to accelerate this deterioration and increase the risk of death, CKD and ESRD in most vulnerable patients. Therefore, we strongly advocate adequate hemodynamic monitoring and follow-up in patients susceptible to renal dysfunction. Additionally, other potential renal stressors, including nephrotoxic medications and iodine-containing contrast fluids, should be avoided. Unfortunately, therapeutic interventions are not yet available. Additional research is warranted and should focus on the prevention of AKI, identification of therapeutic targets and provision of adequate follow-up to those who survive an episode of AKI.

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt loss in renal function and may be caused by a wide variety of clinical conditions. Historically, AKI was described as early as the second century AD by Claudius Galenus [1] and was initially considered a harmless transient entity with limited implications for a patient's prognosis. However, in recent decades, this opinion has radically changed, and AKI has attracted increased interest, reflected by the exponential increase in related publications [2, 3]. Today, AKI is a frequently seen complication of hospitalization and is independently associated with a high risk of mortality and progressive deterioration of renal function, which can lead to chronic kidney disease (CKD) as well as end-stage renal disease (ESRD) and a decrease in the quality of life [4-7]. Furthermore, recent studies suggest that AKI is also a risk factor for other adverse outcomes, including stroke, cardiovascular disease, sepsis, malignancy, bone fracture and upper gastrointestinal hemorrhage [8-16]. The results of these studies suggest that an episode of AKI plays a significant role in the patient's long-term prognosis.

However, whether there is indeed a causal relationship between AKI and long-term adverse outcomes or whether AKI is simply an indicator of poor clinical condition remains a major topic of discussion [17-20]. A large proportion of the currently available literature consists of retrospective cohort studies that were not designed to demonstrate a causal relationship and therefore carry a substantial risk for selection bias, information bias and residual confounding. Furthermore, the impact of AKI on long-term adverse outcomes is highly dependent on the presence of pre-existing comorbidities, including cardiovascular disease, hypertension, diabetes mellitus and, in particular, pre-existing CKD. Independent of AKI, most of these conditions strongly impact outcome measures such as morbidity and mortality. This narrative review offers an overview of the most relevant literature addressing the long-term impact of AKI on mortality and renal function.

DEFINITION AND STAGING

For a long time, a universal definition to describe an acute deterioration in renal function was lacking. A frequently used term was acute renal failure (ARF), which was generally an umbrella term for an acute deterioration in renal function and usually used to describe a situation where emergency

renal replacement therapy (RRT) was necessary. Although ARF was associated with a high hospital mortality and risk for chronic dialysis dependence [21, 22], little was known about milder episodes of renal injury, leading to a call for consensus criteria [23].

In 2004, the Acute Dialysis Quality Initiative (ADQI) group published the Risk, Injury, Failure, Loss, End-stage Renal Disease (RIFLE) criteria, which was the first consensus definition for AKI [24]. Subsequently, the RIFLE criteria were validated and, commensurate with an increased stage of severity, associated with an increased risk of short-term mortality [25, 26]. However, increasing evidence has demonstrated that even minor changes in serum creatinine are associated with an increased risk of mortality [27-29]. Therefore, in 2007, the Acute Kidney Injury Network (AKIN) published a refinement of the RIFLE criteria, and henceforth, the term ARF was officially replaced by AKI [30]. The currently used criteria, shown in table 1, were published in 2012 by the Kidney Disease: Improving Global Outcome (KDIGO) AKI workgroup and represent a unification of the RIFLE and AKIN criteria [31].

TABLE 1 Definition of AKI by the Kidney Disease: Improving Global Outcome criteria [31].

AKI stage	serum creatinine	urine output
I	1.5 to 2.0 times baseline within 7 days or ≥26.4 µmol/L within 48 hours	<0.5 ml/kg/h for 6-12 hours
II	2.0 to 2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
III	≥ 3.0 times baseline or an increase in SCr to ≥ 353.6 µmol/L or the initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 hours or anuria for ≥12 hours

AKI AND LONG-TERM MORTALITY

Even before the publication of the RIFLE criteria in 2004, multiple studies evaluated the long-term consequences of ARF and demonstrated that ARF was associated with an increased risk of mortality and other adverse outcomes. However, these conclusions were mainly based on small, retrospective, uncontrolled cohort studies performed in diverse clinical settings. With the lack of consensus criteria for ARF, this variation resulted in significant differences in study outcomes, which made it difficult to generalize these results to other populations and use them in clinical practice.

One of the first studies that described the long-term effect of AKI compared to the outcomes of patients without AKI after thoracic surgery (n = 88) was performed in 1994 by Schepens et al. [32]. During the post-surgical period, 14% of the cohort developed AKI requiring RRT. The 5-year survival rate was 20% for these patients but was 62% for the patients without RRT (P = 0.001). This paper triggered the publication of numerous papers on the association between AKI and long-term mortality, which further led to an increase in the quality and sample size of these studies. In 2009, Coca et al. performed a systematic review and meta-analysis of 48 studies with follow-up times of between 6 months to 17 years [4]. The clinical setting of the incorporated studies was heterogeneous and included patients undergoing cardiac surgery, percutaneous coronary intervention, and liver or lung transplantation, as well as general ICU patients. Fifteen studies were eligible for long-term survival analysis and provided data on long-term mortality in AKI patients (n = 8,350) as well as in non-AKI controls (n=90,753). Overall, the mortality rate was significantly different between the AKI patients who survived hospital admission (mortality rate = 8.9 per 100 person-years) and the non-AKI controls (4.3 per 100 person-years). Furthermore, the risk of death increased proportionally with the severity of AKI. Due to the heterogeneous AKI definitions used in the studies, the patients were stratified into 3 groups: mild, moderate and severe AKI. Mild AKI was defined as an increase in serum creatinine of >25% or a decrease in creatinine clearance of >10%; moderate AKI was defined as an increase in serum creatinine of >50%, 100%, or >1.0 mg/dl or a creatinine concentration of >1.7 mg/dl; and severe AKI was defined as a necessity for RRT. The pooled rate ratios for mild, moderate and severe AKI compared to that of the non-AKI controls were 1.67, 2.70 and 3.09, respectively.

While the analyses by Coca et al. included only studies with a relatively small study population, the results of more recently published studies with large sample sizes are presented in table 2A [33-42]. The largest study, by Lafrance et al., demonstrated in a retrospective analysis among U.S. veterans (n = 864,933) that patients with an episode of AKI not requiring RRT had an adjusted hazard ratio (HR) of 1.41 for long-term mortality (95% CI = 1.39–1.43) [38]. When stratified by AKI severity according to the AKIN definition, the adjusted HRs were 1.36, 1.46 and 1.59 for stages I, II and III (without RRT), respectively (P < 0.001 for the trend). Similar results were

TABLE 2 Summary of the largest original investigations on long-term risk of mortality or ESRD in adult patients who experienced AKI.*

author	setting	population	number	follow-up
A long-term risk of mortality				
Bihorac et al. [33]	ICU (surgical)	hospital survivors	10,518	max: 14 years
Coca et al. [34]	noncardiac surgery	hospital survivors	35,302	mean: 3.7 years
Fuchs et al. [35]	ICU (overall)	60-day survivors	12,399	max: 2.0 years
Ishani et al. [36]	overall hospitalization	hospital survivors	233,803	max: 2.3 years
James et al. [37]	coronary angiography	all patients	14,782	median: 1.6 years
Lafrance et al. [38]	overall hospitalization	90-day survivors	864,933	mean: 2.3 years
Liotta et al. [39]	CABG	all patients	25,665	mean: 6.0 years
Parikh et al. [40]	AMI	hospital survivors	147,007	max: 10.0 years
Rimes-Stigare et al. [41]	ICU (overall)	all patients	103,363	median: 2.1 years
Ryden et al. [42]	CABG	all patients	27,929	mean: 5.0 years
B long-term risk of ESRD				
Ishani et al. [36]	overall hospitalization	hospital survivors	233,803	max: 2.3 years
James et al. [37]	coronary angiography	all patients	14,782	median: 1.6 years
Rimes-Stigare et al. [41]	ICU (overall)	all patients	103,363	median: 2.1 years
Ryden et al. [61]	CABG	all patients	29,330	mean: 4.3 years

* This table includes only studies with > 10.000 patients. Studies that only evaluated the impact of AKI requiring RRT are not included.

AKI definition	adjusted risk		comments
RIFLE criteria	R	HR (95%–CI) = 1.18 (1.08–1.29)	–
	I	HR (95%–CI) = 1.43 (1.29–1.59)	
	F	HR (95%–CI) = 1.57 (1.40–1.75)	
AKIN criteria	I	HR (95%–CI) = 1.24 (1.17–1.31)	only diabetic veterans included
	II	HR (95%–CI) = 1.64 (1.43–1.88)	
	III	HR (95%–CI) = 1.96 (1.63–2.37)	
AKIN criteria	I	HR (95%–CI) = 1.26 (1.14–1.40)	–
	II	HR (95%–CI) = 1.28 (1.11–1.47)	
	III	HR (95%–CI) = 1.61 (1.30–1.99)	
ICD-9 code	AKI	HR (95%–CI) = 2.38 (2.31–2.46)	only elderly patients ≥ 67 years of age included.
AKIN criteria	I	HR (95%–CI) = 2.00 (1.69–2.36)	–
	II / III	HR (95%–CI) = 3.72 (2.92–4.76)	
AKIN criteria	I	HR (95%–CI) = 1.36 (1.34–1.38)	only veterans included. AKI requiring RRT excluded.
	II	HR (95%–CI) = 1.46 (1.42–1.50)	
	III	HR (95%–CI) = 1.59 (1.54–1.65)	
mild ΔSCr 0.0–0.3 mg/dl moderate ΔSCr 0.3–0.5 mg/dl severe ΔSCr ≥ 5.0 md/dl	mild moderate severe	HR (95%–CI) = 1.07 (1.00–1.15) HR (95%–CI) = 1.33 (1.19–1.48) HR (95%–CI) = 2.11 (1.92–2.32)	–
mild ΔSCr 0.3–0.4 mg/dl moderate ΔSCr 0.5–0.9 mg/dl severe ΔSCr ≥ 1.0 md/dl	mild moderate severe	HR (95%–CI) = 1.15 (1.12–1.18) HR (95%–CI) = 1.23 (1.20–1.26) HR (95%–CI) = 1.33 (1.28–1.38)	only elderly patients ≥ 65 years of age included.
temporary RRT or ICD-10 code or ARF reported in APACHE score or serum creatinine > 354 µmol/L	AKI	MMR (95%–CI) = 1.15 (1.09–1.21)	–
mild ΔSCr 0.3–0.4 mg/dl moderate ΔSCr 0.5–0.9 mg/dl severe ΔSCr ≥ 1.0 md/dl	mild moderate severe	HR (95%–CI) = 1.30 (1.17–1.44) HR (95%–CI) = 1.65 (1.48–1.83) HR (95%–CI) = 2.68 (2.37–3.03)	–
ICD-9 code	AKI	HR (95%–CI) = 6.74 (5.90–7.71)	only elderly patients ≥ 67 years of age included.
AKIN criteria	I	HR (95%–CI) = 4.15 (2.32–7.42)	–
	II / III	HR (95%–CI) = 11.74 (6.38–21.59)	
temporary RRT or ICD-10 code or ARF reported in APACHE score or serum creatinine > 354 µmol/L	AKI	IRR (95%–CI) = 24.1 (13.9–42.0)	–
AKIN criteria	I	HR (95%–CI) = 2.92 (1.87–4.55)	–
	II / III	HR (95%–CI) = 3.81 (2.14–6.79)	

shown for subgroup analyses restricted to patients who survived at least 3 or 6 months after discharge; even more interestingly, the negative effect of AKI persisted in patients who showed only short-term impairment in renal function during hospitalization. These results demonstrate that even a short transient deterioration in renal function is associated with a poorer outcome.

In addition to the severity of AKI, the risk of long-term mortality is strongly determined by other clinical and demographic patient characteristics, including age [43], baseline renal function [43, 44], malignancy [43], severe sepsis and septic shock [45, 46], recurrent episodes of AKI [47] and, particularly, renal recovery [33, 34, 38, 48-58]. There is a gradual association between the proportion of early post-AKI renal recovery and the long-term mortality risk. As shown in table 3, the risk of death increases significantly in patients with partial or no renal recovery following AKI. In addition, the vast majority of patients who experienced an episode of AKI have one or more comorbid conditions, which, given the strong relationship between pre-existing comorbidities and the impact of AKI, may result in the overestimation of long-term mortality risk in patients with a low comorbidity burden. In 2015, Fortrie et al. performed a retrospective cohort study on the long-term sequelae of AKI requiring RRT in critically ill patients without any comorbid conditions. This study demonstrated that in-hospital mortality was equally high among those with or without any comorbid conditions. However, the study also demonstrated that patients without comorbidity that survived an episode of AKI and were discharged from the hospital had a good long-term prognosis; furthermore, compared to survival in the average Dutch population, no increased risk for mortality was found [20]. These conclusions are limited by the retrospective nature and relatively small sample size of the study, as only 96 of the 1,067 patients were not known to have any comorbidity. Nevertheless, the results of this study are intriguing because they add evidence supporting the concept that comorbidity is a key player in the long-term impact of AKI.

AKI AND LONG-TERM RISK FOR CKD AND ESRD

While the association between AKI and long-term mortality seems to be based on a complex interplay between AKI and many other patient-specific factors, this interplay is even more complex for the association between

AKI and long-term deterioration in renal function. Many recent studies have described the association between AKI and progression to CKD or even ESRD, which has led to a discussion on whether there is a causal relationship between AKI and CKD or whether this association is simply the result of methodological differences and pre-existing comorbidities such as diabetes, hypertension, cardiovascular disease and, of course, pre-existing CKD [17, 18, 59, 60]. In 2012, Coca et al. demonstrated, in another meta-analysis including 13 studies with a maximum follow-up of 75 months, a strong association between AKI and the development of CKD as well as ESRD, with adjusted HRs of 8.82 (95% CI = 3.05–25.48) and 3.10 (95% CI = 1.91–5.03), respectively [5]. Furthermore, those authors demonstrated that the risk of CKD as well as that of ESRD increased in a graded fashion with AKI severity. These results are in accordance with the results of the large population-based studies that evaluated the risk of ESRD in AKI survivors presented in table 2B [36, 37, 41, 61]. In addition, a large study by Lo et al. that included more than 500,000 patients with a baseline estimated glomerular filtration rate (eGFR) of >45 ml/min/1.73 m² demonstrated that AKI requiring RRT was strongly associated with the development of stage 4 or 5 CKD, with an adjusted HR of 28.1 (95% CI = 21.1–37.6) [62].

However, the AKI survivor population is very heterogeneous, and AKI etiology varies widely. Therefore, identifying individuals with the highest risk of renal deterioration is greatly important. In addition to AKI, other factors associated with an increased risk of CKD or ESRD include higher age [43, 49, 56], lower baseline renal function [36, 43, 44, 49, 57, 63, 64], diabetes [36, 56], hypertension [36, 49, 63, 64], chronic heart failure [49, 56], low serum albumin [49], proteinuria [64], liver failure [63], higher Charlson comorbidity index score [49, 63] and recurrent episodes of AKI [64]. In summary, those with the highest risk of progression towards CKD or ESRD after an episode of AKI are those who already have an increased risk for CKD progression independent of an episode of AKI. Additionally, the complexity of this association is increased even more because the vast majority of the aforementioned risk factors are associated with an increased risk of AKI itself [49, 65-67].

In 2009, Ishani et al. demonstrated in 200,000 hospitalized elderly that patients with AKI but without pre-existing CKD as well as patients with pre-existing CKD but without AKI have an increased risk of developing ESRD.

TABLE 3 Summary of investigations evaluating the impact of post-AKI renal recovery on mortality and/or CKD and ESRD compared to no-AKI controls.

author	setting	number	follow-up	AKI definition
Bihorac et al. [33]	ICU (surgical)	10,518	max: 14 years	RIFLE criteria
Brown et al. [48]	cardiac surgery	4,873	mean: 2.5 years	AKIN criteria
Bucaloiu et al. [49]	overall hospitalization	20,028	mean: 3.3 years	AKIN criteria
Coca et al. [34]	noncardiac surgery	35,302	mean: 3.7 years	AKIN criteria
Han et al. [50]	CABG	1,899	median: 5.0 years	KDIGO criteria
Hobson et al. [51]	cardiothoracic surgery	2,973	max: 10.0 years	RIFLE criteria
Jones et al. [52]	overall hospitalization	3,809	median: 2.5 years	AKIN criteria
Kuijk et al. [68]	major vascular surgery	1,308	median: 5.0 years	ΔSCr >10% vs. baseline
Lafrance et al. [38]	overall hospitalization	864,933	mean: 2.3 years	AKIN criteria
Loef et al. [53]	cardiac surgery	843	max: 14.3 years	ΔSCr ≥25% vs. baseline
Maioli et al. [54]	coronary angiography	1,490	median: 3.8 years	ΔSCr >0.5 mg/dl vs. baseline
Mehta et al. [55]	CABG	10,415	median: 7.0 years	ΔSCr ≥50% or ≥0.7 mg/dl vs. baseline
Pannu et al. [56]	overall hospitalization	190,714	mean: 2.8 years	ΔSCr ≥100% vs. baseline or RRT requirement
Wu et al. [57]	ICU (surgical)	9,425	median: 4.8 years	RIFLE criteria
Xu et al. [58]	cardiac surgery	3,245	max: 2.0 years	KDIGO criteria

* The chosen endpoints differed between the individual studies. Bucaloiu et al.: new CKD (eGFR <60 ml/min), Jones et al.: new CKD (eGFR <60 ml/min), Kuijk et al.: new CKD (eGFR <60 ml/min and eGFR decrease ≥25% compared to baseline), Pannu et al.: need for chronic RRT dependence or doubling of the SCr compared to baseline, Wu et al.: chronic RRT dependence, Xu et al.: eGFR <30 ml/min.

renal recovery	definition	mortality risk	CKD/ESRD risk*
complete	ΔSCr at discharge ≤50%	HR (95%–CI) = 1.20 (1.10–1.31)	–
partial	ΔSCr at discharge >50%	HR (95%–CI) = 1.45 (1.32–1.58)	
nonrecovery	RRT at discharge	HR (95%–CI) = 2.76 (2.09–3.43)	
transient	ΔSCr at 1–2 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 1.51 (1.19–1.91)	–
	ΔSCr at 3–6 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 1.74 (1.34–2.26)	
	ΔSCr at ≥7 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 3.45 (2.75–4.34)	
nonrecovery	ΔSCr at discharge ≥50%	HR (95%–CI) = 5.75 (4.10–8.07)	
recovery	ΔeGFR at day 90 ≤10%	HR (95%–CI) = 1.48 (1.19–1.82)	HR (95%–CI) = 1.91 (1.75–2.09)
transient	ΔSCr at 1–2 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 1.15 (1.07–1.23)	–
	ΔSCr at 3–6 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 1.50 (1.36–1.66)	
	ΔSCr at ≥7 days ≥50% or >0.3 mg/dl	HR (95%–CI) = 2.01 (1.77–2.28)	
recovery	SCr at 3 months ≤ baseline SCr	HR (95%–CI) = 1.68 (1.35–2.10)	–
nonrecovery	SCr at 3 months > baseline SCr	HR (95%–CI) = 2.06 (1.52–2.79)	
complete	ΔSCr at discharge ≤50%	HR (95%–CI) = 1.28 (1.11–1.48)	–
partial	ΔSCr at discharge >50%	HR (95%–CI) = 1.49 (1.27–1.74)	
nonrecovery	RRT at discharge	HR (95%–CI) = 3.79 (2.46–5.74)	
recovery	ΔSCr at day 7 <10%	HR (95%–CI) = 1.08 (0.93–1.27)	HR (95%–CI) = 3.82 (2.81–5.19)
recovery	ΔSCr at day 3 ≤10%	–	RR (95%–CI) = 3.40 (2.70–4.10)
nonrecovery	ΔSCr at day 3 >10%		RR (95%–CI) = 3.60 (2.80–4.40)
recovery	ΔeGFR at discharge ≤10%	HR (95%–CI) = 1.47 (1.43–1.51)	–
recovery	SCr at discharge ≤ baseline SCr	HR (95%–CI) = 1.66 (1.09–2.53)	–
nonrecovery	SCr at discharge > baseline SCr	HR (95%–CI) = 1.72 (1.00–2.96)	
recovery	ΔSCr at 3 months <25%	HR (95%–CI) = 1.30 (1.10–1.70)	–
nonrecovery	ΔSCr at 3 months ≥25%	HR (95%–CI) = 2.30 (1.30–4.00)	
complete	SCr at day 7 ≤ baseline SCr	HR (95%–CI) = 1.21 (1.07–1.37)	–
partial	ΔSCr at day 7 <50% or <0.7 mg/dl	HR (95%–CI) = 1.58 (1.36–1.82)	
nonrecovery	ΔSCr at day 7 ≥50% or ≥0.7 mg/dl	HR (95%–CI) = 1.42 (1.27–1.59)	
no AKI	no AKI criteria	HR (95%–CI) = 0.69 (0.64–0.75)	HR (95%–CI) = 0.63 (0.54–0.74)
recovery	ΔSCr at 90 days ≤25%	reference	reference
nonrecovery	ΔSCr at 90 days >25%	HR (95%–CI) = 1.28 (1.13–1.46)	HR (95%–CI) = 5.59 (3.77–5.58)
AKI (CKD-) r	ΔSCr at discharge <50%	HR (95%–CI) = 1.96 (1.78–2.16)	HR (95%–CI) = 4.50 (2.43–8.35)
AKI (CKD-) nr	ΔSCr at discharge >50%	HR (95%–CI) = 2.18 (1.24–3.84)	HR (95%–CI) = 60.95 (24.13–153.97)
AKI (CKD+) r	ΔSCr at discharge <50%	HR (95%–CI) = 3.00 (2.35–3.84)	HR (95%–CI) = 74.07 (38.82–141.32)
AKI (CKD+) nr	ΔSCr at discharge >50%	HR (95%–CI) = 4.59 (3.20–6.45)	HR (95%–CI) = 212.73 (105.53–428.83)
recovery	ΔSCr at discharge ≤ 44 µmol/L	RR (95%–CI) = 1.79 (1.20–2.49)	RR (95%–CI) = 1.92 (1.37–2.69)
nonrecovery	ΔSCr at discharge > 44 µmol/L	RR (95%–CI) = 8.64 (6.04–12.34)	RR (95%–CI) = 15.05 (10.88–20.82)

In addition, those authors demonstrated that an episode of AKI in patients with CKD exponentially potentiates the development of ESRD (adjusted HR = 41.2, 95% CI = 34.6–49.1) [36]. These results are in accordance with those published by Wu et al. in 2010 [57], which demonstrated in a population of over 9,000 surgical ICU patients with a median follow-up of 4.6 years that patients with both AKI and CKD had an adjusted HR of 91.6 (95%-CI = 49.3 – 170.1) for ESRD. Furthermore, a subgroup analysis was performed in a cohort stratified by renal recovery at hospital discharge, which was defined as a serum creatinine concentration at discharge of <50% above the baseline serum creatine concentration. Patients who experienced an episode of acute-on-chronic kidney disease without renal function recovery at hospital discharge had the greatest risk for ESRD compared to patients without AKI and CKD (adjusted HR = 212.7), followed by those with acute-on-chronic kidney disease with recovery (HR = 74.1), those with AKI without recovery (HR = 61.0), those with CKD without AKI (HR = 42.6) and those with AKI with recovery (HR = 4.5) (all P-values < 0.001). Although no consensus criteria for renal recovery have been developed, these results are in accordance with the results of most other recently published studies that evaluated the impact of renal recovery or post-AKI renal function on CKD or ESRD (table 3) [49, 52, 56-58, 68]. In contrast, one postoperative study by van Kuijk et al. did not demonstrate a gradual relationship between AKI with or without renal recovery and CKD, and the relative risk was equally high in both groups [68]. This difference could result from the short timeframe in which renal recovery was determined (day 3 after diagnosis). Furthermore, the highest incidence rate of complications after AKI is observed during the first consecutive year but appears to decline in subsequent years. Fortrie et al. showed a strong association between AKI and impaired renal function one year following transplantation in a cohort of patients who underwent cardiac transplantation [69]. However, with longer follow-up, only AKI requiring RRT was associated with further deterioration of renal function. In contrast to AKI, renal function at one year following transplantation was strongly associated with further renal deterioration [70].

In conclusion, AKI is statistically an independent risk factor for CKD as well as for ESRD. However, the magnitude of this risk depends on the presence of premorbid conditions and the susceptibility to accelerated injury with impaired renal recovery. In other words, the impact of AKI on long-

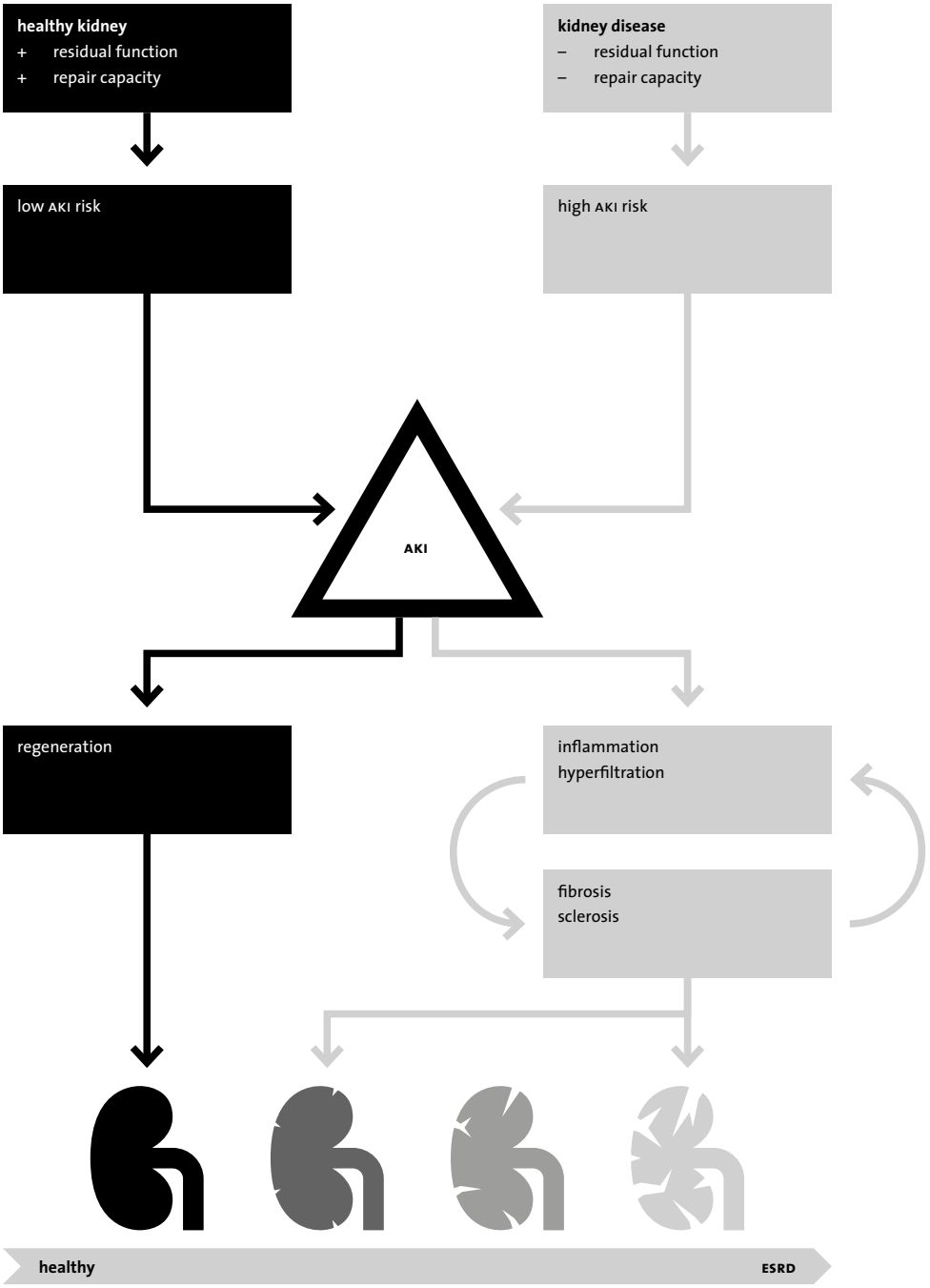
term outcomes depends on the residual renal function and repair capacity after renal stress. Furthermore, hyperfiltration can camouflage structural renal damage in a previously healthy kidney because the estimated glomerular filtration rate can be preserved for an extended duration. However, eventually, the renal self-repair capacity is exceeded due to continued degenerative processes, and the impact of AKI accelerates progression to CKD and ESRD. A schematic representation of this concept is shown in figure 1.

ACUTE AND LONG-TERM PATHOPHYSIOLOGICAL CHANGES ASSOCIATED WITH AKI

The results of epidemiological clinical research are in line with the suggested pathophysiological mechanisms underlying a poor renal outcome after AKI. Currently, the pathophysiology of AKI is still incompletely understood and is mediated by a complex interplay among multiple pathophysiological processes. Whether this process eventually results in continued irreversible renal damage is highly dependent on residual renal function and repair capacity. Over the past decade, more insight has become available on pathophysiologic mechanisms acting during AKI. While these insights are primarily based on animal studies, they provide knowledge on the complex interplay of factors leading to kidney injury and offer potential targets for future therapy [71]. Because the etiology of AKI is very heterogeneous, AKI can initiate multiple pathophysiological pathways, often resulting from an imbalance in oxygen supply and demand. This imbalance results in hypoxemia and oxidative stress, which subsequently lead to endothelial damage, immune system activation and inflammation, and interstitial edema and vasoconstriction, which in return further decrease the oxygen supply [72]. Furthermore, dependent on the etiology of AKI, other factors may contribute to the development of AKI, including venous renal congestion due to heart failure, altered microcirculatory flow distribution due to sepsis, microthrombi due to vascular occlusive disease, tubular obstructions due to cast nephropathy, immune complex precipitation or postrenal obstruction [73-76].

In minor and transient episodes of kidney injury, the kidney possesses multiple mechanisms to limit this damage and even the possibility of tissue repair [71, 77]. However, in prolonged and severe episodes of kidney injury, these mechanisms fail. In patients with sustained AKI or pre-exist-

FIGURE 1 A schematic representation of the long-term sequelae of AKI. The kidney figures represent the baseline renal function.



ing CKD, the integrity and connection between the peritubular capillaries and the tubular cells are lost, resulting in tubular dedifferentiation, apoptosis, continued capillary damage and chronic hypoxemia. These events subsequently activate multiple proinflammatory, profibrotic pathways, which further impairs renal integrity and the tubular regeneration capacity [78-81]. Ultimately, this cascade will result in a self-sustaining process of persistent inflammation, hyperfiltration, progressive tubular damage, glomerulosclerosis and tubulointerstitial fibrosis that eventually leads to CKD, ESRD and associated complications [81-83]. However, this process is also the cornerstone in the development of CKD in general. Therefore, determining whether the continued renal deterioration is the result of AKI as an independent entity or simply an indicator of progressive CKD is difficult. However, these results indicate that AKI, at a minimum, accelerates these processes (figure 1).

IMPLICATIONS FOR THE BEDSIDE AND A GLIMPSE INTO THE FUTURE

Unfortunately, the increased knowledge and awareness of AKI still has a limited impact on clinical practice. In summary, the current treatment regime for AKI has not changed in recent decades and stresses preventive measures, such as limiting nephrotoxic medication and iodine-containing contrast fluids and providing adequate fluid expansion during the use of predictable potential stressors [84, 85]. Additional experimental interventions, including remote ischemic preconditioning and pharmacological interventions, have been studied but have limited effects [86]. The results of the long-awaited *STOP-AKI trial* are recently published [87]. This multicenter double-blind placebo-controlled clinical trial evaluates the safety and efficacy of human recombinant alkaline phosphatase as an anti-inflammatory treatment for patients with septic AKI. While the first published results were promising, human recombinant alkaline phosphatase did not improve short-term renal function. However, the authors demonstrated that there was a significant difference in mortality and major adverse kidney events in favor of the patients treated with recombinant alkaline phosphatase. Therefore, additional research is warranted to evaluate the role of recombinant alkaline phosphatase in the treatment of AKI.

Those at risk for AKI require consequent hemodynamic monitoring, including adequate follow-up of urine output, which is mandatory for the early detection of AKI. Therefore, automated electronic alerts (E-Alerts) for AKI could facilitate the early recognition of AKI. While it seems logical that such an intervention would raise awareness and improve patient care, the results of studies on this topic are conflicting [88-91]. For example, Wilson et al. recently performed a large randomized clinical trial including approximately 2,400 patients and demonstrated that the use of E-Alerts had no beneficial effect [91]. The use of E-Alerts may even be potentially harmful and can lead to overtreatment when the data are misinterpreted.

However, it is of pivotal importance that AKI survivors preserve renal function as much as possible to prevent the further acceleration of renal deterioration. Therefore, tight control of hypertension, proteinuria, diabetes mellitus, cardiovascular disease and other relevant comorbidities seems warranted, as the clinical efficacy of these strategies has been proven to slow or prevent the progression of CKD [92, 93]. In contrast to patients with known CKD, only a small proportion of patients who experience an episode of AKI, even an episode requiring RRT, are offered follow-up by a nephrologist. In 2012, Siew et al. demonstrated in approximately 4,000 AKI survivors that the cumulative incidence of referral to a nephrologist in the first year was only 8.5%, while the mortality rate during this surveillance period was 22%. Furthermore, the severity of AKI did not affect the referral rate [94]. Subsequently, Harel et al. studied the association between follow-up by a nephrologist within 90 days post-AKI and survival. Those authors used propensity score analyses to match patients with and without follow-up by a nephrologist and reported that, overall, only 41% of the patients had follow-up in the outpatient clinic and that these patients were most likely those with pre-existing CKD [95]. More interestingly, Harel et al. found that post-AKI outpatient follow-up was associated with a 24% reduction in mortality after a surveillance period of 2 years. While these results potentially provide a solution to reduce the long-term complications of AKI, clinical trials are required for improved clarity. Currently, a large randomized clinical trial is underway in Canada to address this issue [96]. Publication of the results is expected in 2022 and may have important implications for the long-term follow-up, treatment and outcome of AKI survivors.

CONCLUSIONS

AKI is a highly complex syndrome associated with increased mortality and loss of renal function in the long term. Although most evidence has been obtained through retrospective research, the results of the numerous well-designed large studies indicate that a causal relationship between AKI and a worsened long-term prognosis is highly likely. Furthermore, these studies have offered essential insight into the populations with the greatest risk for poor prognosis, including the elderly, those with pre-existing comorbidities and, particularly, those with pre-existing renal impairment. While these findings are undoubtedly of great importance, they still have limited significance for clinical practice, as effective therapeutic interventions are not yet available. Therefore, the main focus of future research should be on the prevention of AKI, the identification of therapeutic targets and the provision of adequate follow-up and treatment to preserve the renal function of patients who survive an episode of AKI.

AIMS AND OUTLINE OF THIS THESIS

The general goal of this PhD dissertation is to gain more insight in the development of AKI and its long-term sequelae. In particular, we aimed to identify those patients that bear the greatest risk for AKI and subsequent increased risk for long-term mortality and on-going deterioration in renal function.

In **chapter 2** we describe potential risk factors associated with impaired renal function at time of hospital discharge in critically ill patients that survived an episode of AKI requiring RRT. In addition, we hypothesized that those with an impaired renal function at hospital discharge have a great risk for long-term mortality and ESRD. Therefore, **chapter 3** evaluates the degree of renal function at hospital discharge as an independent risk factor for long-term renal survival and overall long-term mortality. While AKI is associated with increased risk for poor long-term prognosis, the magnitude of this risk seems strongly correlated with the patient's pre-existing comorbid disease. This may lead to overestimation of this risk in patients who are not burdened with comorbidity. **Chapter 4** describes overall and renal survival in critically ill patients with AKI requiring RRT stratified by the presence or absence of comorbid conditions.

While large epidemiological studies evaluated the role of AKI in de general ICU setting, little is known about the incidence and impact of AKI after cardiac transplantation. **Chapter 5** evaluates the early post-transplantation incidence of AKI, corresponding risk factors and the impact of AKI on mortality and renal function during the first postoperative year. In addition, **chapter 6** describes the long-term sequelae of AKI after cardiac transplantation.

Today, AKI in the clinical setting is most likely defined by a significant increase in serum creatinine. However, due to various mechanisms, serum creatinine is a poor indicator of renal injury. Therefore, **chapter 7** evaluates the predictive performance variation of urinary biomarkers that precede the rise in serum creatinine and are potential markers for early AKI.

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

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Journal of Critical Care (2013) 28: 126–132

ABSTRACT

Purpose

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

Methods

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

Results

Of the 353 patients in our cohort, 90 (25.5%) patients had pre-existing chronic kidney disease (CKD). An estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m² at hospital discharge occurred in 64.0% of which 63.7% without known renal impairment before hospital admission and 8.2% of all cases left the hospital dialysis-dependent. Multivariable logistic regression showed that age (OR = 1.051, P < 0.001), serum creatinine concentration at start of RRT (OR = 1.004, P < 0.001) and administration of iodine-containing contrast fluid (OR = 0.830, P = 0.045) were associated with an eGFR ≤ 60 ml/min/1.73m². Furthermore, a medical history of CKD (OR = 5.865, P < 0.001) was associated with dialysis dependence.

Conclusions

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

INTRODUCTION

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

In addition, any permanent loss of renal function will be a subsequent risk factor for progressive deterioration of renal function in the years after hospital discharge. This constitutes a substantial risk for reaching end-stage renal disease requiring RRT. In addition, any stage of chronic kidney disease (CKD), in particular when the glomerular filtration rate drops below 60 ml/min/1.73m² (CKD stage 3–5) has unequivocally been associated with increased mortality [13]. Therefore, the degree of renal recovery in RRT-requiring critically ill patients that survive their hospital stay is of pivotal importance for renal and overall survival thereafter.

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

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

MATERIALS AND METHODS

Setting

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

Study population

All consecutive admitted critically ill patients, treated with continuous renal replacement therapy (RRT) between January 1994 and April 2010, were evaluated. Patients with end-stage renal disease dependent on RRT, patients with a kidney transplant and patients with another solid organ transplantation were excluded. The recently published Kidney Disease: Improving Global Outcome serum creatinine criteria were used to evaluate the presence of AKI [17]. Furthermore, for the sake of homogeneity patients with acute vasculitis, glomerulonephritis, interstitial nephritis or thrombotic microangiopathy were excluded and only patients with presumed isolated acute tubulus necrosis were included for analysis. Clinical and demographical data were collected consisting age, sex, comorbidity, cause of AKI, kind of ICU admission, primary indication for ICU admission, non-renal SOFA score, administrations of intravenous iodine-containing contrast during hospital admission and length of ICU stay. Serum creatinine concentrations were determined at baseline (1-6 months before hospital admission), hospital admission, at start of RRT and hospital discharge. Serum creatinine concentrations at baseline and hospital discharge were used to calculate the estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula [18]. We did not calculate the eGFR from the serum creatinine concentrations at hospital admission or at the time of start RRT as the renal function was not stable and essentially unknown at these time-points. The patients were grouped according to their eGFR at baseline and at discharge from the hospital based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for staging the degree of loss of renal function [19]. Patients were categorized

to a separate RRT group if they remained dialysis dependent for at least 3 months and were subsequently registered in RENINE (Dutch abbreviation for REgistratie NIerfunctievervanging NEderland), the Dutch national database for patients on chronic RRT. For statistical analysis, a cutoff eGFR ≤ 60 ml/min/1.73m² was selected because below this value there is a graded association between eGFR and mortality, cardiovascular events and hospitalization [13]. This study was approved by the medical ethical review board of the Erasmus Medical Centre, which waived the requirement of informed consent, because of its retrospective nature.

Definitions

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

The patient charts were used to identify whether patients were known to have pre-existing CKD or comorbidity like diabetes mellitus, hypertension, or cardiovascular disease. Pre-existing CKD was defined as any documented impairment of renal function within the year before admission to the ICU or a known baseline eGFR ≤ 60 ml/min/1.73m². Renal function in patients not documented with pre-existing CKD was considered normal. The cause of AKI was categorized as: sepsis, ischemia, drug-associated and other. Sepsis was defined as the presence of symptoms of systemic inflammatory response syndrome in combination with the persistence of a documented or presumed infection leading to AKI. Ischemia was defined as AKI due to circulatory dysfunction leading to hypotension and ischemia. All patients suffering from AKI due to toxic drugs, contrast and other chemicals that are toxic to the kidney were categorized within the "drug-associated" group. Patients that experienced an episode of AKI due to any other cause then aforementioned, including rhabdomyolysis, tumorlysis syndrome and hemolysis elevated liver enzymes and low platelets (HELLP) syndrome were categorized within the "other" group.

The indication for ICU admission was categorically grouped as: sepsis, thoracic surgery (all surgical interventions within the thoracic cavity), cardiac disease/fluid overload, postoperative other, other/intoxication and traumatic injury.

During hospital admission all radiological investigations with intravenous iodine-containing radiopaque contrast were registered, consisting of computed tomographic scans and cardiac catheterizations.

Statistical analysis

Continuous parameters were expressed as mean ± SD and compared by the Student T-test. Categorical parameters were expressed as number and percentage and compared by $\chi 2$-test. A predefined set of variables was chosen for analysis of association with eGFR ≤ 60 ml/min/1.73m² at hospital discharge (only including patients without CKD). These variables were: age, sex, diabetes mellitus, hypertension, cardiovascular disease, cause of AKI, kind of ICU admission (surgical/medical), length of ICU stay, non-renal SOFA score, the number of administrations with intravenous iodine-containing radiological contrast, the serum creatinine concentration at admission to the ICU and at the start of RRT. Parameters with an unadjusted $P \leq 0.1$ were included in a multivariable logistic regression for the outcome of an eGFR ≤ 60 at hospital discharge. Irrespective of P value the demographic data age and sex were included in the multivariable analysis. Furthermore, all multivariable analyses were adjusted for the year when RRT was performed. Where analysis on eGFR at hospital discharge only included patients with a considered normal baseline renal function, a similar analysis on dialysis dependence at hospital discharge was performed including patients with pre-existing CKD.

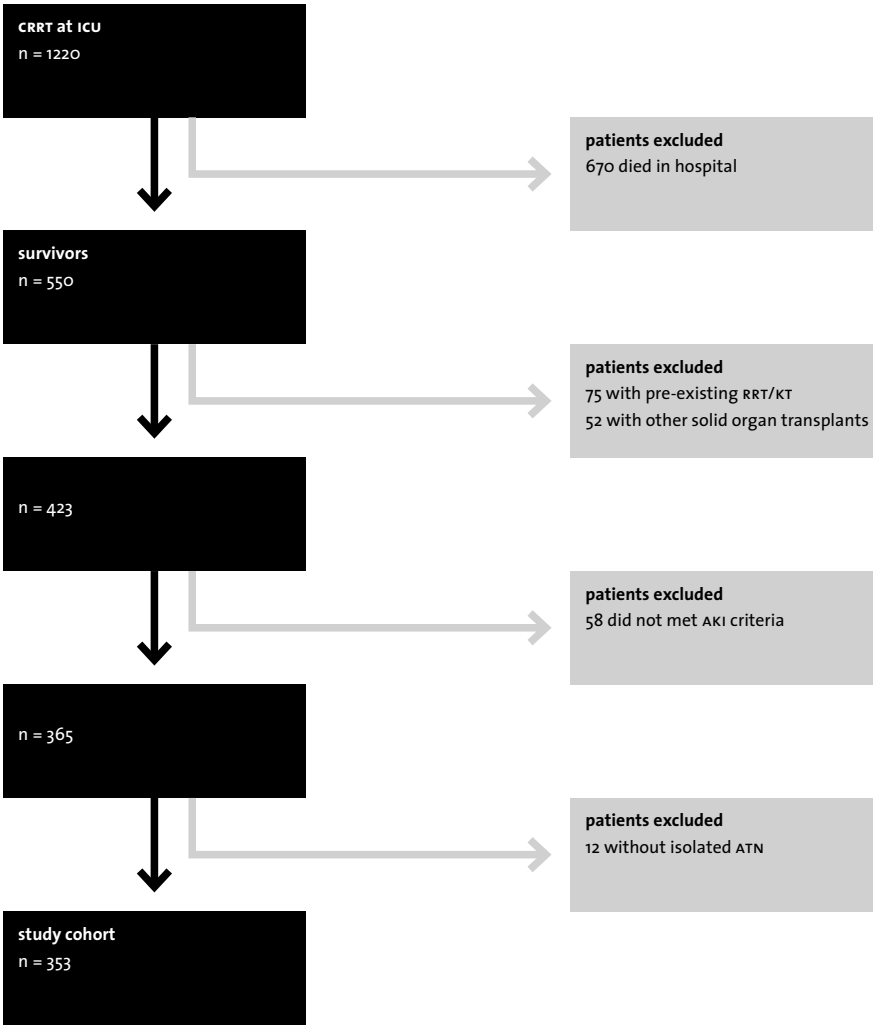
Statistical significance was defined as a 2-tailed $P \leq 0.05$. Analyses were performed with statistical software SPSS version 19.0, copyright 1989, 2010 SPSS Inc (Chicago, IL), an IBM company.

RESULTS

Study population and eGFR at hospital discharge

A total of 1220 patients treated with continuous RRT during ICU admission were recruited. Of these, 670 patients died in hospital yielding an in-hospital mortality rate of 54.9%. Patients that died during hospital admission were excluded for further analysis. After exclusion of patients with RRT, kidney transplant or any other kind of solid organ transplantation, 423 patients remained of which 365 met the AKI criteria. Furthermore, 12 patients were excluded without isolated acute tubulus necrosis (figure 1). Ninety patients (25.5%) of the 353 patients in the study cohort were known with

FIGURE 1 A schematic representation of the long-term sequelae of AKI. The kidney figures represent the baseline renal function.



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

TABLE 1 Clinical and demographical characteristics of study population.

number of patients	353
age (y)	59.5 ± 14.9
sex (male)	241 (68.3)
medical history	
chronic kidney disease	90 (25.5)
diabetes mellitus	90 (25.5)
cardio vascular disease	199 (56.4)
hypertension	110 (31.2)
cause of AKI	
sepsis	110 (31.2)
ischemia	195 (55.2)
drug-associated	32 (9.1)
other	16 (4.5)
surgical/medical (surgical)	240 (68.0)
indication for ICU admission	
sepsis	59 (16.7)
thoracic surgery	116 (32.9)
cardiac disease/fluid overload	46 (13.0)
post-operative other	57 (16.1)
other/intoxication	61 (17.3)
trauma	14 (4.0)
sofa score*	8.2 ± 3.5
length of ICU stay (d)	29.5 ± 28.4
serum creatinine (µmol/L)	
baseline**	140.7 ± 99.2
hospital admission	206.5 ± 172.8
start RRT	496.7 ± 190.8
hospital discharge	175.4 ± 149.4
eGFR (ml/min/1.73m²)	
hospital discharge	59.0 ± 51.5
Iodine-containing contrast fluid (administrations)	1.5 ± 2.0
RRT dependent at hospital discharge	29 (8.2)

Categorical variables are expressed as the number of patients and percentage; continuous variables are expressed as mean and standard deviation (sd), where appropriate.

* Only available in 137 patients

** Only available in 119 patients

pre-existing CKD. Clinical characteristics for this study population are given in table 1. The most common cause of AKI was ischemia (55.2%), followed by sepsis (31.2%), drug-associated (9.1%) and 4.5% of the patients had another cause of AKI. The main reason for admitting patients to the ICU was thoracic surgery (32.9%), followed by other/intoxication (17.3%), sepsis (16.7%), cardiac disease/fluid overload (13.0%), post-operative other (16.1%) and trauma (4.0%).

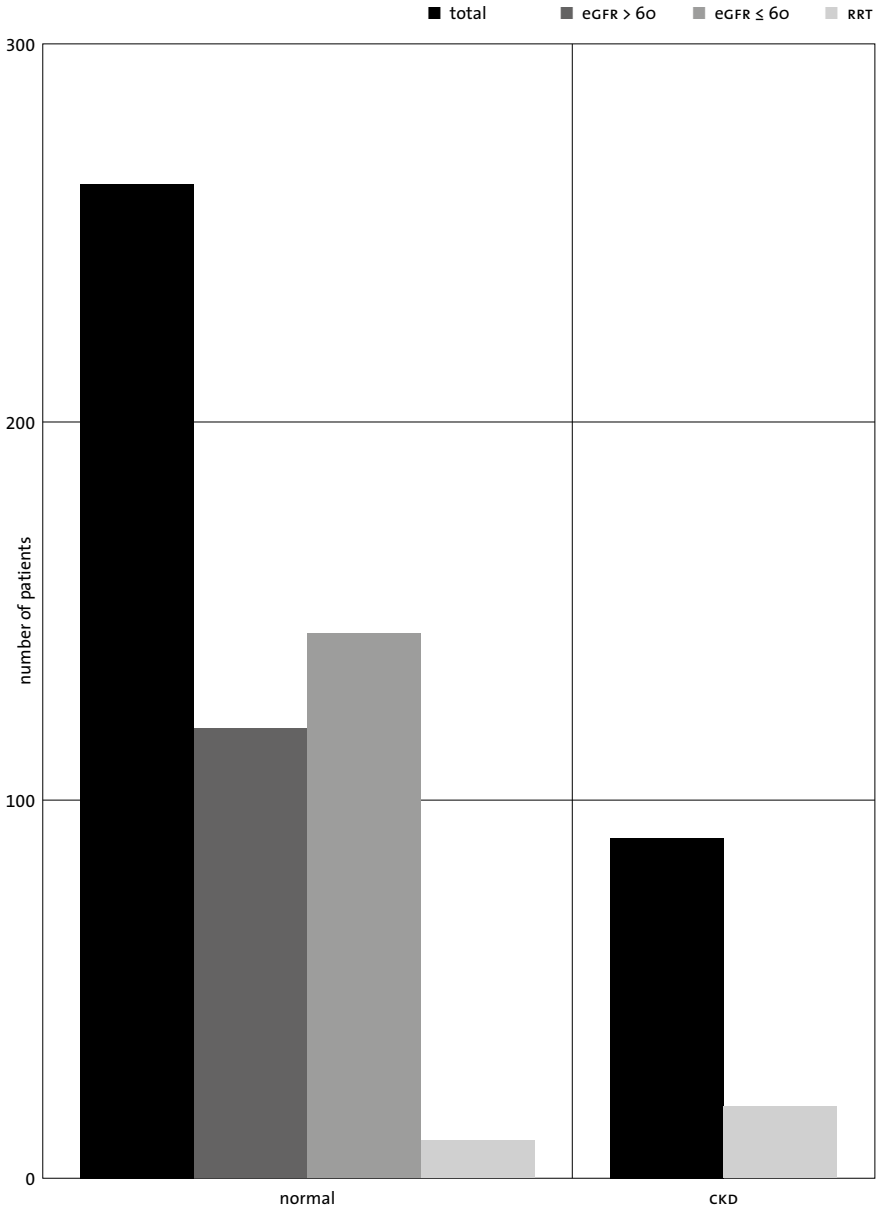
Baseline serum creatinine values were available in 119 cases (33.7%). The mean baseline serum creatinine was 140.7 µmol/L, which is caused by the overrepresentation of patients known with CKD within this group (67/119). At hospital admission, at start of RRT and at hospital discharge serum creatinine values were 206.5, 496.7 and 175.4 µmol/L, respectively.

Of all patients 18.1% left the hospital with an eGFR ≥ 90, 17.8% with an eGFR between 60 and 90, 32.9% with an eGFR between 30 and 60, 17.0% with an eGFR between 15 and 30, 5.9% with an eGFR ≤ 15 without the need of dialysis at hospital discharge and 8.2% while being treated with intermittent hemodialysis. In total, 226 (64.0%) left the hospital with an eGFR ≤ 60 ml/min/1.73m² of which 144 (63.7%) were not known with renal impairment before hospital admission. Of all patients with pre-existing CKD, 21.1% left the hospital dialysis-dependent. This group constituted 65.5% of the total number of patients dependent on dialysis at discharge from the hospital (figure 2). Of the 119 patients with a known baseline eGFR, 67 patients (56.3%) returned to their original class of eGFR, while 52 patients (43.7%) showed significant loss of eGFR resulting in dialysis dependence in 14.3%. Within this latter group of 52 patients, 51.9% were known with CKD.

Determinants of renal function at hospital discharge

Univariable analysis of the clinical parameters for their relation with an eGFR ≤ 60 ml/min/1.73m² at the time of hospital discharge identified an association for age, cardiovascular disease, hypertension, length of ICU stay, serum creatinine concentration at hospital admission and at start of RRT and administration of iodine-containing contrast fluid (table 2). After multivariable analysis, three parameters remained associated with an eGFR ≤ 60 ml/min/1.73m² at time of hospital discharge (table 3); age (OR = 1.051, P < 0.001), serum creatinine concentration at start of RRT (OR = 1.004, P < 0.001), and administration of iodine-containing contrast fluid (OR = 0.830, P = 0.045).

FIGURE 2 Renal function at hospital discharge.



Renal function at hospital discharge stratified by pre-existing kidney disease. Number of patients categorized by renal function at hospital discharge (total, eGFR (estimated glomerular filtration rate) > 60 ml/min/1.73m², eGFR ≤ 60 ml/min/1.73m², renal replacement therapy (RRT).

TABLE 2 Univariable analysis of the association between clinical variables and eGFR ≤60 ml/min/1.73m² at time of discharge from the hospital.

	odds ratio (eGFR ≤60)	95%–CI	P-value
age (y)	1.044	1.026–1.063	<0.001
sex (male)	1.462	0.854–2.503	0.166
medical history			
diabetes mellitus	1.248	0.655–2.343	0.490
cardio vascular disease	1.967	1.202–3.219	0.007
hypertension	2.167	1.180–3.891	0.013
cause of AKI			
sepsis	0.750	0.449–1.254	0.273
ischemia	1.360	0.835–2.213	0.217
drug-associated	1.082	0.457–2.563	0.858
other	0.709	0.152–1.154	0.519
surgical/medical (surgical)	0.924	0.249–2.015	0.768
sofa score*	0.931	0.836–1.037	0.193
length of ICU stay (d)	0.987	0.978–0.996	0.006
serum creatinine (µmol/L)			
hospital admission	1.002	1.000–1.003	0.030
start RRT	1.002	1.001–1.004	0.001
iodine-containing contrast fluid (administrations)	0.797	0.699–0.909	0.001

TABLE 3 Multivariable logistic regression analysis for the association between clinical variables and eGFR ≤60 ml/min/1.73m² at time of discharge from the hospital.

	odds ratio (eGFR ≤60)	95%–CI	P-value
age (y)	1.051	1.028 - 1.076	<0.001
serum creatinine (µmol/L)	1.004	1.002 - 1.006	<0.001
iodine-containing contrast fluid (administrations)	0.830	0.692 - 0.996	0.045

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

DISCUSSION

This is the first study that reports on risk factors in critically ill patients with RRT-requiring AKI for an eGFR ≤ 60 ml/min/1.73m² at hospital discharge. We found within this cohort that age and serum creatinine concentration at start of RRT were the major independent predictors for a modest impaired eGFR at hospital discharge. The independent predictor for dialysis dependence at hospital discharge was a medical history of CKD. In addition, our results clearly show that AKI requiring RRT in critically ill patients has a major impact on eGFR at hospital discharge. Only 45% of the surviving patients with a normal renal function before hospital admission left the hospital with an eGFR < 60 ml/min/1.73m², which may even be an overestimation, as serum creatinine levels will probably be lowered because of loss of muscle mass.

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

AKI leading to RRT is the most severe form of acute kidney injury but a number of studies have pointed out that AKI of any stage has a major impact on subsequent renal function and survival [21-27]. In addition, the outcome of patients with pre-existing CKD who have survived RRT at the ICU will probably be even worse as recent studies have shown that a pre-existing impairment of kidney function has a major impact on the patient's prognosis [20,28,29]. For instance, 2 large cohort studies showed that patients with known CKD that suffered from AKI in an ICU had a significantly higher risk for mortality and chronic dialysis dependence compared to patients without renal impairment before hospital admission [28,29]. One of these studies identified CKD itself as a strong risk factor for the development of AKI [29]. Thus, these patients are not only at a high risk to develop AKI but also have a much higher risk for being dialysis dependent at discharge from the hospital. Given our data, it is necessary that critically ill with CKD should be monitored closely to protect their renal function as much as possible.

Besides the major effect of age on renal function (OR = 1.051), another interesting finding is the association between serum creatinine concentration at the time of RRT initiation and an eGFR ≤ 60 ml/min/1.73m² at time of hospital discharge (OR = 1.004). Of course the renal function reflected by serum creatinine concentration at the initiation of RRT is unknown and the actual GFR may be close to zero. However, serum creatinine concentration may be a reflection of the timing of RRT in these patients and it might be that an early initiation of RRT is beneficial. To the best of our knowledge there are no studies on timing of RRT and association with deterioration in renal function as outcome, but there are studies that focused on dialysis dependency at hospital discharge. Two recent meta-analyses showed that early initiation of RRT is associated with a trend to better renal outcome [30,31]. However both meta-analyses mentioned that the studies included used many different definitions of "early versus late" initiation of RRT. Our data cannot provide the answer to this intriguing possibility as, e.g., it is possible that patients that received early treatment would also recover renal function with conservative therapy and had a less severe hit of AKI leading to a better renal function at hospital discharge.

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

We included the number of investigations involving intravenous iodine-containing contrast fluid in our model as this represents a potential nephrotoxic factor. Taking into count the retrospect nature and long-term observation period the data obtained have a limited level of detail, as we could not document the full amount of iodine containing contrast fluid administered. Remarkably, we found a significant tendency to an OR < 1 for

the relation between the contrast dose a patient received during hospital admission and an eGFR ≤ 60 ml/min/1.73m² at hospital discharge. A possible explanation might be that patients with limited renal recovery after RRT in the ICU were considered to have a contraindication for contrast to protect their residual renal function and therefore ruled out for radiologic investigations involving iodine-containing contrast fluid. Furthermore, it may be a reflection of overall clinical condition. The possibility exists that patients with a better clinical condition were more likely to undergo an investigation with contrast fluid, because they were stable enough for transportation to, for instance, a computed tomographic unit.

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

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

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

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

CONCLUSIONS

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

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

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Clinical Journal of the American Society of Nephrology (2013) 8: 1284–1291

ABSTRACT

Background and objectives

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

Design, setting, participants, & measurements

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

Results

After hospital discharge, median follow-up of survivors (n = 475) was 8.5 years (range = 1–17 years); overall mortality rate was 75%. Only 170 (35%) patients were discharged with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m². Multivariate proportional hazards regression analysis demonstrated that age, nonsurgical type of admission, pre-existing kidney disease, malignancy, and eGFR of 29–15 ml/min/1.73m² (hazard ratio [HR] = 1.62, 95% confidence interval [CI] = 1.01-2.58) and eGFR < 15 ml/min/1.73m² (HR = 1.93, 95%-CI = 1.23-3.02) at discharge were independent predictors of increased mortality. Renal survival was significantly associated with degree of kidney dysfunction at discharge. An eGFR of 29–15 ml/min/1.73m² (HR = 26.26, 95%-CI = 5.59-123.40) and < 15 ml/min/1.73m² (HR = 172.28, 95%-CI = 37.72-786.75) were independent risk factors for initiation of long-term RRT.

Conclusions

Most critically ill patients surviving AKI necessitating RRT have impaired kidney function at hospital discharge. An eGFR < 30 ml/min/1.73m² is a strong risk factor for decreased long-term survival and poor renal survival.

INTRODUCTION

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

Given these data, it is important to identify the risk factors for death and poor renal recovery after AKI in the intensive care unit (ICU). In addition, the factors associated with CKD at hospital discharge and subsequent development of end-stage renal disease (ESRD) or death should be studied. Many studies have identified the following as risk factors for increased mortality after AKI: age older than 65 years, elevated Acute Physiology and Chronic Health Evaluation (APACHE) score, associated organ dysfunction, and the need for continuous renal replacement therapy (CRRT) during ICU stay [9–12]. The need for CRRT during ICU stay is associated with an estimated in-hospital mortality between 14% and 60%, depending on the reason for ICU admission and the cause of renal failure [9,13]. However, our current knowledge about the long-term effects of AKI that necessitates dialysis in critically ill patients after hospital discharge on mortality and renal survival is far from complete. It is clear that incomplete recovery of renal function, specifically dependence on long-term RRT, after an episode of AKI is associated with increased mortality at follow-up [14,15]. However, definitions of AKI and long-term outcome after an episode of AKI vary among studies, and the degree of kidney function impairment at discharge was not calculated per GFR [6,12,16].

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

MATERIALS AND METHODS

Setting

A retrospective cohort study was performed in the ICU of a large academic hospital (Erasmus Medical Center, Rotterdam, The Netherlands). All critically ill patients with AKI who required RRT were treated with continuous arteriovenous hemodialysis (30%) or continuous veno-venous hemofiltration. All patients included after 2005 were treated according to the local protocol: Anticoagulation was performed using citrate, unless contraindicated; in that case, heparin was used as an anticoagulant. Before 2005, the standard anticoagulation used was heparin, unless contraindicated. Intermittent hemodialysis was not performed in this group of patients because most patients in our ICU ward were hemodynamically unstable and the ICU lacks facilities to perform intermittent hemodialysis. The study was approved by the medical ethical review board of the Erasmus Medical Center, which waived the requirement of informed consent, because of its retrospective nature.

Study population and data collection

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

Definitions

Type of ICU admission was defined as surgical when any surgical procedure was performed in the period before ICU admission. This included abdominal, trauma, transplantation, or thoracic (including cardiac and pulmonary) surgery. Nonsurgical reason for admission included all other

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

median age, *yr* (± SD)	59 (19–84)
men, *n* (%)	314 (66)
surgical/medical admission, *n*/*n*	301/174
median hospital stay, *d* (range)	47 (2–297)
median ICU stay, *d* (range)	18 (1–209)
cause of AKI, *n* (%)*	
sepsis	119 (25)
hypotension	191 (40)
toxic/other	68 (14)
indication for ICU admission, *n* (%)	
sepsis	83 (17)
transplantation	41 (9)
thoracic surgery	118 (25)
cardiac disease	67 (14)
general surgery	62 (13)
bleeding	6 (1)
cardiopulmonary resuscitation	16 (3)
trauma	14 (3)
intoxication/other	69 (15)
medical history, *n* (%)	
CKD	97 (20)
diabetes mellitus	110 (23)
cardiovascular disease	241 (50)
heart transplant	24 (5)
lung transplant	1 (0.2)
liver transplant	27 (6)
malignancy	67 (14)
liver disease	54 (11)
hypertension	141 (30)

* Cause of AKI is presented for all patients without pre-existing CKD.

admission types, including sepsis, cardiopulmonary resuscitation, cardiac diseases, and intoxication. These are further specified in table 1. For medical history we included data on diabetes mellitus; cardiac disease (defined as myocardial infarction before admission, cardiac valvular disease, or heart failure); malignancy; hypertension; cardiac, liver, or lung transplantation; or pre-existing CKD. Pre-existing CKD was defined as any documented impairment in renal function in the years before ICU admission that did not necessitate long-term RRT or kidney transplant. Because information on kidney function impairment was not available at a standardized preadmis-

sion time point and for some patients it was not available at all, we did not attempt to categorize these data according to stage of CKD. Preadmission kidney function was considered normal when the patient had documented normal kidney function at the time of admission or within the previous 2 years, without major events that could have compromised kidney function. Furthermore, we categorized causes of AKI as sepsis, hypotension, and toxic/other. Sepsis was defined as the presence of a systemic inflammatory response with a documented or presumed infection. In the group defined as having AKI caused by hypotension, all pre-renal causes were included. All patients with AKI due to toxic drugs, contrast agents, and other nephrotoxic substances were categorized in the "toxic/other" group. Patients who experienced AKI as a result of any other cause (e.g., rhabdomyolysis, vasculitis or other disorders) were also categorized in this group.

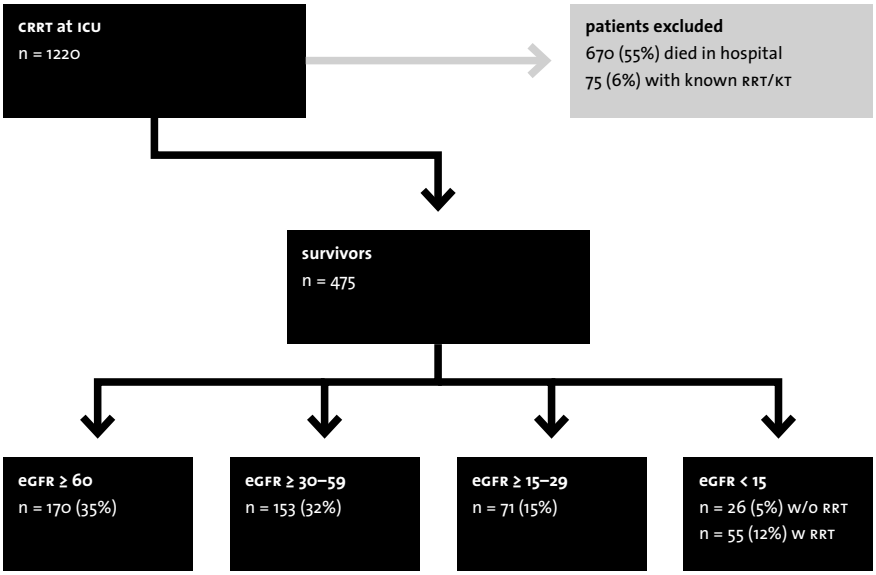
Study outcomes

The main study outcome measures were overall and renal survival; renal survival was defined as the time until long-term RRT. Survival and the need for long-term RRT are reported at 6 and 12 years after discharge. Furthermore, we evaluated whether degree of kidney dysfunction at discharge was associated with both overall and renal survival. We defined the kidney function at discharge arbitrarily per estimate GFR (eGFR) category using the Modification of Diet in Renal Disease (MDRD) formula for the estimation of GFR. Because the MDRD formula performs best in patients with an eGFR < 60 ml/min/1.73m², we grouped together the patients with eGFR > 60 ml/min/1.73m². The second category is defined as eGFR of 30–59 ml/min/1.73m², the third category is defined as eGFR of 15–29 ml/min/1.73m², and the last category is defined as eGFR < 15 ml/min/1.73m² with or without the need for long-term RRT at discharge.

Statistical analyses

Continuous variables are expressed as median and range. Categorical variables are expressed as number of cases and percentages. Curves for patient survival and renal survival censored for death were generated for each eGFR category by Kaplan-Meier analysis. Log-rank test was used to analyze differences between these curves. Cox regression analysis was used to evaluate independent predictors of long-term mortality. Separate analyses were performed to evaluate changing hazards, for follow-up in the first 90 days and from 90 days to the end of follow-up. Potential risk factors for

FIGURE 1 Flowchart of inclusion and eGFR classification at hospital discharge.



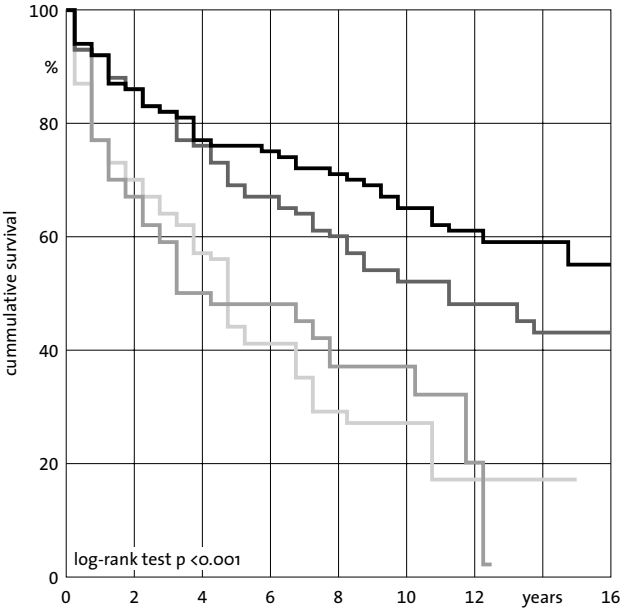
increased mortality were tested with univariate analysis. When variables were significant in univariate analysis ($P < 0.05$), they were included in a multivariate proportional hazards Cox regression analysis using a multiple forward stepwise approach. Statistical significance was defined by $P < 0.05$. Time-dependent variables were created to evaluate whether hazards were proportionate. Predictive ability of the multivariate proportional hazards model was tested by Harrel C-statistic. Analyses were performed with SPSS software, version 19.0, (SPSS Inc., an IBM company, Chicago, IL).

RESULTS

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

Between 1994 and 2010, a total of 1220 patients received CRRT in the ICU (figure 1). Seventy-five patients (6%) were known to have received dialysis or have undergone kidney transplantation before hospital admission and were excluded from further analysis. Of the remaining patients, 670 (55%) died in the hospital. Patients alive at hospital discharge (n=475 [39%])

FIGURE 2 Kaplan-Meier curves for overall survival after hospital discharge, per category at hospital discharge.



eGFR ≥ 60 ml/min/1.73m²	170	138	102	76	57	41	32	16	9
eGFR 30–59 ml/min/1.73m²	153	128	92	64	44	28	17	7	3
eGFR 15–29 ml/min/1.73m²	71	41	27	17	10	8	3	0	0
eGFR < 15 ml/min/1.73m²	81	55	37	22	9	6	1	1	0

were divided into categories according to their eGFR at discharge (figure 1). Median hospital length of stay was 47 days (range = 2-297 days). More than 60% of the patients had eGFR loss at hospital discharge, of which 12% needed long-term RRT at this time.

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

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

Follow-up after hospital discharge varied from 1 to 17 years, with a median follow-up of 8.5 years. Survival rates for patients alive at hospital discharge at 6 years and 12 years were 62% and 44%, respectively. Cumulative survival per category was determined by Kaplan-Meier analysis (figure 2). A log-rank test comparing all categories showed a significant difference in patient long-term survival ($P < 0.001$). Compared with patients discharged with an eGFR 60 ml/min/1.73m², survival curves for patients with an eGFR of 15–29 ml/min/1.73m² (hazard ratio [HR] = 1.62, 95% confidence interval [CI] = 1.01-2.58) and an eGFR < 15 ml/min/1.73m² at hospital discharge were significantly worse (HR = 1.93, 95%-CI = 1.23-3.02). The unadjusted 6- and 12-year patient survival rates per category are shown in table 2. Most of the patients discharged with an eGFR < 15 ml/min/1.73m² experienced acute-on-chronic kidney injury (56% of patients in this category had pre-existing CKD).

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

	6-yr overall survival (%)	12-yr overall survival (%)	6-yr renal survival (%)	12-yr renal survival (%)
eGFR ≥ 60 ml/min/1.73m²	75	60	100	96
eGFR 30–59 ml/min/1.73m²	67	47	95	93
eGFR 15–29 ml/min/1.73m²	48	22	86	47
eGFR < 15 ml/min/1.73m²	41	17	21	9

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

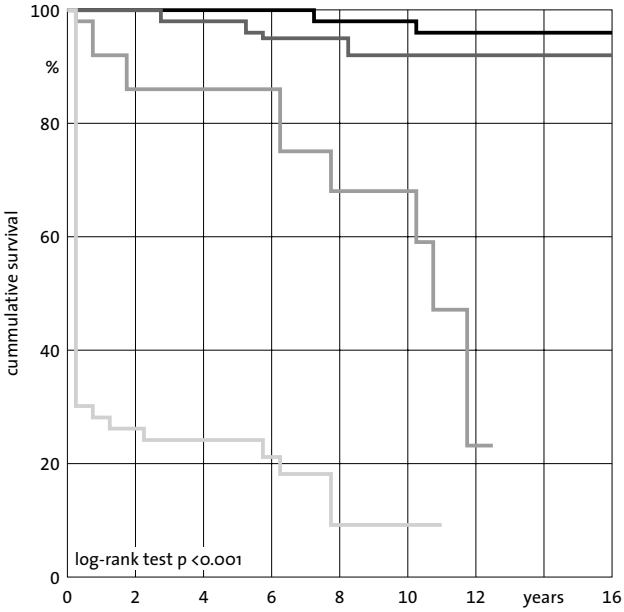
Univariate analysis identified several clinical variables associated with worse long-term patient survival, as shown in table 3. Age, date of ICU admission, nonsurgical reason for ICU admission, malignancy, and eGFR < 30 ml/min/1.73m² at hospital discharge remained significantly associated with patient survival after multivariate proportional hazards analysis (table 3). Separate analysis for the first 90 days after discharge and from 90 days until the end of follow-up showed that hazards were proportionate during follow-up. The predictive ability of this multivariate proportional hazards model was tested by Harrel C-statistics. We found a concordance of 0.69 (SEM, 0.02).

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

	Univariate analysis		Multivariate analysis	
	HR (95%-CI)	**P-value**	**HR (95%-CI)**	**P-value**
age	1.04 (1.03–1.05)	<0.001	1.04 (1.02–1.05)	<0.001
medical	0.68 (0.51–0.89)	0.01	0.60 (0.43–0.83)	0.002
kidney function at admission				
normal	1		1	
pre-existing CKD	2.21 (1.57–3.09)	<0.001	1.42 (0.96–2.10)	0.08
no data available	1.14 (0.82–1.59)	0.44	0.84 (0.58–1.21)	0.34
admission diagnosis				
sepsis	0.70 (0.46–1.06)	0.09	0.80 (0.51–1.24)	0.31
thoracic surgery	1.11 (0.80–1.52)	0.54	0.99 (0.66–1.50)	0.97
other	1			
eGFR at discharge				
≥ 60 ml/min/1.73m²	1		1	
30-59 ml/min/1.73m²	1.35 (0.93–1.96)	0.12	1.06 (0.71–1.57)	0.78
15-29 ml/min/1.73m²	2.87 (1.90–4.35)	<0.001	1.62 (1.01–2.58)	0.04
< 15 ml/min/1.73m²	2.94 (1.99–4.36)	<0.001	1.93 (1.23–3.02)	0.004
malignancy	1.85 (1.29–2.65)	0.001	1.73 (1.17–2.55)	0.006
cardiovascular disease	1.66 (1.25–2.20)	0.001	1.22 (0.85–1.74)	0.28
diabetes mellitus	1.69 (1.25–2.30)	0.001	1.15 (0.83–1.59)	0.40
hypertension	1.72 (1.29–2.30)	<0.001	0.94 (0.69–1.29)	0.71
year of admission	0.98 (0.95–1.01)	0.21	0.96 (0.92–0.99)	0.02

Variables tested in multivariate analysis: age, medical admission type, pre-existing CKD, admission diagnosis sepsis, thoracic surgery or other, class of estimated GFR at discharge, malignancy, cardiovascular disease, diabetes mellitus, hypertension, and year of admission.

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



■ eGFR ≥ 60 ml/min/1.73m²	170	138	102	76	56	40	32	16	9
■ eGFR 30–59 ml/min/1.73m²	153	128	90	61	41	27	17	7	3
■ eGFR 15–29 ml/min/1.73m²	71	36	25	16	9	7	1	0	0
■ eGFR < 15 ml/min/1.73m²	26	17	11	6	1	1	0	0	0

Association of eGFR at hospital discharge with renal survival

Renal survival rates after hospital discharge at 6 and 12 years were 83% and 74%, respectively. Comparing renal survival censored for death showed an overall significant difference between eGFR categories (P < 0.001) (figure 3). Compared with patients discharged with an eGFR > 60 ml/min/1.73m², renal survival curves for patients with an eGFR < 30 ml/min/1.73m² at hospital discharge were worse (eGFR 15–29 ml/min/1.73m²: HR = 27.40 [95% CI = 5.79-129.60], eGFR < 15 ml/min/1.73m²: HR = 176.96 [95% CI = 38.59-811.50]). The unadjusted 6- and 12-year renal survival censored for death per eGFR category shows the association between an increased incidence of initiation of RRT and impaired eGFR at hospital discharge (table 2).

After multivariate proportional hazards analysis, the following variables were strongly associated with decreased renal survival: pre-existing CKD (compared with patients with documented normal prior kidney function) and an eGFR < 30 ml/min/1.73m² at hospital discharge (table 4). Hazards were proportionate during follow-up.

The results show that an eGFR < 30 ml/min/1.73m² at hospital discharge is an independent and strong predictor of poor long-term renal survival. The predictive ability of this multivariate proportional hazards model was tested by Harrel C-statistics. We found a concordance of 0.96 (SEM = 0.03).

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

	Univariate analysis		Multivariate analysis	
	HR (95%-CI)	**P-value**	**HR (95%-CI)**	**P-value**
age	1.01 (1.00–1.03)	0.14	1.00 (0.98–1.01)	0.66
medical	0.63 (0.41–0.97)	0.04	1.13 (0.69–1.83)	0.63
kidney function at admission				
normal	1		1	
pre-existing CKD	9.19 (5.34–15.82)	<0.001	1.82 (1.01–3.33)	0.05
no data available	0.97 (0.49–1.95)	0.94	0.49 (0.23–1.04)	0.06
admission diagnosis				
sepsis	0.54 (0.28–1.02)	0.06	1.06 (0.54–2.08)	0.88
thoracic surgery	0.37 (0.19–0.72)	0.003	0.74 (0.34–1.62)	0.46
other	1			
eGFR at discharge				
≥ 60 ml/min/1.73m²	1		1	
30-59 ml/min/1.73m²	3.18 (0.62–16.40)	0.17	3.77 (0.72–19.77)	0.12
15-29 ml/min/1.73m²	27.19 (6.09–121.46)	<0.001	27.40 (5.79–129.60)	<0.001
< 15 ml/min/1.73m²	184.69 (43.32–787.37)	<0.001	176.96 (38.59–811.50)	<0.001
malignancy	1.51 (0.86–2.65)	0.15	1.56 (0.85–2.85)	0.15
cardiovascular disease	0.87 (0.56–1.33)	0.51	1.07 (0.65–1.78)	0.79
diabetes mellitus	1.57 (0.98–2.52)	0.06	0.85 (0.50–1.46)	0.56
hypertension	3.09 (2.00–4.76)	<0.001	1.29 (0.78–2.15)	0.32
year of admission	1.00 (0.95–1.05)	0.98	0.98 (0.93–1.04)	0.56

Variables tested in multivariate analysis: age, medical admission type, pre-existing CKD, admission diagnosis sepsis, thoracic surgery or other, class of estimated GFR at discharge, malignancy, cardiovascular disease, diabetes mellitus, hypertension, and year of admission.

DISCUSSION

The results of this study show that after an episode of AKI necessitating RRT in the ICU, long-term survival and renal survival were both strongly related to the degree of kidney function impairment at hospital discharge. In particular, an eGFR < 30 ml/min/1.73m² is an independent predictor of death and worse renal survival at long-term follow-up. About a third of all patients who survive their ICU stay and leave the hospital are discharged with an eGFR < 30 ml/min/1.73m². In addition, the majority of patients in our cohort (>60%) had impaired kidney function at hospital discharge. Therefore, our findings are clinically relevant because they indicate that most of the patients who have received RRT in the ICU are at risk for CKD and, therefore, further deterioration of kidney function and increased mortality in the years thereafter.

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

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

Only a few studies have evaluated the mortality rate and renal survival of patients who received RRT in the ICU after their hospital discharge [6,20-22]. The largest study population was described by Wald et al. and consisted of 3769 patients enrolled during a 10-year period; the patients were compared with matched control ICU patients without AKI or RRT [6]. The AKI group had a significantly increased risk for long-term RRT (HR = 3.23),

but overall survival (50% mortality after 8 years) was similar to that in the control ICU patient group. In our study, patients discharged with an eGFR < 30 ml/min/1.73m² (including patients receiving long-term RRT) showed a persistent association with long-term mortality after multivariate analysis. Only one published study is similar in design to ours [14]; that study followed 226 survivors of RRT in the ICU for 5 years. Cumulative survival at 5 years was 47%, and partial recovery of renal function after RRT in the ICU was an independent predictor of poor long-term survival.

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

We cannot conclude with certainty that the association between an eGFR < 30 ml/min/1.73m² at hospital discharge and worse long-term survival implies causality. However, the association persisted even after adjustment for possible covariates that included known risk factors for CKD and progression of CKD, such as age and cardiovascular risk factors and pre-existing CKD. Many studies have consistently shown that patients developing ESRD are at higher risk for cardiovascular events and have a higher mortality risk [8,24,25]. All these observations agree with data from the general population in which mortality risk exponentially increases when GFR decreases below 60 ml/min/1.73m² [8]. Therefore, prevention of (further) renal function deterioration in patients experiencing AKI by avoiding nephrotoxic drugs as much as possible could improve overall survival and prevent patients from reaching ESRD. Long-term nephrologic follow-up is necessary for patients who experience incomplete renal recovery after

an episode of AKI, especially patients discharged with an eGFR <30 ml/min/1.73m², to minimize the complications of CKD.

Limitations of our study include its retrospective single-center cohort design. We did not calculate GFR by inulin clearance or a 24-hour urine collection but rather used eGFR according to the MDRD formula. Although this formula considers sex and age, it cannot correct for changes in body composition, as may be expected in formerly critically ill patients. However, because a substantial loss of muscle mass has most likely occurred in ICU patients, the eGFR at hospital discharge probably overestimates the true GFR and subsequently underestimates the number of patients discharged with an eGFR < 30 ml/min/1.73m². Therefore, the effect of eGFR loss may be even greater than recorded in this study. On the other hand, follow-up of kidney function after discharge is not available in our cohort, and some patients may have shown a variable degree of recovery of eGFR over time that we could not account for in our analysis.

Because of the large time span of our patient registry, we depended on the analog and digital patient data management systems that have been used over time. Organ failure scores are available only since 2005 and have not always been used in our ICU; unfortunately, it is not possible to analyze the influence of severity of illness on overall and renal survival. In addition, treatment modalities for RRT and overall treatment strategies for ICU patients have changed over time. Date of admission was therefore included in our multivariate analyses but did not affect the overall conclusions.
The in-hospital mortality rate (55%) in our cohort, the percentage of patients discharged with the need for long-term RRT, and the overall survival of our patients after hospital discharge are similar to the results of previous studies [12,14,26–29]. Furthermore, our cohort contains a diverse population of ICU patients, including a large group of patients admitted after thoracic surgery and septic patients. We found no differences in survival between admission types after multivariate analysis. Therefore, the patients in our cohort seem to represent an average population of ICU patients. These findings add credibility to the generalization of our major finding that impaired kidney function at hospital discharge is independently associated with worse long-term overall and renal survival.

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

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PLoS ONE (2015) 10: e-publication

ABSTRACT

Background and objectives

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

Design, Setting, Participants, and Measurements

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

Results

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

Conclusions

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

INTRODUCTION

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

MATERIALS AND METHODS

Study design and population

A retrospective cohort study was performed including data obtained from patients admitted to a large tertiary care center (Erasmus Medical Center, Rotterdam, The Netherlands). All critically ill patients ≥ 18 years treated with continuous renal replacement therapy (CRRT) between January 1994 and April 2010 were evaluated. Patients with RRT or kidney transplant prior to hospital admission were excluded from analysis. Furthermore, patients in the study population were categorized by the presence of comorbidity in two groups, patients with (comorbid+) and patients without comorbidity (comorbid-). When a patient experienced multiple hospital admissions re-

quiring RRT, only the first hospital admission was used for further analysis. The modalities used for CRRT were continuous arteriovenous haemodialysis (CAVHD) or continuous venovenous haemofiltration (CVVH). Initially, CAVHD was the standard modality for CRRT, which was later gradually replaced by CVVH. CRRT was prescribed by the attending nephrologist and delivered by the haemodialysis nursing team. Intermittent haemodialysis was not performed because most patients in the ICU ward were haemodynamically unstable and the ICU lacks facilities to perform intermittent haemodialysis. The study was approved by the medical ethical review board of the Erasmus Medical Center, which waived the requirement for informed consent, because of its retrospective design.

Data collection

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

Definitions

The patient records were used to identify whether patients were known with malignancy, solid organ transplantation, intravenous drug abuse and pre-existing chronic diseases such as CKD, hypertension, diabetes mellitus, liver failure, cardiovascular diseases, autoimmune diseases, chronic obstructive pulmonary disease (COPD), connective tissue diseases and chronic infectious diseases like HIV and hepatitis. Patients without one of these conditions were categorized in the comorbid- group, while patients with one or more of these conditions were categorized in the comorbid+ group.

The primary cause of AKI was categorized as: sepsis, ischemia, drug-associated and other. Sepsis was defined in accordance to the Surviving Sepsis Campaign International Guidelines [26]. Ischemia was defined as AKI due to hypotension and pre-renal kidney failure. All patients suffering from AKI due to drugs, contrast and other substances that are nephrotoxic were categorized in the drug-associated group. Patients that experienced an episode of AKI due to any other cause then aforementioned, consisting rhabdomyolysis and glomerulonephritis were categorized in the "other" group. Indications for ICU admittance were categorized as: sepsis, postoperative, traumatic injury, intoxication and other. A postoperative ICU indication was defined as the need for ICU admission for treatment and monitoring due to perioperative haemodynamic instability. Reasons for surgery included acute pancreatitis, stomach and bowel perforations, an intra abdominal abscess and a total hip prosthesis. For estimation of the GFR we used the modified diet in renal diseases (MDRD) formula adjust for age and sex [27].

Study outcomes

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

Statistical analysis

Continuous parameters were expressed as median and interquartile range. Categorical parameters were expressed as number and percentage. Logistic regression analysis adjusted for age, sex and year of treatment was performed to compare hospital mortality in patients with and without comorbidity. In patients without comorbidity, logistic regression analysis was performed to determine independent predictors for hospital mortality. Parameters with a p-value $\leq$ 0.1 reported by univariable analysis were considered eligible for multivariable analysis. Irrespective of p-value the variables age, sex and year of treatment were included in multivariable analysis.

Overall and renal survival after hospital discharge stratified by presence of comorbidity was evaluated by Kaplan-Meier analysis. Log-rank test was used to analyze crude differences pooled over strata and cox proportional hazards analysis was used to adjust for age, sex and year of treatment. The standardized mortality ratio (SMR) was calculated by comparing mortality after hospital discharge with the expected mortality in the general Dutch population. The SMR is the ratio of observed to expected number of deaths. The expected number of deaths is calculated by multiplying the total number of years lived by patients in the study population for each calendar period in each age and sex category by the age and sex specific mortality rates of the Dutch population for each calendar period. A two-tailed p-value ≤ 0.05 was considered significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL, USA) and GraphPad Prism version 5.0a for Mac (Graph-Pad Software, La Jolla, CA, USA)

RESULTS

Study population

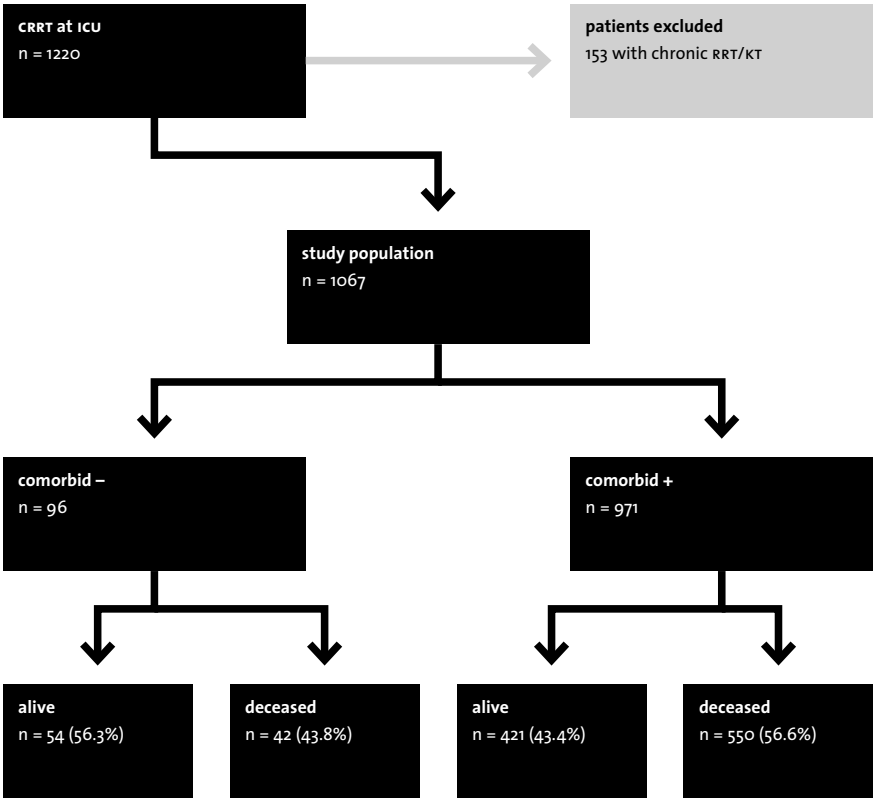
A total of 1220 patients treated with CRRT during ICU admission were evaluated during the study period. After exclusion of 153 patients on chronic RRT or with a kidney transplant the study population included 1067 patients of which 96 (9.0%) had no comorbidity (figure 1).

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

Hospital mortality

In the group without comorbidity 42 (43.8%) patients deceased during hospitalization compare to 550 (56.6%) of those with comorbidity, respectively (P = 0.02). Adjusted for age, sex and year of treatment, patients without

FIGURE 1 Flowchart of inclusion and hospital mortality stratified by presence of comorbidity.



comorbidity had a similar hospital mortality risk (Odds ratio [OR] = 0.74, 95% confidence interval [CI] = 0.47-1.15). In subgroup analysis on patients without comorbidity, univariable analysis identified several clinical variables associated with hospital mortality presented in table 2. Only serum creatinine at start of CRRT (OR = 0.96, 95%-CI = 0.93-0.99) and length of ICU stay (OR = 0.96, 95%-CI = 0.94-0.99) remained associated with hospital mortality after multivariable logistic regression analysis.

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

age in years (interquartile range)	45 (35–60)
male sex (%)	53 (55.2)
cause of AKI (%)	
sepsis	56 (58.3)
ischemia	24 (25.0)
drug-associated	9 (9.4)
other	7 (7.3)
surgical admission (%)	64 (66.7)
indication for ICU admission (%)	
sepsis	36 (37.5)
post-operative	12 (12.5)
intoxication	10 (10.4)
trauma	30 (31.3)
other	8 (8.3)
CRRT modality (%)	
CAVHD	39 (40.6)
CVVH	57 (59.4)
non-renal SOFA score (interquartile range)*	10 (8–13)
serum creatinine in µmol/L (interquartile range)	
hospital admission	177 (94–350)
start CRRT	427 (298–569)
days of ICU stay (interquartile range)	21 (11–38)

Categorical variables are expressed as number and percentage; continuous variables are expressed as median and interquartile range.

* Score available in 50 cases.

Survival after hospital discharge

In total, 475 patients left the hospital alive of which 54 had no comorbidity. Median follow-up time was 4.4 years (2.1-8.0). In general, the percentage of survival at 1, 5 and 10 years in those that survived hospitalization was 87.2%, 64.7% and 50.4%, respectively. Stratified by presence of comorbidity survival rates were 85.7%, 61.1% and 45.0% compared to 96.3%, 91,6% and 86.0% in patients with and without comorbidity, respectively (table 3). Survival curves are presented in figure 2 and log-rank test comparing both groups showed a crude significant difference in survival ($P < 0.001$). Adjusted for age, sex and year of treatment, patients without comorbidity had a significant better survival rate (Hazard-ratio [HR] = 0.28, 95%-CI = 0.14-0.58). Compared to the predicted survival in the Dutch population patients

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

	univariable analysis		multivariable analysis	
	OR (95%-CI)	P-value	OR (95%-CI)	P-value
age in years	1.02 (0.99–1.05)	0.13	1.03 (1.00–1.07)	0.08
male sex	1.37 (0.60–3.09)	0.45	2.46 (0.67–9.02)	0.18
surgical admission	1.00 (0.43–2.35)	1.00	–	–
indication for ICU admission				
sepsis	1		1	
post-operative	0.50 (0.13–1.96)	0.32	1.11 (0.21–5.85)	0.90
intoxication	0.43 (0.10–1.93)	0.27	0.49 (0.09–2.73)	0.42
trauma	1.14 (0.43–3.02)	0.79	3.17 (0.81–12.37)	0.10
other	0.14 (0.02–1.28)	0.08	0.44 (0.04–5.46)	0.52
CVVH as CRRT modality	0.60 (0.26–1.36)	0.22	–	–
non-renal SOFA score*	1.07 (0.93–1.24)	0.36	–	–
serum creatinine in µmol/L per 10 pts				
hospital admission	0.99 (0.97–1.01)	0.40	–	–
start CRRT	0.98 (0.96–1.00)	0.04	0.96 (0.93–0.99)	0.01
days of ICU stay	0.98 (0.96–0.99)	0.01	0.96 (0.94–0.99)	0.003
year of treatment	0.96 (0.88–1.04)	0.31	0.94 (0.83–1.05	0.28

* Score available in 50 cases.

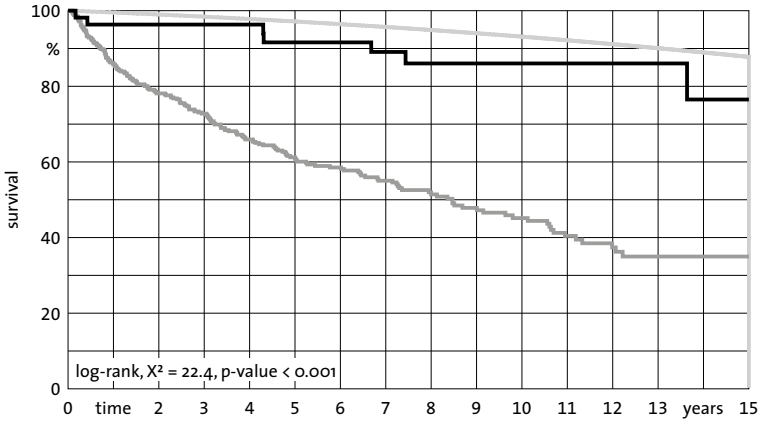
TABLE 3 Overall and renal survival of patients that survived hospital admission.

	overall survival (%)			renal survival (%)		
	1 yr	5 yr	10 yr	1 yr	5 yr	10 yr
comorbid +	85.7	61.1	45.0	85.8	82.9	76.0
comorbid –	96.3	91.6	86.0	96.3	96.3	92.9

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

without comorbidity had a similar mortality risk (SMR = 1.6, 95%-CI = 0.7-3.2), while this risk was significantly increased in patients with comorbidity (SMR = 4.8, 95%-CI = 4.1-5.5) (table 4). A reference curve, shown in figure 2, represents the predicted survival in the Dutch population matched for age, sex and calendar period to patients without comorbidity.

FIGURE 2 Kaplan-Meier curves for overall survival after hospital discharge stratified by comorbidity. The reference curve represents the predicted survival in the Dutch population matched for age, sex and calendar period to patients without comorbidity.



no. at risk

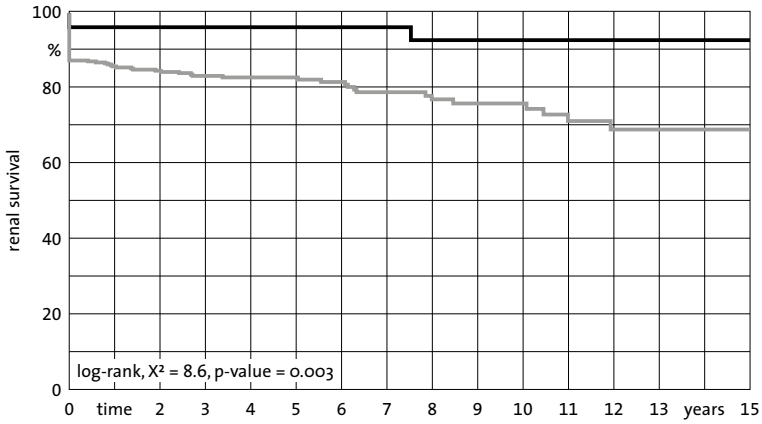
■ comorbid –	54	52	49	46	45	37	36	32	27	27	22	19	19	10	7	6
■ comorbid +	421	362	314	253	213	165	142	116	92	74	60	47	33	20	17	15

■ reference

TABLE 4 Standardized mortality ratio analysis in patients that survived hospital admission.

	sex	n° in group	n° of deaths	person years	SMR (95%-CI)	P-value
comorbid +	male	286	133	1441.8	4.3 (3.6–5.6)	<0.001
	female	135	59	691.8	6.5 (4.9–8.4)	<0.001
	overall	421	192	2133.6	4.8 (4.1–5,5)	<0.001
comorbid –	male	29	6	255.6	1.7 (0.6–3.6)	0.15
	female	25	2	206.9	1.5 (0.2–5.2)	0.40
	overall	54	8	462.4	1.6 (0.7–3.2)	0.10

FIGURE 3 Kaplan-Meier curves for renal survival stratified by comorbidity. Defined as years after discharge until chronic replacement therapy is initiated, censored for death.



no. at risk

■ comorbid –	54	50	47	45	44	37	36	32	26	26	21	19	19	10	7	6
■ comorbid +	421	315	274	219	184	143	123	103	80	63	53	41	31	19	16	14

Renal function and renal survival after hospital discharge

At time of hospital discharge 55 (11.6%) of all patients were dialysis dependent of which 53 (12.6%) and 2 (3.7%) with and without comorbidity, respectively (P = 0.07). Renal survival rates at 1, 5 and 10 years were, respectively, 85.8%, 82.9% and 76.0% versus 96.3%, 96.3% and 92.9% in patients with and without comorbidity (table 3). Renal survival curves stratified by comorbidity are presented in figure 3 and log-rank test comparing both groups showed a crude significant difference in renal survival (P = 0.003). Adjusted for age, sex and year of treatment patients without comorbidity had a significant better renal survival rate (HR = 0.24, 95%-CI = 0.07-0.76). At hospital discharge, grouped by eGFR, 28 (51.9%) patients without comorbidity had an eGFR ≥ 90, 9 (16.7%) an eGFR = 60-89, 9 (16.7%) an eGFR = 30-59, 3 (5.6%) an eGFR = 15-29 and 5 (9.3%) patients left the hospital with an eGFR < 15 ml/min/1.73m².

DISCUSSION

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

Hospital mortality and associated risk factors

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

Long-term survival after hospitalization

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

Renal survival after hospitalization

At hospital discharge 11.6% of all patients were dependent on RRT, which is about average compared to results of previous studies that reported a percentage ranging from 0 to 32% [15,16,33,39,40]. Our result demonstrated that in patients without comorbidity only 3,7% patients left the hospital dependent on RRT, which is low compared to most of the aforementioned studies. However, Schiffl et al. reported that none of the 425 critically ill patients included in their study reached dialysis dependence at hospital discharge [39]. Interestingly, this is the only study that excluded all patients with a pre-existing impaired renal function. These results suggest that in particular an impaired renal function prior AKI is an important risk factor for dialysis dependence thereafter. Furthermore, in a previous study of our research group we found that in the presence of chronic kidney disease no other comorbid condition was significantly associated with the need for RRT at hospital discharge in patients surviving AKI requiring RRT [16]. After hospital discharge only one more patient became chronic dialysis dependent after 7.5 years of follow-up. This 33-year-old male patient was admitted

to the ICU after a severe trauma (motor accident) and left the hospital with an eGFR of 28 ml/min/1.73m², which slowly decreased towards ESRD necessitating dialysis. An explanation for the high renal survival rate reported in our study is the low number of patients that left the hospital with an impaired renal function, which is, as reported by Stads et al., an important predictor for progression towards ESRD requiring RRT [38].

Limitations

There are certain limitations to our study that should be taken into consideration before interpretation of the results. First, the single center retrospective design has its inherent drawbacks and does not offer the possibility to establish causality and it is not known if the results can be generalized to other ICU populations. Second, the population of patients without comorbidity was rather small, which results in a lack of statistical power. Third, our study included patients over a period of 16 years and it is likely that patterns of referral to and treatment in the ICU have changed over time. Therefore, the year of therapy was included in all multivariable analyses to adjust for possible confounding. Third, it is possible that patients without comorbidity had chronic renal impairment before hospital admission, which could bias the results of our study. However, even if some patients with unknown chronic renal impairment were included it would strengthen our conclusion, because the long-term prognosis in patients without comorbidity would be even better. Fourth, it was not possible to collect information on progressive loss of renal function besides progression towards ESRD or renal function at time of hospital discharge. Thus, it is possible that besides the low number of patients that progressed towards ESRD there actually was deterioration in renal function. Fifth, besides modality of CRRT, no further detailed information was available including type of dialysis access, type of anticoagulation regime, subsequent complications, etc. However, given these limitations, the results of this study are of interest as the presence or absence of comorbidity seems to have a substantial effect on the prognosis of the critically ill patient and this study offers an interesting perspective on such a complex syndrome as AKI.

Conclusions

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

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Acute kidney injury as a complication of cardiac transplantation: incidence, risk factors, and impact on 1-year mortality and renal function

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Transplantation (2016) 100: 1740-1749

ABSTRACT

Background

Although chronic deterioration in renal function is frequently seen after cardiac transplantation, which is partly explained by the use of calcineurin inhibitors, data on the consequences of acute kidney injury (AKI) after cardiac transplantation are scarce. In the current study, the incidence of AKI and its impact on mortality and renal function was evaluated.

Methods

Five hundred thirty-one cardiac transplant recipients (age ≥ 18 years) were evaluated for the postoperative incidence of AKI defined by the Kidney Disease Improving Global Outcome criteria. Secondary outcomes were renal function and mortality during the first postoperative year.

Results

Overall, 405 (76%) recipients met the AKI criteria of which 211 (40%) had AKI stage I, 119 (22%) stage II, 75 (14%) stage III, and 25 patients (5%) required renal replacement therapy (RRT). One-year mortality rates in patients without AKI, stages I, II, and III were 4.8%, 7.6%, 11.8%, and 14.7%, respectively (log-rank test for trend, P = 0.008). In patients that required RRT 1-year mortality was 28.2% (log-rank test P = 0.001). In multivariable analysis only AKI requiring RRT was an independent predictor of 1-year mortality (hazard ratio, 2.75; P = 0.03). Improvement in renal function, compared with baseline values, occurred in 27% of recipients 1 month after transplantation. This was less likely to occur after previous AKI (P ≤ 0.04). The AKI stages I to III were independently proportionally associated with a worse renal function 1 year after transplantation (P ≤ 0.01).

Conclusions

Acute kidney injury is highly frequent after cardiac transplantation, and the stage of AKI is associated with increased mortality and impaired renal function in the first postoperative year.

INTRODUCTION

Since the introduction of the current immunosuppressive therapy, such as calcineurin inhibitors (CNIs), cardiac transplantation has evolved into a life-sustaining treatment for end-stage heart failure with a median survival about 11 years [1,2]. The downsides of this regime are the nephrotoxic effects of CNI usage, which is recognized as one of the most important complications after cardiac transplantation [2-7]. Previous studies reported that cardiac transplantation recipients are prone for progressive deterioration in renal function which in the worst scenario leads to end-stage renal disease that occurs in up to 20% in the first 10 postoperative years [8-16]. Furthermore, cardiac transplantation recipients are at risk for developing acute kidney injury (AKI) in the early postoperative phase. Although AKI is a frequently seen complication and established risk factor for mortality and renal impairment after non-transplantation cardiac surgery [17-21], little is known about AKI after cardiac transplantation. Since the first consensus criteria for AKI were published [22], few studies investigated the incidence of AKI after cardiac transplantation and reported inconsistent results with an incidence ranging from 25% to 70% [23-28]. In addition, results regarding the impact of AKI on mortality and renal function are conflicting, probably caused by difference in study design, AKI definition and small sample size. Therefore, we performed a study with the objective to evaluate the early post-transplantation incidence of AKI, defined by the recent published AKI criteria proposed by the Kidney Disease: Improving Global Outcome (KDIGO) group [29], corresponding risk factors and the impact of AKI on mortality and renal function during the first postoperative year.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective cohort study evaluating all consecutive cardiac transplantation recipients in the Erasmus MC (The Netherlands), between 1984 and 2012. Combined cardiac/kidney transplantations are not performed at the Erasmus MC. Exclusion criteria were age younger than 18 years, re-transplantation within 7 days, renal replacement therapy (RRT) preceding transplantation, or death within 48 hours thereafter. Data were obtained from a computerized database, electronic patient records, and chart review. Patients that required RRT after cardiac transplantation were

treated with either continuous venovenous hemofiltration, continuous arteriovenous hemodialysis or intermitted hemodialysis. Renal replacement therapy was prescribed by the attending nephrologist and delivered by the hemodialysis nursing team.

Immunosuppressive protocol

The immunosuppressive protocol has changed over the last 30 years and included usually induction therapy with polyclonal antithymocyte globulins (ATG) [2]. The use of induction therapy was first introduced in 1987 and in the majority of cases consisted of horse ATG (1987-2008) and rabbit ATG (2009 and thereafter). Maintenance therapy after the very early postoperative phase was based on CNIs, either cyclosporine-based (1984-1999), or tacrolimus-based (2000 and thereafter). From 1984 to 1999, immunosuppression was complemented usually by prednisone monotherapy, which was replaced in 2000 by a combination of prednisone and/or mycophenolate mofetil. In patients that did not receive induction therapy, the use of CNIs was initiated perioperative or directly postoperative, whereas it was delayed in those who did receive induction therapy. The postoperative time point when therapy with either cyclosporine or tacrolimus was initiated varied from 2 to 7 days after transplantation, which depended on the former immunosuppressive protocol.

Study endpoints and definitions

The primary study endpoint was the incidence of AKI stratified by severity stage during the first 7 days after transplantation defined by the KDIGO criteria (table 1). Demographic and clinical characteristics were evaluated for the association with AKI and are shown in table 2. Secondary endpoints included the impact of AKI on mortality and renal function during the first year after transplantation. Taking into consideration the change of the immunosuppressive protocol during the study period, subgroup analyses were performed stratified by the use of induction therapy. For the evaluation of renal function after transplantation serum, creatinine concentrations were collected at baseline, days 0 to 7 and 1, 3, 6, 9 and 12 months, respectively. The baseline serum creatinine concentration was defined as the most recent outpatient concentration up to 6 months before transplantation.

When unavailable, the serum creatinine concentration at hospital admission was considered baseline. The estimated glomerular filtration

TABLE 1 Definition of AKI by the Kidney Disease Improving Global Outcome criteria.

AKI stage	serum creatinine
I	≥26.4 µmol/L within 48 hours, or; 1.5 to 2.0 times baseline within 7 days
II	2.0 to 2.9 times baseline
III	≥ 3.0 times baseline, or; increase in SCr to ≥ 353.6 µmol/L, or; initiation of renal replacement therapy

Modified from the Kidney Disease Improving Global Outcome: Acute Kidney Injury Workgroup [29].
Serum creatinine concentration at baseline was defined as the most recent outpatient serum concentration up to six months prior to transplantation. When unavailable serum creatinine concentration at hospital admission was considered baseline. Urine output criteria were not used, because required data was not available.

rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula adjusted for age and sex [31]. Patients were grouped according to their eGFR at baseline based on the Kidney Disease Outcomes Quality Initiative guidelines [32]. Since previous studies have demonstrated that chronic kidney disease (CKD) is one of the most important risk factors for AKI [33-35], separate analyses were performed to evaluate the association between an impaired renal function at baseline and the aforementioned study endpoints. Complementary, recipients were evaluated for renal improvement after transplantation, which was defined as an improvement in eGFR of 20% or greater compared with baseline 1 month after transplantation. To determine whether the development of AKI did influence the prescribed dosage of CNIs, serum concentrations of either tacrolimus or cyclosporine were collected at months 1, 3, 6, 9, and 12, respectively. The study was approved by the medical ethical review board of the Erasmus MC.

Statistical analyses

Continuous parameters were expressed as median and interquartile range and compared by Mann-Whitney U test or Kruskal-Wallis test. Categorical parameters were expressed as number and percentage and compared by Fisher exact test or Linear-by-Linear Association. Multivariable ordinal logistic regression analysis was performed for the identification of risk factors associated with AKI stratified by stage of severity. Kaplan-Meier curves stratified by AKI stage were constructed for the evaluation of mortality

TABLE 2 Demographic and clinical characteristics of study population stratified by AKI stage.

	no AKI n = 126	AKI stage I n = 211	AKI stage II n = 119	AKI stage III n = 75	P-value
age in years	51 (45–55)	52 (43–58)	50 (43–56)	48 (41–55)	0.22
male gender	96 (76.2)	163 (77.3)	94 (79.0)	62 (82.7)	0.74
BMI in kg/m²	22.3 (20.0–24.3)	23.1 (21.0–25.2)	23.5 (21.0–25.3)	23.9 (21.8–26.8)	0.001
eGFR stage at baseline in ml/min/1.73m²					0.005
≥90	17 (13.5)	14 (6.6)	11 (9.2)	2 (2.7)	–
60–89	63 (50.0)	77 (36.5)	55 (46.2)	30 (40.0)	–
30–59	45 (35.7)	115 (54.5)	50 (42.0)	39 (52.0)	–
15–29	1 (0.8)	5 (2.4)	3 (2.5)	4 (5.3)	–
primary cardiac disease					0.42
cardiomyopathy	58 (46.0)	98 (46.4)	47 (39.5)	39 (52.0)	–
ischemic cardiac disease	62 (49.2)	108 (51.2)	66 (55.5)	32 (42.7)	–
valvular disease	6 (4.8)	5 (2.4)	6 (5.0)	4 (5.3)	–
comorbid conditions					
diabetes mellitus	2 (1.6)	16 (7.6)	6 (5.0)	9 (12.0)	0.01
hypertension	9 (7.1)	27 (12.8)	10 (8.4)	6 (8.0)	0.34
previous thoracic surgery	33 (26.2)	60 (28.4)	34 (28.6)	22 (29.3)	0.96
hemodynamic support					
inotropic medication	37 (29.4)	45 (21.3)	25 (21.0)	26 (34.7)	0.06
IABP	9 (7.1)	13 (6.2)	9 (7.6)	8 (10.7)	0.63
LVAD	7 (5.6)	3 (1.4)	2 (1.7)	2 (2.7)	0.15
ECMO	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	0.36
urgency status on waiting list					0.005
elective	56 (44.4)	120 (56.9)	75 (63.0)	33 (44.0)	–
urgent	51 (40.5)	53 (25.1)	23 (19.3)	24 (32.0)	–
unknown	19 (15.1)	38 (18.0)	21 (17.6)	18 (24.0)	–
days on waiting list	105 (44–233)	171 (50–378)	183 (49–327)	102 (24–286)	0.02
hospitalized before transplantation	59 (46.8)	71 (33.6)	40 (33.6)	36 (48.0)	0.02
donor					
age in years	30 (20–42)	32 (22–43)	34 (22–43)	38 (23–47)	0.10
male gender	70 (55.6)	112 (53.1)	60 (50.4)	34 (45.3)	0.54
donor cause of death					0.96
trauma	58 (46.0)	94 (44.5)	49 (41.2)	33 (44.0)	–
CVA/SAB	64 (50.8)	106 (50.2)	66 (55.5)	39 (52.0)	–
other	4 (3.2)	8 (3.8)	4 (3.4)	3 (4.0)	–
unknown	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	–
time of ischemia donor heart in minutes	162 (135–195)	170 (141–203)	174 (150–203)	165 (145–198)	0.25

TABLE 2 *continued*

	no AKI n = 126	AKI stage I n = 211	AKI stage II n = 119	AKI stage III n = 75	P-value
transplantation complication					0.03
none	100 (79.4)	170 (80.6)	91 (76.5)	44 (58.7)	–
RV failure**	6 (4.8)	13 (6.2)	11 (9.2)	15 (20.0)	–
reoperation	12 (9.5)	16 (7.6)	8 (6.7)	11 (14.7)	–
primary graft failure**	3 (2.4)	4 (1.9)	4 (3.4)	1 (1.3)	–
other*	5 (4.0)	8 (3.8)	5 (4.2)	4 (5.3)	–
induction therapy	114 (90.5)	168 (79.6)	86 (72.3)	45 (60.0)	<0.001

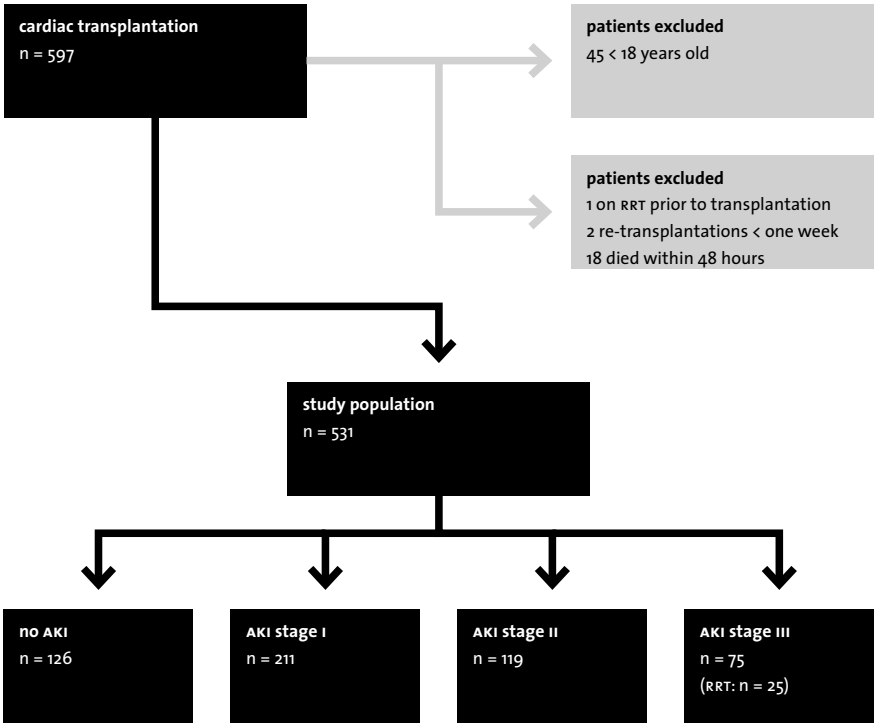
Continuous variables are presented as median, interquartile range and compared by Kruskal-Wallis Test. Categorical variables are presented as number, percentage and compared by Fisher's exact test.

* Transplantation complications categorized as "other" included haemodynamic instability caused by perioperative bleeding, cardiac arrest, under dosing of inotropic medication, pacemaker malfunction, fluid overload, acute rejection and instability of an unknown cause. In 2 cases it was not possible to close the thoracic cavity directly after transplantation procedure.

** Right ventricle and primary graft failure were defined by the International Society for Heart and Lung Transplantation consensus guidelines [51].

the first year after transplantation. Differences pooled over strata were compared by log-rank test and log-rank test for trend. A multivariable Cox proportional hazards analysis was performed for identification of parameters associated with mortality, and a general linear model analysis was performed for the association with eGFR 1 year after transplantation. A multivariable logistic regression model was performed for the identification of parameters associated with renal improvement. All multivariable models were constructed by a manually stepwise manner. Step 1: all parameters with a P value less than 0.2 were included in the model. Step 2: all parameters with a P value greater than 0.1 were deleted one by one. Step 3: parameters not selected at step 1 were individually evaluated and included in the model when statistically significant ($P < 0.05$). The difference in renal function or CNI serum concentrations over time was objectified making use of linear mixed model analyses. Two-tailed P value less than 0.05 was considered significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

FIGURE 1 Flowchart of study population stratified AKI stage.

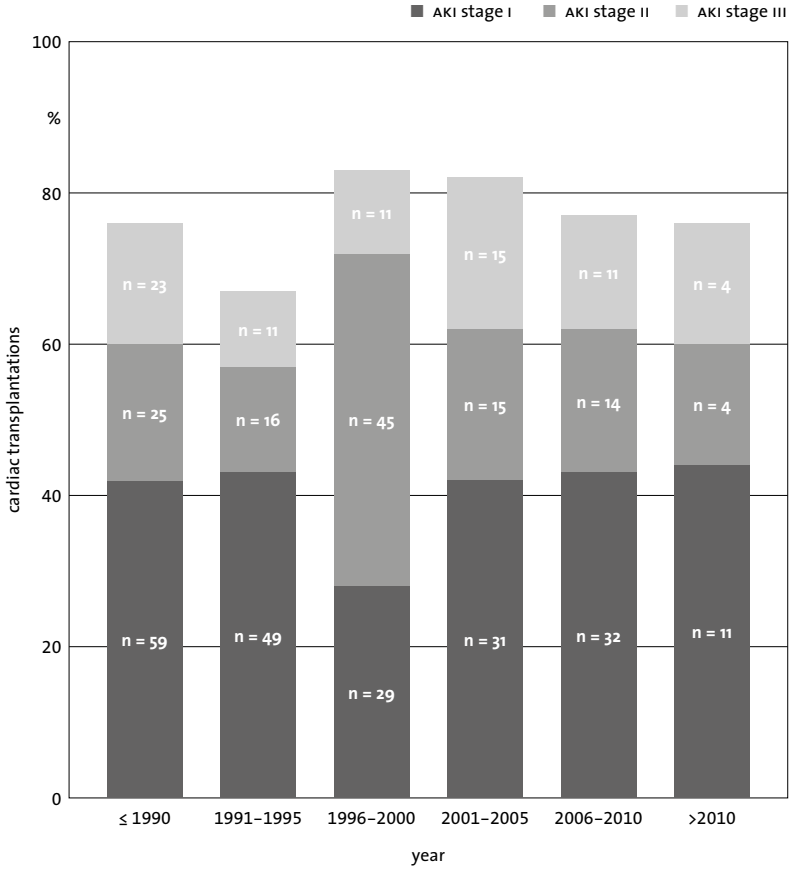


RESULTS

AKI and associated risk factors

During the study period, 597 cardiac transplantations were performed, of which 531 recipients were included for further analysis (figure 1). In total, 405 (76%) developed AKI, of which 211 (40%) stage I, 119 (22%) stage II, and 75 (14%) stage III, respectively. Overall, 25 (5%) recipients required RRT. Nineteen received continuous venovenous hemofiltration, 4 continuous arteriovenous hemodialysis, and 2 intermitted hemodialysis, respectively, with a median duration of 5 (interquartile range, 4-17) days. The incidence of AKI over time during the study period is presented in figure 2, and no significant increase or decrease was observed (P = 0.44). Overall, 413 (78%) of the transplantation recipients were treated with induction therapy, and the incidence of AKI was significantly lower (P < 0.001) in those treated

FIGURE 2 Proportion of AKI stratified by stage of severity between 1984 and 2012. Linear-by-linear Association, P = 0.44.



with induction therapy (72%) in the early postoperative phase compared to those without induction therapy (90%), respectively (supplemental figure 1). Furthermore, when stratified by baseline renal function, a significant association existed (P = 0.005) between a lower grouped eGFR at baseline and an increased risk for development of AKI (supplemental figure 2). Other demographic and clinical characteristics stratified by AKI stage are presented in table 2. In addition to the association for induction therapy and baseline renal function, univariable analysis for the relationship with AKI furthermore identified an association for: body mass index (BMI), diabetes mellitus, urgent status on the waiting list, donor age, and right ventricle (RV) failure. Factors independently associated with the development of AKI,

TABLE 3 Multivariable ordinal logistic regression analysis of characteristics for the association with acute kidney injury and increase in severity.

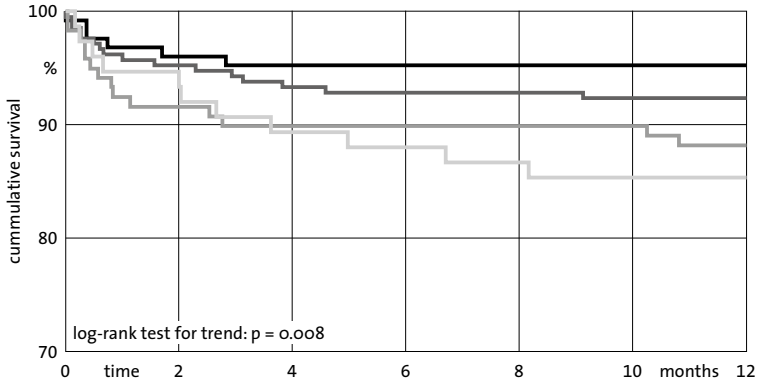
	OR	95%-CI	P-value
age in years	0.98	0.96–0.99	0.004
BMI in kg/m²	1.11	1.05–1.17	<0.001
eGFR stage at baseline in ml/min/1.73m²			
≥90	1	–	–
60–89	1.77	0.95–3.29	0.07
30–59	2.35	1.24–4.44	0.009
15–29	5.05	1.54–16.53	0.007
diabetes mellitus	2.22	1.04–3.93	0.04
transplantation complication			
none	1	–	–
RV failure	3.23	1.81–5.76	<0.001
reoperation	1.39	0.80–2.43	0.24
primary graft failure	1.64	0.57–4.72	0.36
other	1.22	0.55–2.68	0.63
Induction therapy	0.34	0.22–0.49	<0.001

and subsequent increase in severity, were a higher BMI, a baseline eGFR less than 60 mL/min per 1.73 m², diabetes mellitus, and postoperative RV failure (table 3). Protective factors were older age and treatment with induction therapy compared to direct treatment with a CNI.

Mortality in the first year after transplantation

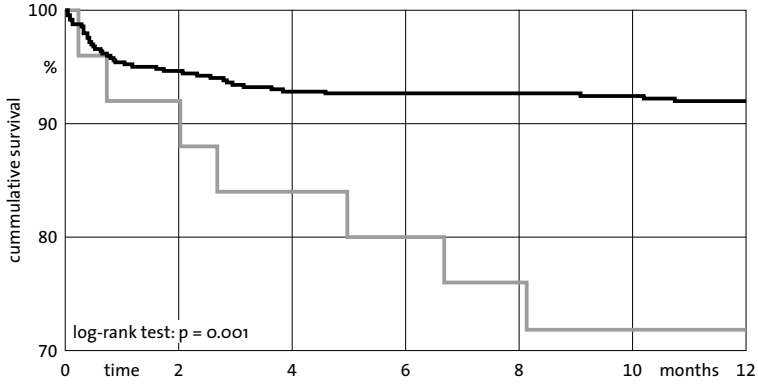
In total, 47 deaths were observed during follow-up the first year after transplantation. The most frequent cause of death was sepsis (n = 11, 23%) followed by rejection (n = 10, 21%), hypovolemic shock (n = 7, 15%), graft failure (n = 5, 11%), cerebrovascular accident (n = 3, 6%), non-Hodgkin lymphoma (n = 3, 6%), cardiac tamponade (n = 2, 4%), and vena cava inferior syndrome (n = 1, 2%), respectively. In 5 (11%) recipients, the cause of death was either unclear or a combination of the aforementioned. Overall hospital mortality was 6% and stratified by AKI stage hospital mortality was 3.2%, 4.7%, 9.2%, and 9.3% for those without AKI, AKI stages I, II and III, respectively (P = 0.02). Recipients with RRT had a hospital mortality of 20% compared to 5.3% in those without RRT (P = 0.01). Overall 1-year mortality was 8.9% and survival curves stratified by AKI stage or RRT requirement are presented in figures 3A to B, and 1-year mortality was 4.8%, 7.6%, 11.8%, and 14.7%

FIGURE 3A Kaplan-Meier curves for survival during the first year after transplantation. Analysis stratified by AKI stage.



no AKI	126	121	120	120	119	117	116
AKI stage I	211	198	194	191	190	189	188
AKI stage II	119	108	106	106	106	106	104
AKI stage III	75	71	67	66	65	63	63

FIGURE 3B Kaplan-Meier curves for survival during the first year after transplantation. Analysis stratified for RRT in the first 7 postoperative days.



no RRT	506	475	466	463	461	458	454
RRT	25	23	21	20	19	17	17

TABLE 4 Multivariable Cox proportional-hazards analysis of characteristics for the association with mortality during the first year after transplantation.

	HR	95%-CI	P-value
age in years	1.04	1.00–1.07	0.04
urgency status on waiting list			
elective	1	–	–
urgent	0.43	0.19–1.00	0.05
unknown	0.97	0.43–2.18	0.93
transplantation complication			
none	1	–	–
RV failure	3.06	1.32–7.07	0.009
reoperation	2.18	0.82–5.80	0.12
primary graft failure	12.42	4.65–33.23	<0.001
other	6.38	2.70–15.08	<0.001
RRT requirement	2.75	1.13–6.63	0.03

for recipients without AKI, AKI stages I, II and III, respectively (Log-rank for trend, P = 0.008). Recipients with RRT had a 1-year mortality of 28.2% compared with 7.9% in those without RRT, respectively (P = 0.001). Subgroup analysis demonstrated a similar pattern, with an increase in mortality rate commensurate to an increase in AKI stage, in recipients without and with the use of induction therapy (log-rank for trend, P = 0.17 vs P = 0.01), respectively (supplemental figure 3). Furthermore, when stratified by renal function at baseline (eGFR ≥ 60 vs < 60 ml/min/1.73m²), a trend towards a more pronounced effect of AKI on mortality was reported in recipients with a baseline eGFR less than 60 ml/min/1.73m² (log-rank for trend, P = 0.09) compared with those with a baseline eGFR of 60 ml/min/1.73m² or greater (log-rank for trend, P = 0.06), respectively (supplemental figure 4). Univariable analysis for the relationship with mortality identified an association for age, baseline eGFR, urgent waiting list status, donor age, transplantation complicated by RV failure, primary graft failure or other, AKI stage III, and RRT requirement. As presented in table 4, factors independently associated with 1-year mortality were older age, a transplantation complicated by RV failure, primary graft failure, other, and RRT requirement. Urgent waiting list status was associated with decreased mortality.

Renal function and CNI dosage in the first year after transplantation

The course of renal function (eGFR) stratified by AKI stage or RRT requirement during the first year after transplantation is presented in figures 4A to B. Median baseline eGFR was 65, 56, 63, and 56 ml/min/1.73m² in recipients without AKI, stages I, II, and III, respectively (P < 0.001). Of the 471 recipients alive, median eGFR at 1 year was 50, 45, 46, and 44 mL/min per 1.73 m², respectively (P = 0.007). During the first year, only 3 recipients became chronically dependent on RRT, which corresponds with an RRT free survival of 99%. Linear mixed model analyses demonstrated a significant decrease in eGFR during the first year after transplantation (P < 0.001), and there was a significant difference for pooled analysis of eGFR between AKI stages (P < 0.001). Furthermore, a significant difference in slope of eGFR over time between AKI stages was reported (P = 0.005). Linear mixed model analysis demonstrated a similar pattern when stratified by AKI requiring RRT. Subgroup analyses stratified by the use of induction therapy or by eGFR at baseline are presented in supplemental figure 5 and 6. Univariable analysis for the relationship with eGFR at 1 year identified an association for age, male sex, BMI, year of transplantation, baseline eGFR, valvular disease as primary cardiac disease, and AKI stages I to III. As presented in table 5, factors independently associated with a lower eGFR 1 year after transplantation were higher age, higher BMI, baseline eGFR less than 90 ml/min/1.73m² and AKI stages I, II, and III. Protective factors were male sex and a more recent year of transplantation. Both serum cyclosporine and tacrolimus concentrations showed a significant decrease during the first year (P < 0.001). Furthermore, in patients that received tacrolimus, a significant difference between AKI stages was reported (P = 0.02). Serum concentrations of cyclosporine or tacrolimus stratified by AKI stage during the first year after transplantation are presented in figures 5A and B.

Renal improvement 1 month after transplantation

Renal function at baseline may be influenced by a low cardiac output and or medication (eg, angiotensin converting enzyme inhibitors) that directly influence intrarenal hemodynamics. Therefore, in the weeks after transplantation, the renal function may actually improve, specifically in patients without AKI. Indeed, we could show an improvement of renal function during the first month after transplantation (defined as an increase in renal function ≥20% compared to baseline renal function) in 136 of 505 (27%)

FIGURE 4A Renal function during the first year after transplantation stratified by AKI stage.

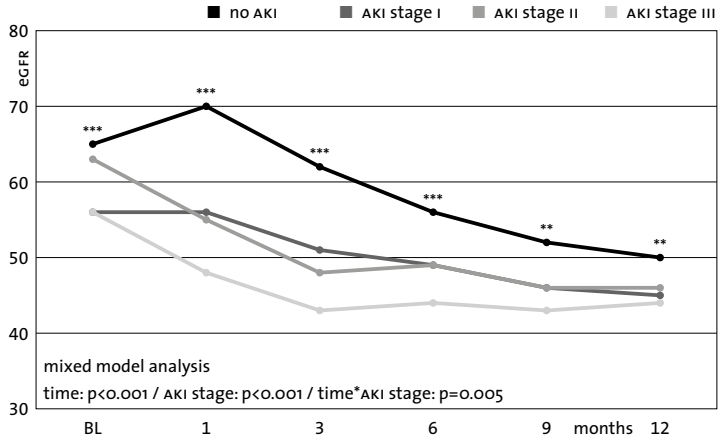
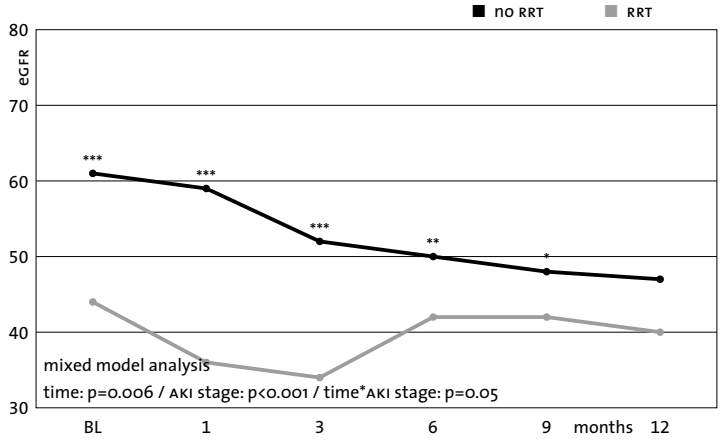


FIGURE 4B Renal function during the first year after transplantation stratified by AKI requiring renal replacement therapy.



Differences in median eGFR at time of baseline, 1, 3, 6, 9 and 12 months are calculated by Kruskal-Wallis or Mann-Whitney U test.

* P < 0.05

** P < 0.01

*** P < 0.001

TABLE 5 Multivariable general linear model analysis of characteristics for the association with renal function (eGFR) one year after cardiac transplantation.

	ß	95%-CI	P-value
age in years	−0.25	(−0.44;−0.05)	0.01
male gender	9.03	(4.55;13.53)	<0.001
BMI in kg/m²	−0.60	(−1.16;−0.03)	0.04
year of transplantation	0.59	(0.35;0.84)	<0.001
eGFR stage at baseline in ml/min/1.73m²			
≥90	0	–	–
60–89	−9.61	(−16.25;−2.96)	0.005
30–59	−16.22	(−23.10;−9.34)	<0.001
15–29	−17.67	(−31.19;−4.14)	0.01
primary cardiac disease			
cardiomyopathy	0	0	–
ischemic cardiac disease	−1.73	(−2.14;5.60)	0.38
valvular disease	−8.83	(−17.65;−0.01)	0.05
AKI stage			
no AKI	0	–	–
stage I	−5.77	(−10.21;−1.34)	0.01
stage II	−6.76	(−11.80;−1.73)	0.009
stage III	−8.76	(−14.76;−2.76)	0.004

recipients alive at 1 month. Furthermore, of these 136 patients, 94 (69%) had AKI after cardiac transplantation compared with 289 (78%) in those without renal improvement (P = 0.03), respectively (supplemental figure 7). The course of renal function over time for recipients with and without renal improvement are presented in figures 6A and B, and both showed a significant difference in eGFR over time (P < 0.001) and between AKI stages (P = 0.04 vs P < 0.001), respectively. Furthermore, a significant difference in slope over time between AKI stages was reported in those without renal improvement (P = 0.003). Univariable analysis for the relationship with renal improvement identified an association for baseline eGFR, inotropic medication, intra-aortic balloon pump, hospitalization before transplantation, and AKI stage II. As presented in table 6, factors independently associated with renal improvement were an eGFR at baseline < 60 ml/min/1.73m², intra-aortic balloon pump, and hospitalization before transplantation. In addition, higher BMI and AKI stages I to III were independently associated with an adverse effect on renal improvement.

FIGURE 5A Serum tacrolimus concentration in ng/ml during the first year after transplantation.

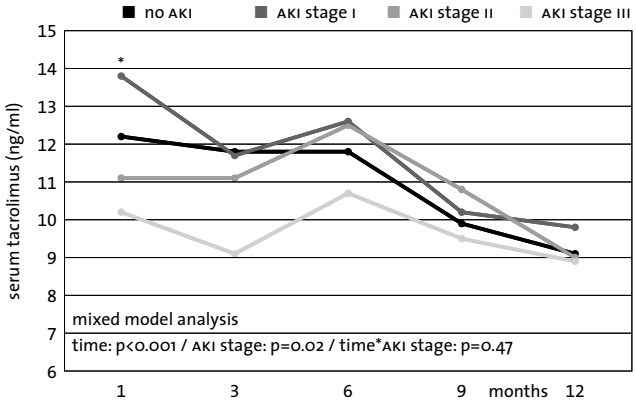
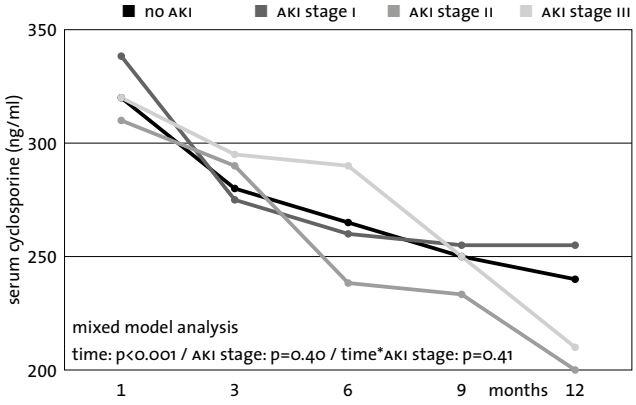


FIGURE 5B Serum cyclosporine concentration in ng/ml during the first year after transplantation.



Complete through CNI serum concentrations were available in 99 and 169 recipients for tacrolimus and cyclosporine, respectively. Differences in median CNI concentrations at 1, 3, 6, 9, and 12 months are calculated by Kruskal-Wallis test.

* $P < 0.05$

FIGURE 6A The effect of improvement in renal function (≥ 20%) during the first postoperative month on renal function in the first year after transplantation.

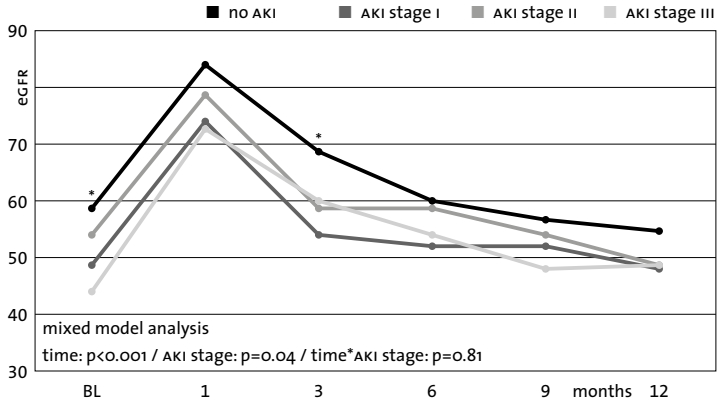
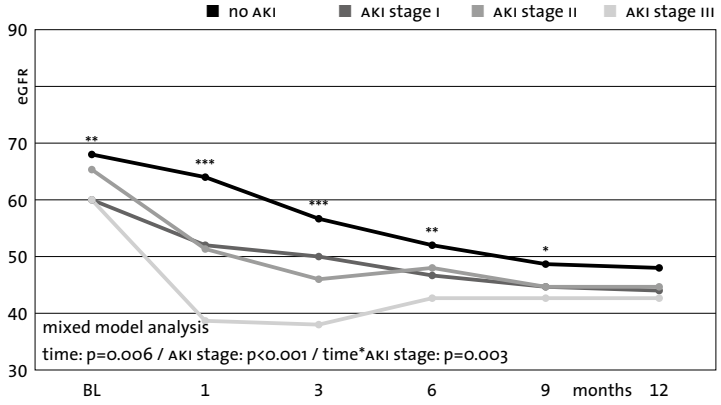


FIGURE 6B The effect of improvement in renal function (< 20%) during the first postoperative month on renal function in the first year after transplantation.



Differences in median eGFR at time of baseline, 1, 3, 6, 9 and 12 months are calculated by Kruskal-Wallis or Mann-Whitney U test.

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

TABLE 6 Multivariable logistic regression analysis of characteristics for the association with renal improvement one month after transplantation.

	OR	95%-CI	P-value
male gender	1.72	(4.55;13.53)	<0.001
BMI in kg/m²	0.92	(−1.16;−0.03)	0.04
eGFR stage at baseline in ml/min/1.73m²			
≥90	1	–	–
60–89	3.34	0.96–11.67	0.06
30–59	10.38	3.97–36.29	<0.001
15–29	76.03	12.14–475.88	<0.001
IABP	2.17	1.01–4.66	0.05
hospitalized before transplantation	1.74	1.09–2.77	0.02
AKI stage			
no AKI	1	–	–
stage I	0.57	0.33–0.98	0.04
stage II	0.41	0.21–0.79	0.008
stage III	0.39	0.18–0.82	0.01

DISCUSSION

Where the incidence and impact of AKI have been extensively studied, in the intensive care unit setting [36-40] or after general cardiac surgery [17-21], little is known about its role after cardiac transplantation. This is the first study evaluating the incidence and impact of AKI stratified by the consensus criteria for AKI recently published by the KDIGO workgroup [29]. With an incidence of 76%, as demonstrated in our study, AKI was a highly frequent complication of transplantation and associated with important implications for the recipient's prognosis. Furthermore, the results of this study underline the complexity of AKI as a clinical syndrome and its aftermath, which is to be believed, highly affected by pre-existing comorbid conditions including CKD as well as the etiology of AKI [41,42]. Moreover, this seems to be even more complex in the cardiac transplantation setting where recipients are prone to suffer from pre-renal kidney impairment due to pre-existing severe cardiac failure. In addition, the role of CNIs after cardiac transplantation must be taken into account, which may potentially obscure or amplify the impact of AKI.

As compared to the current literature, we reported a high incidence of AKI, where previous studies have shown large variation in incidence ranging from 25% up to 70% [23-27], which is caused by the difference in study design and population but more important by the criteria used for definition of AKI. Previous studies generally used the Risk, Injury, Failure, Loss, End-Stage Renal Disease [22] or Acute Kidney Injury Network criteria [43]. The major difference between the KDIGO and Risk, Injury, Failure, Loss, End-Stage Renal Disease criteria is the sensitivity of the KDIGO criteria for a small increase in serum creatinine concentration, which results in a larger number of patients classified as AKI stage I [29,44]. The Acute Kidney Injury Network criteria include a similar definition for AKI compared to the KDIGO criteria and the only difference is a slight modification in staging of AKI. In contrast to the high overall incidence of AKI, the need for RRT (5%) in our study was remarkably low, as previous studies reported a need for RRT in 6% to 29% [23,25-28]. This could be explained by the variability in threshold for the initiation of RRT or because we evaluated its incidence only within the first 7 postoperative days.

Taken into account the long study period, no significant change in incidence of AKI was reported over time, which is remarkable given the

substantial progress in medical care over the last decades. However, the threshold whether a potential recipient is suitable for transplantation has been lowered, which results in a bigger proportion of recipients with a high burden of comorbidity and poorer clinical condition compared to the past [2,45]. This is supported by the fact that our study demonstrated that comorbid conditions, such as an impaired baseline renal function and diabetes mellitus, were independently associated with an increased risk for AKI and subsequent stage of severity. More surprisingly, this also applied to the recipient's BMI. Although a high BMI is known as an independent risk factor for developing CKD in the long term [46,47], little is known about the role of overweight in the development of AKI. Two studies on the impact of BMI on AKI in patients that underwent cardiac surgery reported that patients with a BMI of 40 or greater had a crude up to 4-fold increased risk for AKI [48,49]. Given the fact that potential recipients with a BMI of 40 or greater are not eligible for transplantation, and are therefore not included in this study, this is the first study to report that also less severe forms of obesity pose a risk for AKI. A recent review suggested that the increased susceptibility for the development of AKI in patients with obesity is probably the result of a complex interplay of multiple mechanisms including the increase of pro-inflammatory cytokines, oxidative stress, a difference in hemodynamic management and intravascular volume assessment, and altered pharmacokinetics of nephrotoxic drugs [50]. Another striking finding was the protective association between higher age and the development of AKI. This is in contrast to the general consensus that age is an important risk factor for the development of AKI and is associated with poor outcome [51] It is difficult to provide an adequate explanation for this unexpected finding, but it may be partly explained by a possible selection bias where the elderly recipient is perhaps in a better clinical condition to be eligible for transplantation.

With regard to mortality, AKI constituted a crude predictor proportional to stage of severity for both hospital and 1-year mortality. Furthermore, similar patterns of survival were observed when stratified by either the use of induction therapy or baseline renal function. In addition, a trend toward a more pronounced effect of AKI on mortality was observed in recipients that required induction therapy or had a baseline eGFR less than 60 ml/min/1.73m^2. However, after multivariable adjustment only AKI requiring

RRT was associated with an increased risk for mortality. Results that discuss the impact of AKI on mortality after cardiac transplantation are conflicting. Only 2 studies [25,27] reported a crude association between AKI and mortality, of which one [25] concluded that AKI was an independent risk factor for mortality. This is in contrast to our results and can be partly explained by the fact that they did not adjust for postoperative complications. The fact that AKI requiring RRT was an independent risk factor for mortality is unanimously supported by the studies that performed subgroup analyses on this topic [23,25-28], and 1 study reported an increased risk for mortality with an odds ratio (OR) of 17.4 [28]. Our association was less pronounced (odds ratio, 2.8), which was probably the result of a lower crude mortality rate in our study (20% versus 50%). Interestingly, the results of our study demonstrated that an urgency status on the waiting list was independently associated with a lower mortality risk. When further explored, the latter result may be partly explained by the fact that those with an urgency status on the waiting list were more likely to be of younger age, less likely to suffer from comorbid conditions, such as diabetes mellitus, and had shorter time on the waiting list (data not shown).

Although only AKI in its most severe form was associated with increased mortality, the results of our study show that AKI, even in its mildest form, had its repercussions on renal function during the first year after transplantation. Besides the overall drop in renal function, which can be explained by the well-known nephrotoxic effect of prolonged CNI usage [3-7], the results of our study demonstrated that AKI was associated with lower renal function 1 year after transplantation even after adjustment for potential confounders, including baseline renal function. In addition, it is likely that the true impact of AKI is underestimated in our study, especially in recipients that used tacrolimus as immunosuppressive therapy from 2000 onward. Our results suggest that patient that developed AKI stage II or III were more likely to receive a lower dosage of tacrolimus during the first months after transplantation as part of a renal protective strategy. In line with our results, 2 studies reported on renal function stratified by AKI stage. Although one found a crude association between AKI and drop in renal function [25], the other concluded that there was a significant difference in renal function measured by serum creatinine concentration between patients that experienced either AKI or AKI requiring RRT and patients

without AKI. However, curves of renal function converged 6 months after transplantation and 2 years after transplantation, no significant difference was found [26]. In addition to the impact of AKI on renal function, it was noticed that in particular recipients without AKI showed an improvement of renal function during the first month after transplantation. This can be explained by the improved hemodynamics after placement of a well-functioning cardiac transplant, which leads to improvement of renal function in those with pre-existing pre-renal failure. This was confirmed by the fact that patients with an impaired baseline renal function were more likely to have an improvement in renal function after transplantation compared to those with a normal baseline renal function. On the other hand, the development of AKI was independently associated with an adverse effect on renal improvement.

There are certain limitations to our study that should be taken into consideration while interpreting the results. At first, the retrospective observational study design does not offer the possibility to establish causality, and the single-center design limits the possibility to transpose the results of our study to other populations. However, due to the large sample size and detailed and thorough reviewing of the patient records, it was possible to perform extended multivariable analyses with the purpose to rule out confounding or modifying effects as far as possible. Furthermore, the period of inclusion for participation in this study is long, and it is likely that the selection procedure patients eligible for transplantation has changed over the last decades as well as postoperative protocols and quality of care, which could affect the outcome in our study. However, during the process of multivariable modeling, the effect of the year of transplantation was evaluated and included when it had a significant contribution to the model. This was only applicable to the analysis on renal function 1 year after transplantation.

In conclusion, our study demonstrates that AKI is a highly frequent complication of cardiac transplantation, and the results of this study suggest that it is not an innocent bystander in the postoperative course of the transplant recipient. Even AKI in its mildest form is independently associated with adverse effects in the transplant recipient, which increases proportionally with the severity of the experienced episode of AKI. Prevention or mitigation of the severity of AKI after cardiac transplantation is therefore an important goal of perioperative care.

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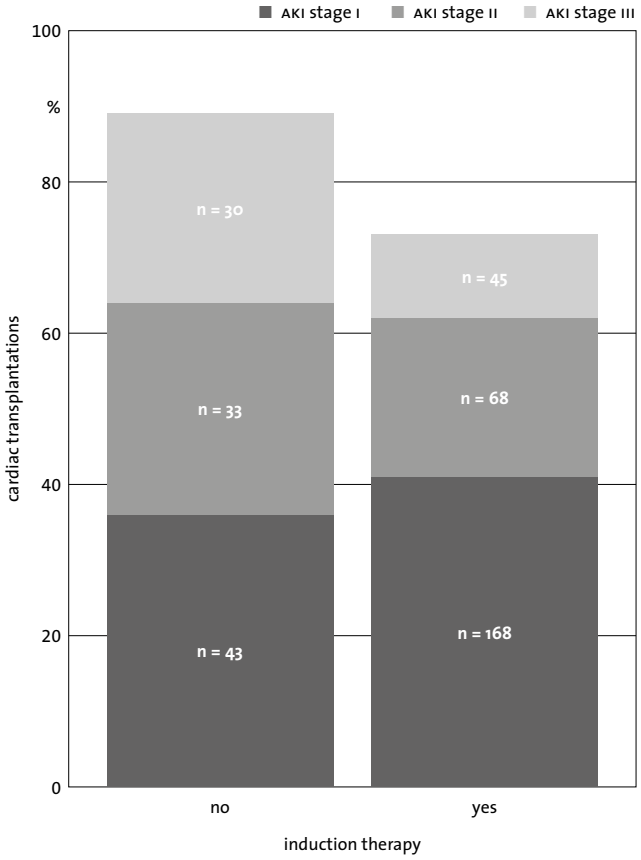
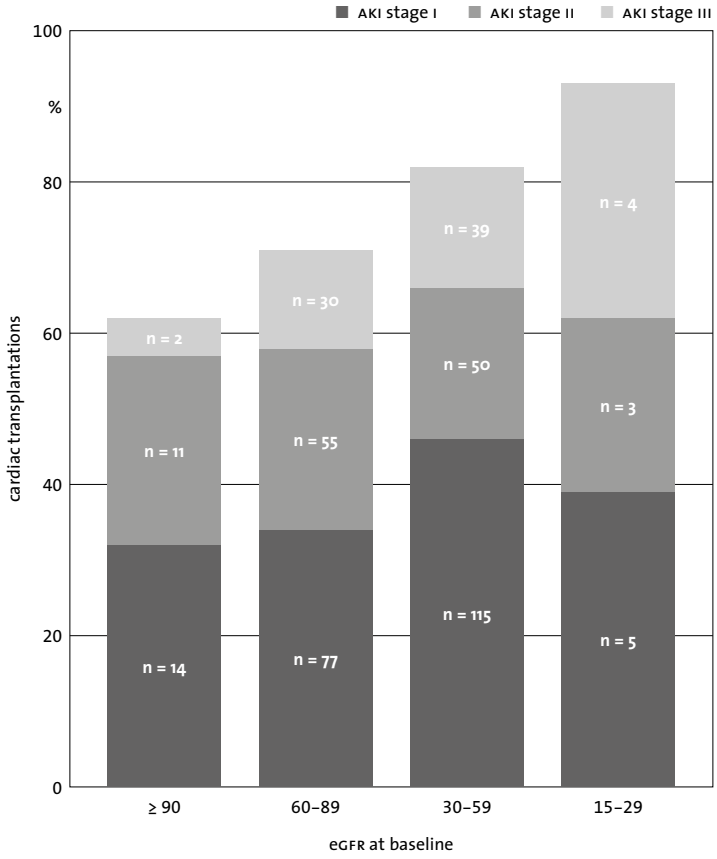
SUPPLEMENTAL FIGURE 1 Proportion of AKI categorized by the use of induction therapy.



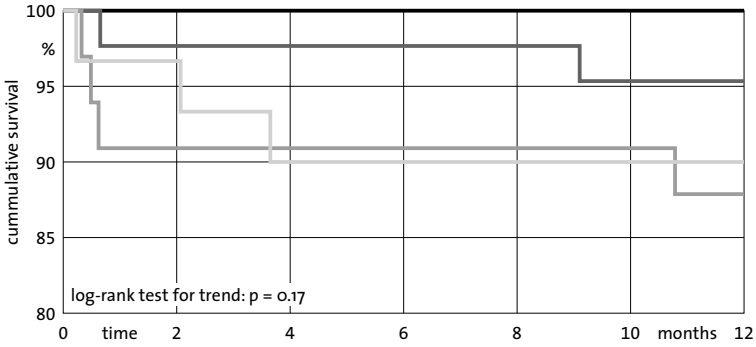
Linear-by-Linear Association, P < 0.001

SUPPLEMENTAL FIGURE 2 Proportion of AKI categorized by eGFR at baseline.



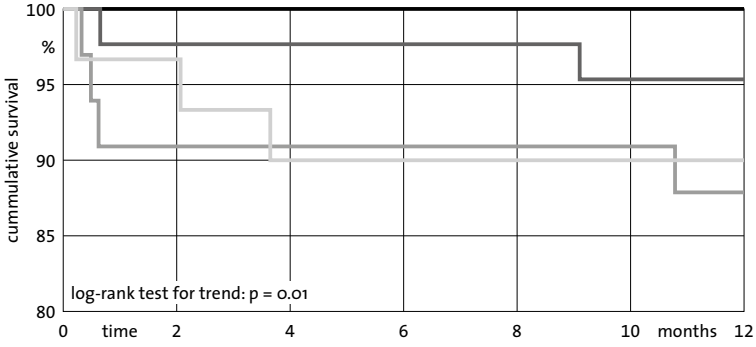
Linear-by-Linear Association, P = 0.005

SUPPLEMENTAL FIGURE 3A Kaplan-Meier curves for survival stratified by AKI stage during the first year after transplantation. No induction therapy.



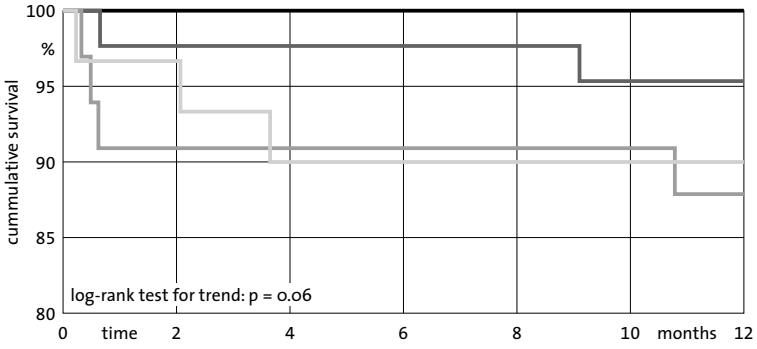
no AKI	12	12	12	12	12	12	12
AKI stage I	43	42	42	42	42	41	41
AKI stage II	33	30	30	30	30	30	29
AKI stage III	30	29	27	27	27	27	27

SUPPLEMENTAL FIGURE 3B Kaplan-Meier curves for survival stratified by AKI stage during the first year after transplantation. Induction therapy.



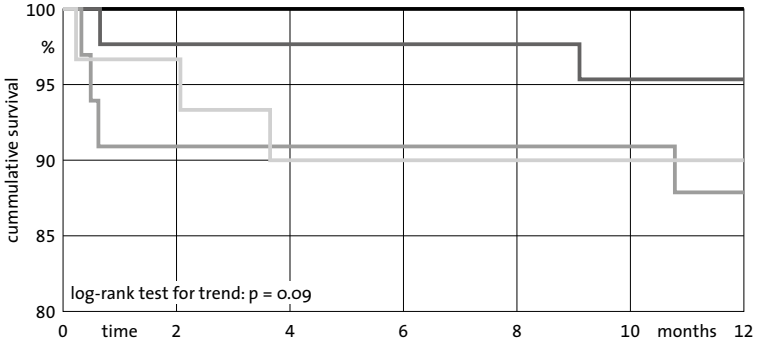
no AKI	114	109	108	108	107	105	104
AKI stage I	168	156	152	149	148	148	147
AKI stage II	86	78	76	76	76	76	75
AKI stage III	45	42	40	39	38	36	36

SUPPLEMENTAL FIGURE 4A Kaplan-Meier curves for survival stratified by AKI stage during the first year after transplantation. eGFR at baseline ≥ 60.



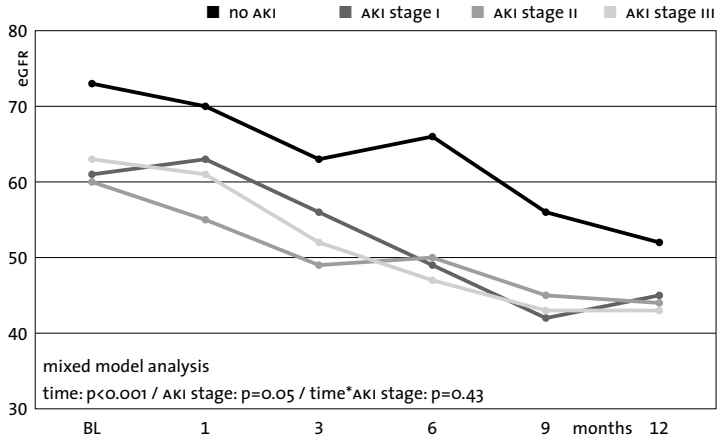
no AKI	80	77	76	76	76	74	73
AKI stage I	91	87	86	84	84	83	82
AKI stage II	66	62	61	61	61	61	60
AKI stage III	32	29	28	28	27	27	27

SUPPLEMENTAL FIGURE 4B Kaplan-Meier curves for survival stratified by AKI stage during the first year after transplantation. eGFR at baseline < 60.

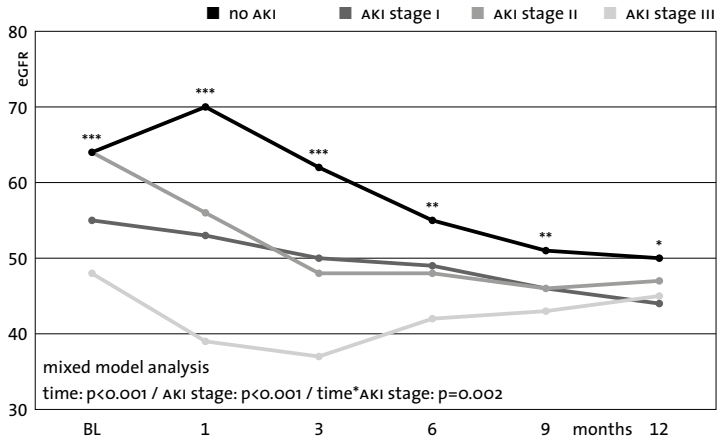


no AKI	46	44	44	44	43	43	43
AKI stage I	120	111	108	107	106	106	106
AKI stage II	53	46	45	45	45	45	44
AKI stage III	43	42	39	38	38	36	36

SUPPLEMENTAL FIGURE 5A Renal function during the first year after transplantation presented as median eGFR. No induction.



SUPPLEMENTAL FIGURE 5B Renal function during the first year after transplantation presented as median eGFR. Induction.



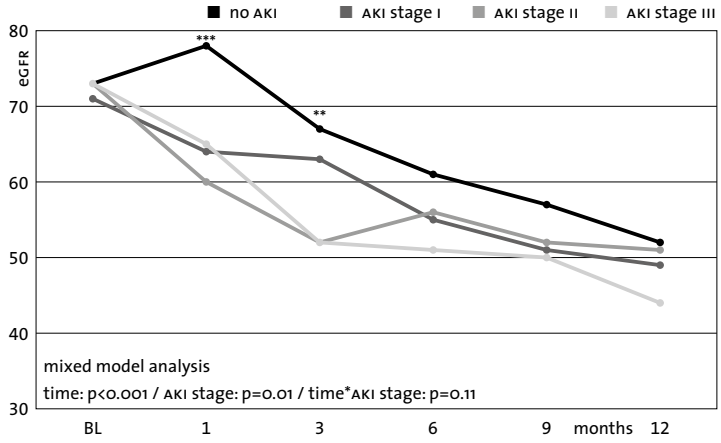
Differences in median eGFR at time of baseline, 1, 3, 6, 9 and 12 months are calculated by Kruskal-Wallis test.

* P < 0.05

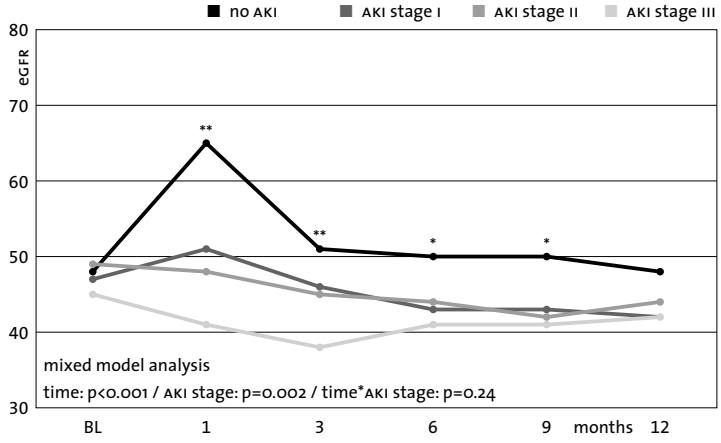
** P < 0.01

*** P < 0.001

SUPPLEMENTAL FIGURE 6A Renal function during the first year after transplantation presented as median eGFR. eGFR at baseline ≥ 60.



SUPPLEMENTAL FIGURE 6B Renal function during the first year after transplantation presented as median eGFR. eGFR at baseline < 60.



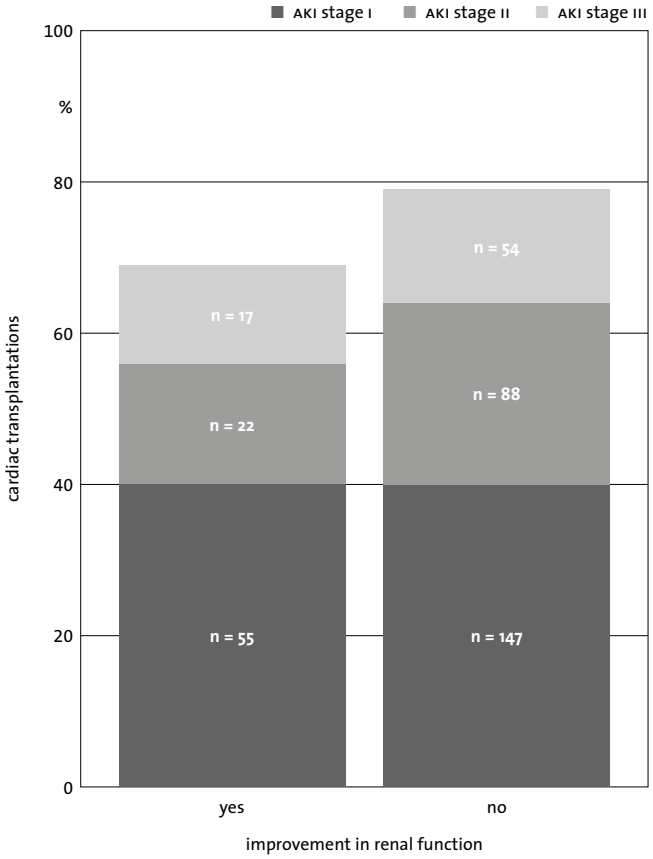
Differences in median eGFR at time of baseline, 1, 3, 6, 9 and 12 months are calculated by Kruskal-Wallis test.

* P < 0.05

** P < 0.01

*** P < 0.001

SUPPLEMENTAL FIGURE 7 Proportion of AKI categorized by improvement of renal function at one month.



Linear-by-Linear Association, P = 0.03

Renal function at 1 year after cardiac transplantation rather than acute kidney injury is highly associated with long-term patient survival and loss of renal function: a retrospective cohort study

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Transplantation international (2017) 30: 788-798

ABSTRACT

This study aimed to assess the association between acute kidney injury (AKI), renal function 1 year after transplantation, and long-term adverse outcomes after cardiac transplantation. A retrospective cohort study was performed including 471 adult cardiac transplantation recipients that survived the first postoperative year between 1984 and 2012. Primary outcome variables were long-term overall and renal survival. During the first postoperative week, 40% (n = 188) of the recipients developed AKI stage I, 22% (n = 104) stage II, and 13% (n = 63) stage III, and 4% (n = 17) required temporary renal replacement therapy (RRT). No crude association was found between the development of AKI and long-term mortality (P = 0.50) or chronic RRT dependence (P = 0.27). In multivariable analysis, only AKI requiring RRT was associated with an increased risk for mortality (HR = 2.59, 95%-CI = 1.17–5.73) and chronic RRT dependence (HR = 13.14, 95%-CI = 3.26–52.92). While less severe episodes of AKI did not affect the recipient's long-term prognosis, renal function 1 year after transplantation had a strong association with long-term outcome. An eGFR < 30 ml/min/1.73m² was independently associated with mortality (HR = 2.69, 95%-CI = 1.68–4.32) and an eGFR < 60 ml/min/1.73m² with chronic RRT dependence (eGFR 30–59: HR = 3.57, 95%-CI = 1.41–9.01; eGFR <30: HR = 16.53, 95%-CI = 5.72–47.78). In conclusion, besides AKI requiring RRT, less severe episodes of AKI have limited implications for the recipient's prognosis and long-term outcome after cardiac transplantation is strongly determined by the degree of renal impairment 1 year after transplantation.

INTRODUCTION

The first successful heart transplant in 1967 was a major step forward in the treatment of irreversible heart failure [1]. By the improvement in clinical practice and the development of immunosuppressive therapy, cardiac transplantation has evolved into a well-established life-sustaining treatment for those where less invasive treatments are no longer considered an option [2-7]. However, due to complications of surgery, underlying comorbid conditions and the use of nephrotoxic calcineurine inhibitors (CNIs), transplantation recipients are prone for the development of acute kidney injury (AKI) [8-14]. While it was initially assumed that AKI was a transient phenomenon without any clinical consequences, AKI is no longer considered an innocent bystander. Large epidemiologic studies performed in the general ICU population have shown that the development of AKI is strongly associated with an increased risk for mortality as well as progressive deterioration in renal function, which can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [15]. Furthermore, it is generally accepted that this risk extends way beyond hospital discharge and that experiencing an episode of AKI can significantly compromise a patient's long-term prognosis [16]. In cardiac transplantation recipients, AKI is highly frequent during the early postoperative phase and occurs in 25-76% of the recipients [9-12]. In addition, few studies have shown that the development of AKI, especially when renal replacement therapy (RRT) is required, significantly increases the risk for mortality and deterioration in renal function during the first postoperative years [8-14]. In spite of the studies that report on the incidence and short-term outcome, little is known about the long-term sequelae of AKI after cardiac transplantation. In view of the fact that the risk for complications and therefore mortality is the highest during the first year following transplantation, we performed a study with the objective to evaluate the association between the development of AKI in the early postoperative phase and the long-term overall and renal survival in cardiac transplantation recipients that survived the first postoperative year.

PATIENTS AND METHODS

Study design and population

This study describes the long-term sequelae of AKI after cardiac transplantation and is a continuation of a previous study performed by our

group. Materials and methods are similar to those described in the aforementioned study [14]. A retrospective cohort study was performed in the Erasmus MC (the Netherlands) evaluating all adult (age ≥ 18 years) cardiac transplantation recipients between 1984 and 2012 that survived the first postoperative year. Exclusion criteria were re-transplantation within 7 days and RRT preceding transplantation. Data were obtained from a computerized database, electronic patient records, and chart review. Patients that required temporary RRT were treated with either continuous venovenous hemofiltration (CVVH) or continuous arteriovenous hemodialysis (CAVHD). Patients that developed chronic RRT dependence during follow-up were treated with intermitted hemodialysis (IHD), peritoneal dialysis (PD), or preemptive kidney transplantation. RRT was prescribed by the attending nephrologist and delivered by the hemodialysis nursing team.

Immunosuppressive protocol

The immunosuppressive protocol has changed over the last 30 years and included usually induction therapy with polyclonal antithymocyte globulins (ATG) [7,14]. The use of induction therapy was first introduced in 1987 and in the majority of cases consisted of horse ATG (1987-2008) and rabbit ATG (2009 and thereafter). Maintenance therapy after the very early postoperative phase was based on CNIs either cyclosporine-based (1984-1999) or tacrolimus-based (2000 and thereafter). From 1984 to 1999, immunosuppression was complemented usually by prednisone monotherapy, which was replaced in 2000 by a combination of prednisone and/or mycophenolate mofetil. In patients that did not receive induction therapy, the use of CNIs was initiated peri- or directly postoperative, while it was delayed in those who did receive induction therapy. The postoperative time point when therapy with either cyclosporine or tacrolimus was initiated varied from 2 to 7 days after transplantation, which depended on the former immunosuppressive protocol. Target levels for tacrolimus were set at 10-16 µg/ml within the first 9 months and 6-10 µg/ml thereafter. Target levels for cyclosporine were set at 200-250 and 80-150 µg/ml, respectively.

Study endpoints and definitions

Primary study endpoints were overall and renal survival in cardiac transplantation recipients that survived the first postoperative year. Renal survival, censored for death, was defined as the time until start of chronic RRT or kidney transplant. The secondary study endpoint was renal function,

TABLE 1 Definition of AKI by the Kidney Disease Improving Global Outcome criteria.

AKI stage	serum creatinine
I	≥26.4 µmol/L within 48 hours, or; 1.5 to 2.0 times baseline within 7 days
II	2.0 to 2.9 times baseline
III	≥ 3.0 times baseline, or; increase in SCr to ≥ 353.6 µmol/L, or; initiation of renal replacement therapy

Modified from the Kidney Disease Improving Global Outcome: Acute Kidney Injury Workgroup [17].
Serum creatinine concentration at baseline was defined as the most recent outpatient serum concentration up to six months prior to transplantation (n = 400). When unavailable serum creatinine concentration at hospital admission was considered baseline (n = 71). Urine output criteria were not used, because required data was not available.

presented as estimated glomerular filtration rate (eGFR), 10 years after transplantation. This endpoint was chosen because of the decrease of cases during follow-up. To identify whether there was an association between AKI and the aforementioned endpoints, all analyses were stratified by the development of AKI defined and staged by the Kidney Disease Improving Global Outcome (KDIGO) criteria [17] (table 1) or AKI requiring RRT within the first 7 days following transplantation. Additional analysis was performed for long-term overall and renal survival stratified by renal function 1 year following transplantation. To identify whether the type of immunosuppressive medication (cyclosporine versus tacrolimus) or the period in which transplantation was performed (before the year 2000 vs. 2000 and thereafter) did affect the primary endpoints, subgroup analyses were performed. Due to the limited time of follow-up, these subgroup analyses were restricted to a maximum follow-up time of 10 years. To identify other potential predictors for mortality, chronic RRT dependence and renal function 10 years after transplantation, uni- and multivariable analyses were performed including demographic and clinical characteristics presented in table 2. For the evaluation of renal function after transplantation, serum creatinine concentrations were collected at baseline, days 0-7, and from then on every successive year during follow-up. Baseline serum creatinine concentration was defined as the most recent outpatient concentration

TABLE 2 Clinical and demographic characteristics of study population (n = 471).

age at transplantation in years	51 (42–56)
male gender	371 (78.8)
BMI in kg/m²	23.1 (21.0–25.2)
eGFR stage at baseline in ml/min/1.73m²	
baseline	61 (48–73)
year one	47 (38–58)
primary cardiac disease	
cardiomyopathy	208 (44.2)
ischemic cardiac disease	243 (51.6)
valvular disease	20 (4.2)
comorbid conditions	
diabetes mellitus	28 (5.9)
hypertension	44 (9.3)
previous thoracic surgery	129 (27.4)
hemodynamic support	
inotropic medication	116 (24.6)
IABP	35 (7.4)
LVAD	13 (2.8)
ECMO	2 (0.4)
urgency status on waiting list	
elective	243 (51.6)
urgent	140 (29.7)
unknown	88 (18.7)
days on waiting list	131 (44–300)
hospitalized before transplantation	183 (38.9)
donor	
age in years	32 (21–43)
male gender	252 (53.5)
donor cause of death	
trauma	213 (45.2)
CVA/SAB	237 (50.3)
other	18 (3.8)
unknown	3 (0.6)
time of ischemia donor heart in minutes	166 (142–197)
transplantation complication	
none	371 (78.8)
RV failure**	36 (7.6)
reoperation	42 (8.9)
overall graft failure**	7 (1.5)
other*	15 (3.2)
induction therapy	362 (76.9)

TABLE 2 *continued*

CNI at one year	
cyclosporine	348 (73.9)
tacrolimus	123 (26.1)
AKI stage	
no AKI	116 (24.6)
stage I	188 (39.9)
stage II	104 (22.1)
stage III	63 (13.4)
AKI requiring RRT	17 (3.6)
length of ICU stay in days	3 (2–4)
length of hospital stay in days	23 (17–33)

Continuous variables are presented as median and interquartile range and categorical variables are presented as number and percentage.

* Transplantation complications categorized as "other" included haemodynamic instability caused by perioperative bleeding, cardiac arrest, under dosing of inotropic medication, pacemaker malfunction, fluid overload, acute rejection and instability of an unknown cause. In two cases it was not possible to close the thoracic cavity directly after transplantation procedure.

** Right ventricle and primary graft failure were defined by the International Society for Heart and Lung Transplantation consensus guidelines [33].

up to 6 months prior to transplantation. When unavailable, the serum creatinine concentration at hospital admission was considered baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula adjusted for age and gender [18]. Patients were grouped according to their eGFR at baseline and at year one based on the Kidney Disease Outcomes Quality Initiative guidelines [19]. For multivariable analysis, eGFR at baseline was categorized as ≥ 60 or < 60 ml/min/1.73m², due to the low number of recipients with an eGFR ≥ 90 or < 30. For the same reason, eGFR at year one was categorized as ≥ 60, 30– 59, or < 30, due to the low number of recipients with an eGFR ≥ 90 or < 15. The study was approved by the medical ethical review board of the Erasmus MC.

Statistical analyses

Continuous parameters were expressed as median and interquartile range and compared by Mann– Whitney U test or Kruskal-Wallis test. Categorical parameters were expressed as number and percentage and compared by Fisher's exact test or chi-square test. Kaplan-Meier curves stratified by AKI

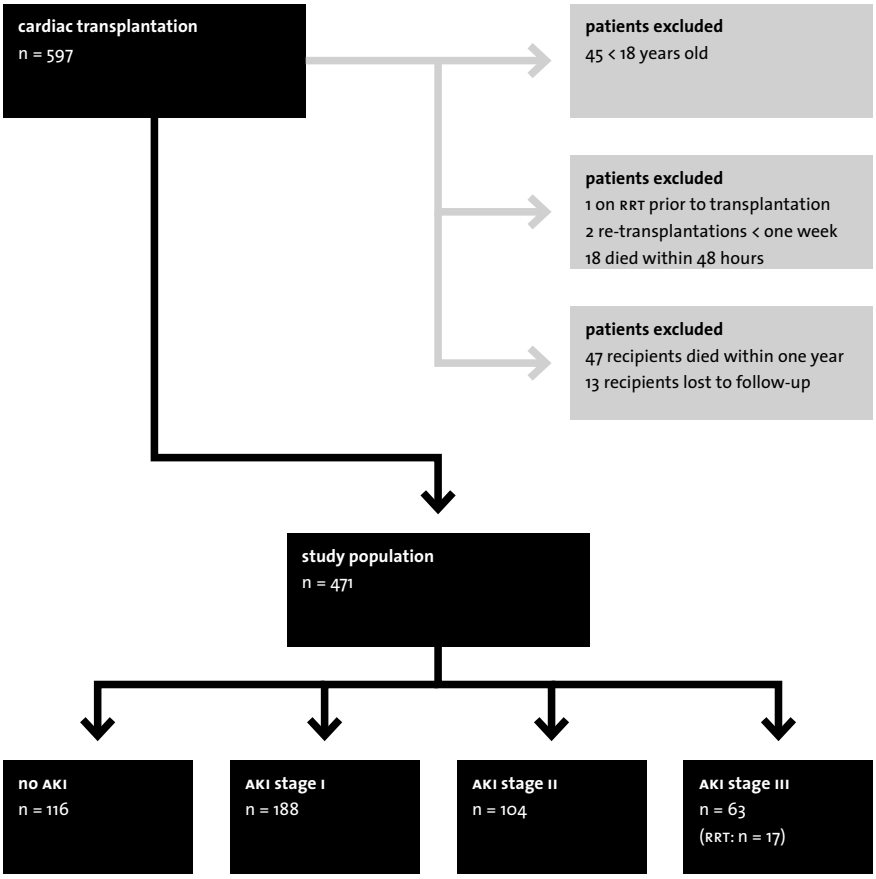
stage, AKI requiring RRT, or renal function at year one were constructed for the evaluation of overall and renal survival. Differences pooled over strata were compared by log-rank test and log-rank test for trend. Multivariable Cox proportional hazards analyses were performed for identification of parameters associated with mortality or chronic RRT dependence. Furthermore, general linear model analysis was performed for the association with eGFR 10 years after transplantation. All multivariable models were constructed by a manually stepwise manner. Step 1: All parameters with a P < 0.2 were included in the model. Step 2: All parameters with a P > 0.1 were deleted one by one. Step 3: Parameters not selected at step 1 were individually evaluated in order from lowest to highest P -value as result from univariable analysis and included in the model when statistical significant (P < 0.05). The potential difference in renal function (eGFR) over time was objectified making use of linear mixed-model analyses. Two-tailed P < 0.05 was considered significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL, USA) and GRAPHPAD PRISM version 5.0a for Mac (GraphPad Software, La Jolla, CA, USA).

RESULTS

Study population and characteristics

During the study period, 597 recipients underwent cardiac transplantation in the Erasmus MC, of which 45 recipients were under 18 years old, two required re-transplantation within 1 week, 18 died within 48 hour, and one recipient required RRT preliminary to transplantation, respectively. Of the remaining 531 recipients that constituted the initial study cohort, 471 survived the first postoperative year of which 355 (75.4%) met the AKI criteria during the first postoperative week. One hundred and eighty-eight recipients (39.9%) developed AKI stage I, 104 (22.1%) stage II, and 63 (13.4%) stage III, respectively. Of those who developed stage III, temporarily support by RRT was required in 17 (3.6%) recipients (figure 1). Thirteen recipients were treated with CVVH and four with CAVHD with a median duration of 5 (IQR: 3-17) days. Demographic and clinical characteristics of the study population are presented in table 2. Extended information on the demographic and clinical characteristics of the initial study cohort can be found in supplemental table 2. The median age in the study population was 51 years (IQR: 42-56) and 371 (78.8%) of the recipients were of male gender. Median eGFR

FIGURE 1 Flowchart of study population stratified by AKI stage.

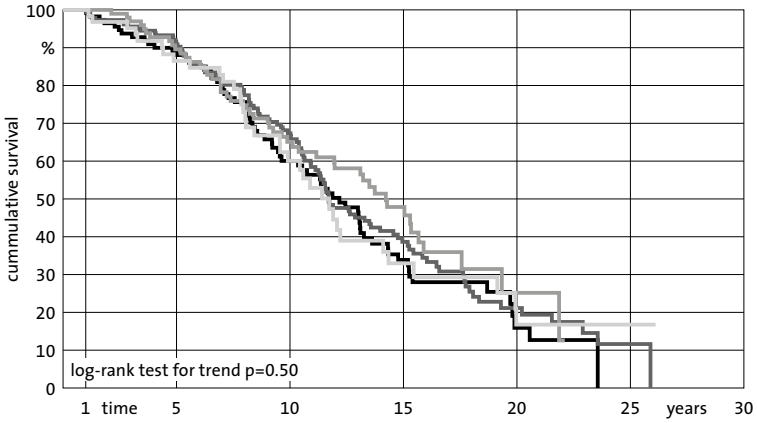


at baseline was 61 (IQR: 48-73) ml/min/1.73m² and 47 (IQR: 38-58) 1 year after transplantation. At 1 year, four recipients had an eGFR < 15, of which two were treated with IHD and one with PD and the fourth recipient did not receive chronic RRT yet.

AKI and long-term overall survival

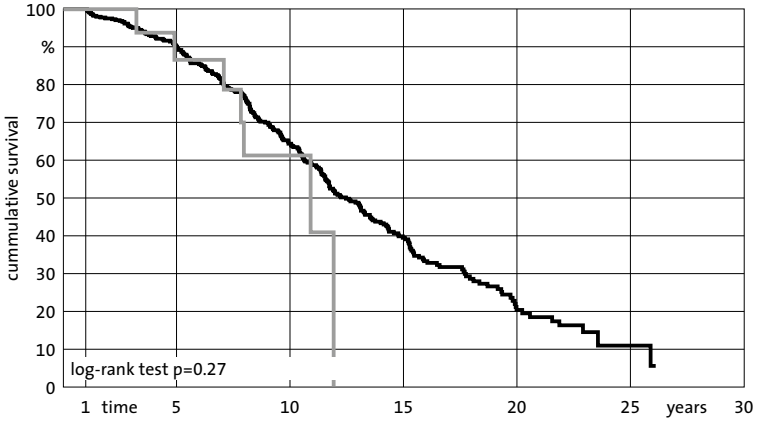
Median follow-up was 9.5 (IQR: 5.6-13.7) years with a maximum of 26 years and 258 deaths were observed during follow-up. The most frequent cause of death was sepsis (n = 50, 19.4%) followed by malignancy (n = 41, 15.9%), graft failure: chronic failure or acute myocardial infarction (n = 31, 12.0%), hypovolemic shock (n = 16, 6.2%), rejection (n = 12, 4.7%), cerebrovascular

FIGURE 2A Kaplan-Meier curves for long-term overall survival. Analysis stratified by AKI stage.



■ no AKI	116	92	51	23	5	0
■ AKI stage I	188	151	87	39	13	2
■ AKI stage II	104	83	49	23	3	0
■ AKI stage III	63	49	26	9	4	0

FIGURE 2B Kaplan-Meier curves for long-term overall survival. Analysis stratified for RRT in the first 7 postoperative days.



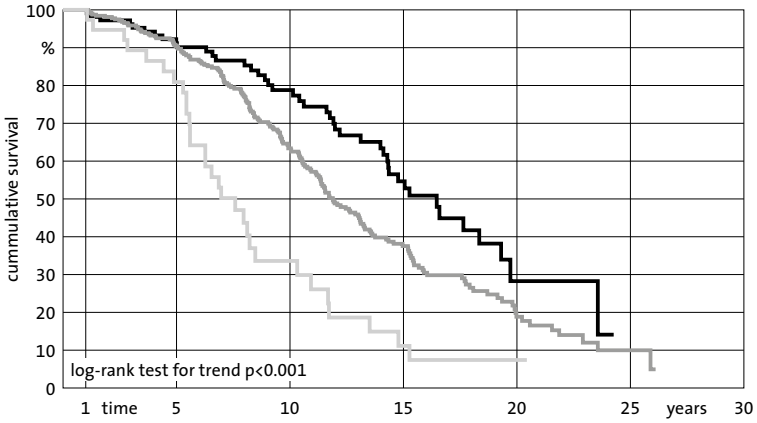
■ no RRT	454	363	209	94	25	4
■ RRT	17	12	4	0	0	0

TABLE 3 Multivariable Cox proportional hazards analysis for the association with mortality (n = 471).

	HR	95%-CI	P-value
age at transplantation in years	1.03	1.02–1.05	<0.001
year of transplantation	0.93	0.90–0.95	<0.001
eGFR stage at year one in ml/min/1.73m²			
≥60	1		
30–59	1.29	0.91–1.83	0.15
<30	2.69	1.68–4.32	<0.001
primary cardiac disease			
cardiomyopathy	1		
ischemic cardiac disease	1.36	1.04–1.78	0.03
valvular disease	1.69	0.94–3.04	0.08
AKI requiring RRT	2.59	1.17–5.73	0.02

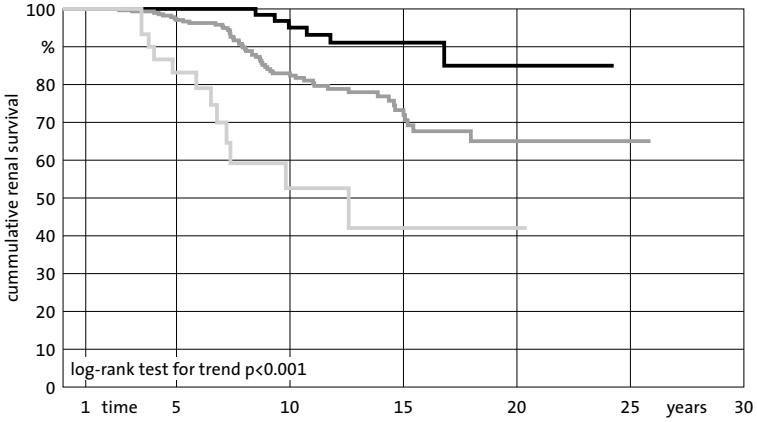
accident or other intracranial bleeding (n = 12, 4.7%), ESRD (n = 8, 3.1%), and other (n = 4, 1.6%). In 84 (32.6%) recipients, the cause of death was either unclear or considered multifactorial. Cumulative long-term overall and renal survival rates stratified by AKI stage or AKI requiring RRT are presented in figure 2A and B and supplemental table 2. No crude association was found between the development of AKI stratified by stage of severity (log-rank test for trend, P = 0.50) or AKI requiring RRT (log-rank test, P = 0.27) and an increased risk for mortality. Univariable analysis identified several demographic and clinical characteristics associated with mortality including age, year of transplantation, eGFR at baseline, eGFR at year one, ischemic and valvular cardiac disease as primary cardiac disease, hypertension, previous thoracic surgery, days on waiting list, and AKI requiring RRT. Factors independently associated with an increased risk for mortality were higher age, an eGFR < 30 ml/min/1.73m² at 1 year, ischemic cardiac disease, and AKI requiring RRT (table 3). A protective factor was a more recent year of transplantation. Additional, overall survival curves stratified by renal function 1 year after transplantation are presented in figure 3A and show a significant increased risk for mortality in recipients with lower renal function 1 year following transplantation.

FIGURE 3A Kaplan-Meier curves for long-term overall survival stratified by renal function (eGFR) at year one.



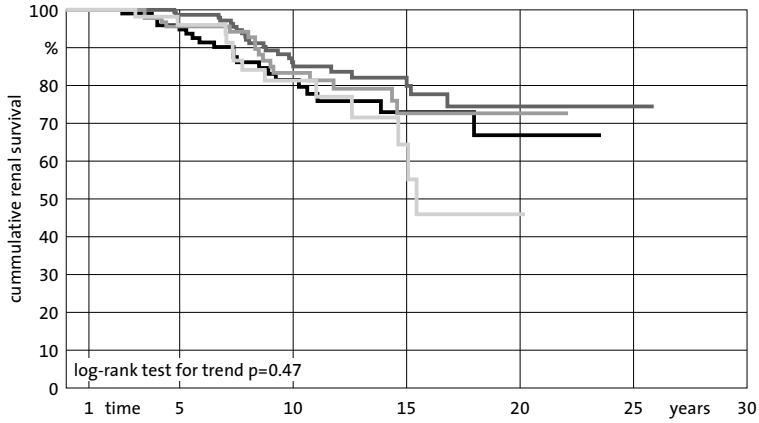
eGFR ≥60	102	81	50	28	5	0
eGFR 30–59	323	259	148	62	19	4
eGFR <30	46	35	15	4	1	0

FIGURE 3B Kaplan-Meier curves for long-term renal survival stratified by renal function (eGFR) at year one.



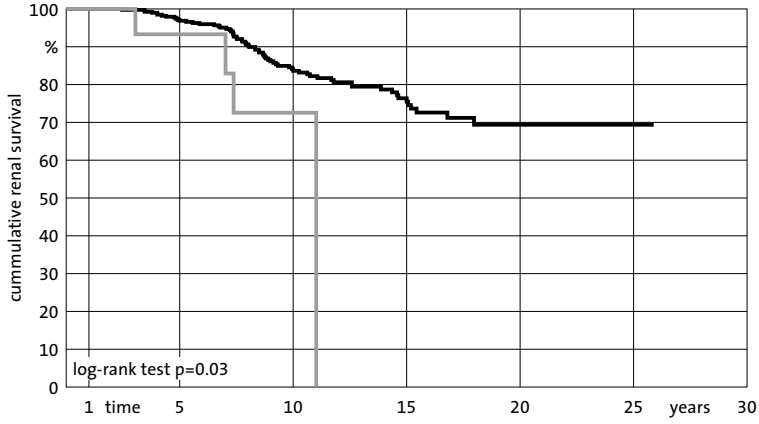
eGFR ≥60	102	81	49	28	5	0
eGFR 30–59	323	251	134	54	16	2
eGFR <30	43	29	12	4	1	0

FIGURE 4A Kaplan-Meier curves for long-term renal survival. Analysis stratified by AKI stage.



no AKI	116	87	46	22	5	0
AKI stage I	188	149	79	38	13	2
AKI stage II	103	80	45	19	2	0
AKI stage III	61	45	25	7	2	0

FIGURE 4B Kaplan-Meier curves for long-term renal survival. Analysis stratified for RRT in the first 7 postoperative days.



no RRT	452	351	191	86	22	2
RRT	16	10	4	0	0	0

TABLE 4 Multivariable Cox proportional hazards analysis for the association with chronic RRT dependence (n = 468*).

	HR	95%-CI	P-value
male gender	2.27	1.08–4.77	0.03
year of transplantation	0.84	0.79–0.90	<0.001
eGFR at year one in ml/min/1.73m²			
≥60	1		
30–59	3.57	1.41–9.01	0.007
<30	16.53	5.72–47.78	<0.001
AKI stage			
no AKI	1		
stage I	0.55	0.30–1.02	0.06
stage II	1.20	0.61–2.34	0.61
stage III	0.79	0.35–1.75	0.56
AKI requiring RRT	13.14	3.26–52.92	<0.001

* recipients (n = 3) on chronic RRT at year one were excluded.

AKI and long-term renal survival

During follow-up, a total of 74 recipients became chronic RRT dependent of which three recipients were excluded for further analyses because they were already RRT dependent at 1 year following transplantation. Regarding the RRT modality, 40 recipients received IHD, 31 PD, and three underwent pre-emptive kidney transplantation, respectively. Cumulative long-term renal survival censored for death stratified by AKI stage or requirement for RRT are presented in figure 4A and B and supplemental table 2. No crude association was found between the development of AKI of any stage of severity and long-term renal survival (log-rank for trend, P = 0.47). Stratified by the need for RRT, a crude association was found between AKI requiring RRT and long-term renal survival (log-rank, P = 0.03). Univariable analysis identified several demographic and clinical characteristics associated with chronic RRT dependence including year of transplantation, eGFR at year one, the preoperative use of inotropic medication, and urgent status on the waiting list, days on waiting list, donor age, tacrolimus usage at 1 year following transplantation and AKI requiring RRT. Factors independently associated with an increased risk for chronic RRT dependence were male gender, eGFR < 60 ml/min/1.73m² at 1 year, and AKI requiring RRT (table 4). A protective factor was a more recent year of transplantation. Additional, renal survival curves stratified by renal function 1

TABLE 5 Multivariable general linear model analysis of characteristics for the association with renal function (eGFR) 10 years after cardiac transplantation (n = 203*).

	ß	95%-CI	P-value
eGFR in ml/min/1.73m²			
baseline			
≥60	0		
<60	−5.56	−11.67;0.55	0.07
year one			
≥60	0		
30–59	−19.67	−26.78;−12.56	<0.001
<30	−34.12	−46,68;−21.56	<0.001
CNI at year one			
cyclosporine	0		
tacrolimus	17.91	6.8; 29.03	0.002
AKI requiring RRT	−29.72	−54.57;−4.87	0.02

* recipients alive at 10 years following transplantation

year after transplantation are presented in figure 3B and show a significant increased risk for chronic RRT dependence in recipients with lower renal function 1 year following transplantation (log-rank test for trend, P < 0.001). Subgroup analyses demonstrated that this significant difference was lost when a recipient was either transplanted after the year 2000 (log-rank test for trend, P = 0.6) or received tacrolimus as immunosuppressive medication (log-rank test for trend, P = 1.0), respectively (supplemental figures 3 and 4).

AKI and renal function 10 years after cardiac transplantation

The course of renal function (eGFR) during follow-up, stratified by AKI stage or RRT requirement, is presented in figure 5A and B. Linear mixed-model analyses demonstrated a significant decrease in eGFR during 10 years of follow- up (P < 0.001) and a significant difference in eGFR between AKI stages (P = 0.03). However, no significant difference in slope was demonstrated (P = 0.93). A similar pattern was demonstrated when stratified by AKI requiring RRT. Univariable analysis identified several demographic and clinical characteristics associated with renal function 10 years following transplantation including age, male gender, eGFR at baseline, eGFR at year one, and tacrolimus usage at 1 year following transplantation. Factors independently associated with lower renal function 10 years after transplantation were an eGFR < 60 ml/min/1.73m² and AKI requiring RRT (table 5). A protective factor was the use of tacrolimus at 1 year following transplantation.

FIGURE 5A Renal function during the 10 years after transplantation presented as median eGFR.
Renal function stratified by AKI stage.

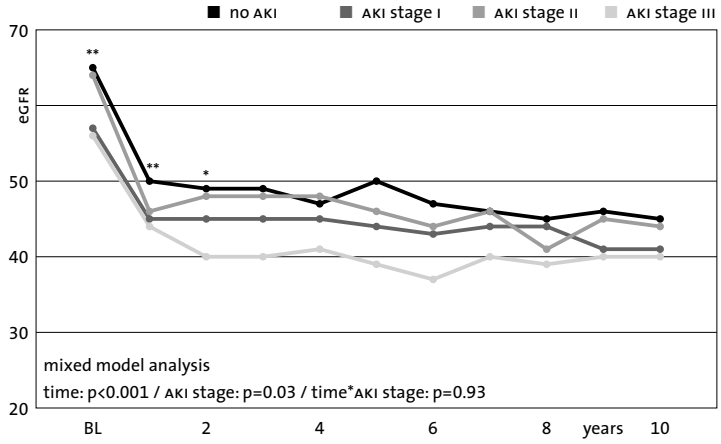
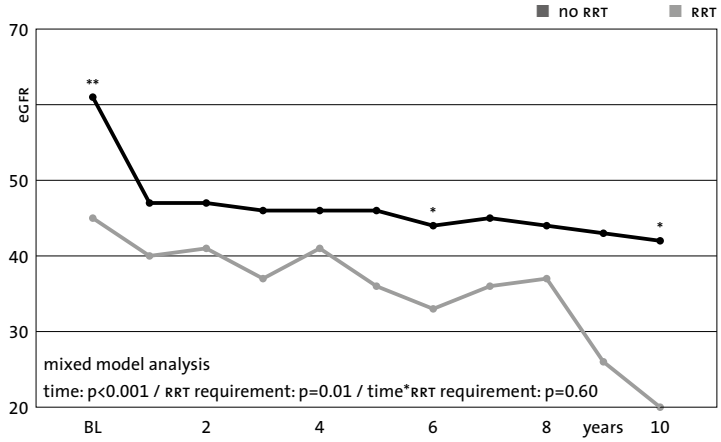


FIGURE 5B Renal function during the 10 years after transplantation presented as median eGFR.
Renal function stratified by AKI requiring renal replacement therapy.



Differences in median eGFR at time of baseline, 1-10 years are calculated by Kruskal-Wallis or Mann-Whitney U test.

* P < 0.05

** P < 0.01

DISCUSSION

This study is the continuation of a former study by Fortrie et al. published in 2015, which demonstrated that AKI is a highly frequent complication during the first week following cardiac transplantation that occurred in 76% of the recipients. Furthermore, it demonstrated that only a severe episode of AKI requiring RRT was associated with an increased risk for mortality during the first postoperative year, while AKI stage I or higher was strongly associated with an impaired renal function 1 year after transplantation [14]. The current results are conditional to one-year survival and this study addresses the long-term sequelae of AKI following cardiac transplantation with extensive follow-up with a maximum of 26 years. In contrast to what we expected, the main results of this study show that AKI defined and staged by the KDIGO AKI criteria is not associated with an impaired long-term prognosis in cardiac transplantation recipients. However, when temporary RRT was required, AKI was independently associated with an increased risk for long-term mortality and loss of renal function thereafter. Strikingly, after 12 years of follow-up none of the recipients that experienced AKI requiring RRT were alive, while after 25 years of follow-up cumulative survival in those who did not require RRT was still 10.7%, respectively. A similar pattern was demonstrated for the association between AKI requiring RRT and renal survival.

While only few studies have evaluated the association between AKI and outcome in the cardiac transplantation setting, none of them described its long-term sequelae. However, AKI has been extensively studied in a wide variety of clinical settings and two large meta-analyses by Coca et al. [16,20] evaluated the impact of AKI on either long-term overall as well as renal survival. They demonstrated in a pooled analysis that AKI, even in a mild form, was associated with an increased risk for long-term mortality and that patients with AKI requiring RRT had a threefold increased risk for long-term mortality compared with those without the need for RRT [16]. Furthermore, they demonstrated that patients that experienced AKI requiring RRT had an up to eightfold increased risk for chronic RRT dependence [20]. Thus, the results of our study suggest that the impact of AKI requiring RRT on the long-term prognosis after cardiac transplantation is of a similar order of magnitude compared with its impact in other clinical settings. When specifically focused on the outcome of AKI after cardiac surgery, two large single-center studies by Hobson et al. (n = 2973) and Lopez-Delgado et al.

(n = 2940) concluded that patients who developed AKI after general cardiac surgery had a significant higher risk for long-term mortality, which proportionally increased with AKI stage of severity as defined by the Risk, Injury, Failure, Loss, and ESRD (RIFLE) criteria [21-23]. In addition, a large nationwide study performed in Sweden (n = 29 330) [24] demonstrated that patients who received a coronary artery bypass graft (CABG) had an almost threefold and fourfold increased risk for ESRD in patients that developed AKI stage I and AKI stage II or greater, respectively, as defined by the Acute Kidney Injury Network (AKIN) criteria [25].

However, we did not demonstrate an association between less severe episodes of AKI and an increased risk for mortality or chronic RRT dependence. This may be partly explained by the results of the difference in sample size. However, it is unlikely that the smaller sample size alone accounts for the reported difference. Another explanation for this difference could be that, in contrast to the current study, the aforementioned studies included patients that deceased during the first year following an episode of AKI. The results of previous studies clearly show that the greatest difference in patient survival occurs within the first year following transplantation and that the survival curves thereafter show a more or less parallel slope [22,23]. Therefore, in order to prevent that the high incidence of death during the first year obscures the long-term results, we specifically decided to exclude recipients that died during the first postoperative year. Furthermore, in comparison with the current literature, our study population had a distinct lower median age and patients were less likely to suffer from comorbid conditions such as diabetes mellitus and hypertension [22,23], which most likely has a positive effect on the recipient's prognosis. On the other hand, it is possible that the AKI criteria do not offer the ideal measurement for an acute episode of renal deterioration in the cardiac transplantation setting due to the large proportion of recipients with pre-existing pre-renal kidney disease. As demonstrated previously, a large proportion of recipients (27%) showed a significant improvement (≥ 20%) in renal function compared with baseline during the first month following transplantation, which can lead to misclassification and obscure the prognostic value of the AKI criteria [14].

While a mild to modest episode of AKI does not seem to play a significant role in predicting long-term outcome, a strong association was found

between an impaired renal function at 1 year following transplantation and an increased risk for mortality, deterioration in renal function, and chronic dialysis dependence. These findings are in accordance with the results of previous studies, which showed that a decreased renal function at 1 year after transplantation was significantly associated with a continuing decline in the consecutive years thereafter [26] and an increased risk for mortality [27-29]. Furthermore, the greatest degree of deterioration in renal function occurs within the first year following transplantation after which a stable or slow deterioration in renal function occurs [29-31]. As demonstrated previously, the development of AKI was in fact independently associated with a the decrease in renal function during the first year following transplantation creating a paradox as renal function at 1 year but not AKI in the week after cardiac transplantation was associated with overall and renal survival. However, at 12 months after transplantation, the differences in eGFR between the AKI groups were relatively small with a tendency to converge, which could be partly explained by adjustments in CNI dosing to lower trough levels in the AKI group. In addition, the relation between AKI stage and survival post-transplantation was most pronounced within the first 6 months. Therefore, our results support the contention that the negative effects of even severe post-transplantation AKI become irrelevant after 1 year, unless RRT was needed. Our data strongly advocate the importance of conserving renal function after transplantation, which shows the greatest decrease within the first year even in the no AKI group [14].

The current study has several limitations, which need to be considered for interpretation of the results. First, the retrospective observational study design lacks the ability to identify a causal relationship. However, the data related to cardiac transplantation recipients is carefully and for the most part prospectively collected in the Erasmus MC. In addition, because of the large study population and extensive and in-depth evaluation of the patient records, multivariable analyses were performed to rule out confounding or modifying effects as far as possible. Second, the single-center study design has its inherent drawbacks and it is not known whether the results can be transposed to other cardiac transplantation populations. For instance, our study population contained a low proportion of recipients with DM, hypertension, and previous thoracic surgery prior to transplantation compared with cardiac transplantation recipients in the USA [32]. The

long inclusion period may offer a possible explanation, because the selection criteria for cardiac transplantation during the early study period were much more strictly compared to the criteria nowadays. Furthermore, underreporting is possible because of the retrospective nature of the study. Third, as aforementioned the current study has a long period of inclusion, which could significantly affect the results of this study due to improvement in medical care, a difference in selection criteria and immunosuppressive regime during the study period. Therefore, the effect of the year of transplantation was evaluated and included in the multivariable model, when applicable, to adjust for difference in study period and additional subgroup analyses were performed stratified by the type of immunosuppressive medication (tacrolimus versus cyclosporine) or the period in which transplantation was performed (before the year 2000 vs. 2000 and thereafter). Interestingly, the effect of renal function at 1 year on overall and renal survival was lost in recipients transplanted after the year 2000 or treated with tacrolimus, respectively. However, due to the low number of events and limited follow-up, these subgroup analyses do not offer the possibility to draw conclusions yet and therefore further research is warranted.

In conclusion, the results of the current study demonstrate that AKI requiring RRT following cardiac transplantation is independently associated with an increased risk for long-term mortality and chronic dialysis dependence. However, when a less severe episode of AKI is experienced and the deterioration in renal function during the first postoperative year can be limited, the cardiac transplantation recipient has a relatively good long-term prognosis. Therefore, the results of the current study emphasize the need for prospective studies that focus on renoprotective strategies during the early postoperative phase and the years thereafter.

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SUPPLEMENTAL TABLE 1 Demographic and clinical characteristics of study population stratified by AKI stage.

	overall n = 531	excluded n = 119	study population n = 471	P-value
age at transplantation in years	51 (43–56)	53 (45–59)	51 (42–56)	0.08
male gender	415 (78.2)	44 (73.3)	371 (78.8)	0.32
BMI in kg/m²	23.1 (21.0–25.2)	22.7 (20.8–25.5)	23.1 (21.0–25.2)	0.79
eGFR stage at baseline in ml/min/1.73m²				
baseline	60 (48–73)	56 (42–71)	61 (48–73)	0.11
year one	47 (38–58)	–	47 (38–58)	–
primary cardiac disease				0.171
cardiomyopathy	242 (45.6)	34 (56.7)	208 (44.2)	–
ischemic cardiac disease	268 (50.5)	25 (41.7)	243 (51.6)	–
valvular disease	21 (4.0)	1 (1.7)	20 (4.2)	–
comorbid conditions				
diabetes mellitus	33 (6.2)	5 (8.3)	28 (5.9)	0.41
hypertension	52 (9.8)	8 (13.3)	44 (9.3)	0.35
previous thoracic surgery	149 (28.1)	20 (33.3)	129 (27.4)	0.36
hemodynamic support				
inotropic medication	133 (25.0)	17 (28.3)	116 (24.6)	0.53
IABP	39 (7.3)	4 (6.7)	35 (7.4)	1.00
LVAD	14 (2.6)	1(1.7)	13 (2.8)	1.00
ECMO	2 (0.4)	0 (0.0)	2 (0.4)	1.00
urgency status on waiting list				0.05
elective	284 (53.3)	41 (68.3)	243 (51.6)	–
urgent	151 (28.4)	11 (18.3)	140 (29.7)	–
unknown	96 (18.1)	8 (13.3)	88 (18.7)	–
days on waiting list	144 (45–320)	281 (81–485)	131 (44–300)	0.003
hospitalized before transplantation	206 (38.8)	23 (38.3)	183 (38.9)	1.00
donor				
age in years	33 (22–43)	42 (24–51)	32 (21–43)	0.001
male gender	276 (52.0)	24 (40.0)	252 (53.5)	0.06
donor cause of death				0.29
trauma	234 (44.1)	21 (35.0)	213 (45.2)	–
CVA/SAB	275 (51.8)	38 (63.3)	237 (50.3)	–
other	19 (3.6)	1 (1.7)	18 (3.8)	–
unknown	3 (0.6)	0 (0.0)	3 (0.6)	–
time of ischemia donor heart in minutes	169 (143–201)	180 (150–229)	166 (142–197)	0.01*

SUPPLEMENTAL TABLE 1 *continued*

	overall n = 531	excluded n = 119	study population n = 471	P-value
transplantation complication				<0.001
none	405 (76.3)	34 (56.7)	371 (78.8)	–
RV failure**	45 (8.5)	9 (15.0)	36 (7.6)	–
reoperation	47 (8.9)	5 (8.3)	42 (8.9)	–
overall graft failure**	12 (2.3)	5 (8.3)	7 (1.5)	–
other***	22 (4.1)	7 (11.7)	15 (3.2)	–
induction therapy	413 (77.8)	51 (85.0)	362 (76.9)	0.19
CNI at one year				
cyclosporine	348 (73.9)	–	348 (73.9)	–
tacrolimus	123 (26.1)	–	123 (26.1)	–
AKI stage				0.34
no AKI	126 (23.7)	10 (16.7)	116 (24.6)	–
stage I	211 (39.7)	23 (38.3)	188 (39.9)	–
stage II	119 (22.4)	15 (25.0)	104 (22.1)	–
stage III	75 (14.1)	12 (20.0)	63 (13.4)	–
AKI requiring RRT	25 (4.7)	8 (13.3)	17 (3.6)	0.004
length of ICU stay in days	3 (2–4)	4 (2–8)	3 (2–4)	0.05
length of hospital stay in days	23 (17–33)	24 (13–34)	23 (17–33)	0.59

Continuous variables are presented as median and interquartile range and compared by Mann-Witney U test. Categorical variables are presented as number and percentage and compared by Fisher's exact test.

* Overall population consists of recipient's ≥18 years old, survived the first postoperative 48hrs, not on RRT prior to transplantation and did not receive re-transplantation within one week.

** Transplantation complications categorized as "other" included haemodynamic instability caused by perioperative bleeding, cardiac arrest, under dosing of inotropic medication, pacemaker malfunction, fluid overload, acute rejection and instability of an unknown cause. In 2 cases it was not possible to close the thoracic cavity directly after transplantation procedure.

*** Right ventricle and primary graft failure were defined by the International Society for Heart and Lung Transplantation consensus guidelines [33].

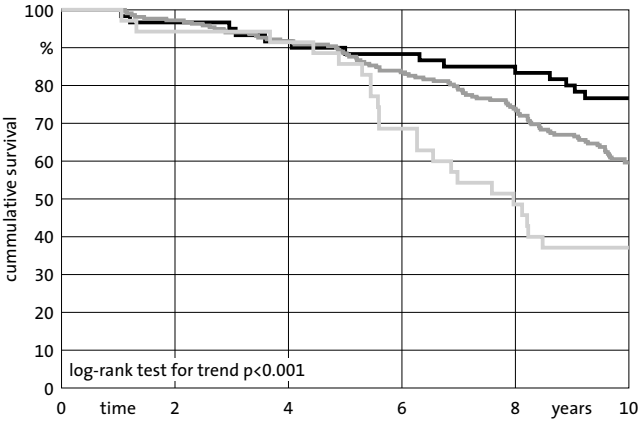
SUPPLEMENTAL TABLE 2 Long-term overall and renal survival in cardiac transplantation recipients that survived the first postoperative year.

	overall survival (%)					renal survival (%)				
	5 yr	10 yr	15 yr	20 yr	25 yr	5 yr	10 yr	15 yr	20 yr	25 yr
overall* (n = 471)	89.8	64.1	38.9	20.0	10.6	96.7	83.7	75.6	68.7	68.7
AKI stage										
no AKI (n = 116)	90.9	60.1	33.9	15.9	0.0	94.8	81.5	72.9	66.9	–
stage I (n = 188)	91.5	67.4	38.7	21.1	11.6	98.7	86.2	82.1	74.5	74.5
stage II* (n = 104)	89.6	65.1	47.9	25.2	–	95.6	83.3	72.7	72.7	–
stage III* (n = 63)	86.5	60.0	33.0	16.8	16.8	96.0	81.3	64.4	46.0	–
AKI requiring RRT										
no RRT (n = 454)	89.9	64.3	39.3	20.2	10.7	96.6	84.1	76.4	69.4	69.4
RRT* (n = 17)	86.5	61.2	0.0	0.0	0.0	93.3	72.6	0.0	0.0	0.0

Data are given as percentage of cumulative overall survival and renal survival at 5, 10, 15, 20, 25 years stratified by AKI stage or requirement of RRT.

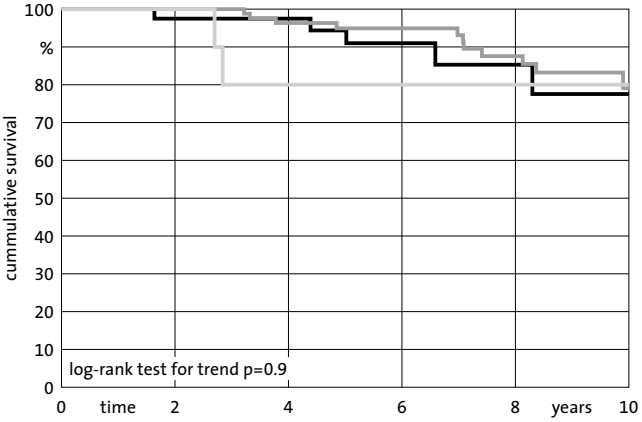
* Overall population for renal survival analysis included 468 recipients because 3 recipients received chronic RRT at one year post-transplantation (AKI stage II, n = 103; AKI stage III, n = 61; AKI requiring no-RRT, n = 452; AKI requiring RRT, n = 16)

SUPPLEMENTAL FIGURE 1A Kaplan-Meier curves for survival stratified by renal function (eGFR) at year one. Era < 2000.



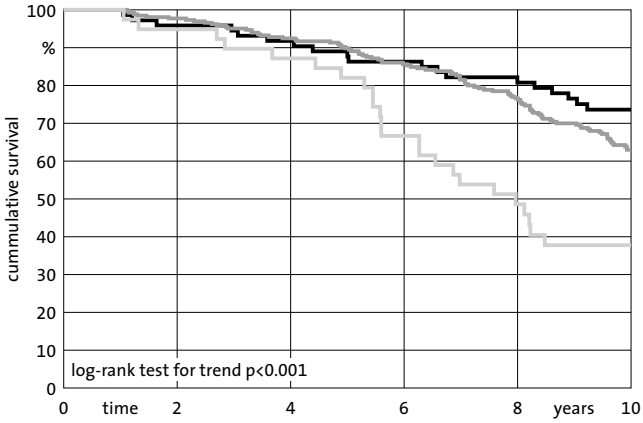
■ eGFR ≥60	60	58	55	53	51	46
■ eGFR 30–59	218	212	200	182	161	130
■ eGFR <30	35	32	32	24	17	13

SUPPLEMENTAL FIGURE 1B Kaplan-Meier curves for survival stratified by renal function (eGFR) at year one. Era ≥ 2000.



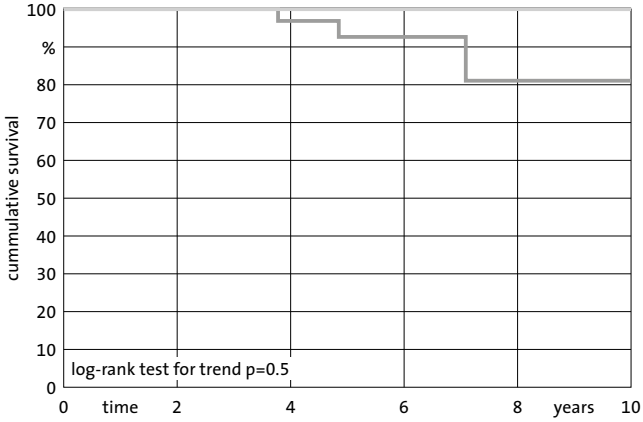
■ eGFR ≥60	42	37	31	20	11	4
■ eGFR 30–59	105	95	75	60	43	18
■ eGFR <30	11	10	5	5	2	2

SUPPLEMENTAL FIGURE 2A Kaplan-Meier curves for survival stratified by renal function (eGFR) at year one. Cyclosporine.



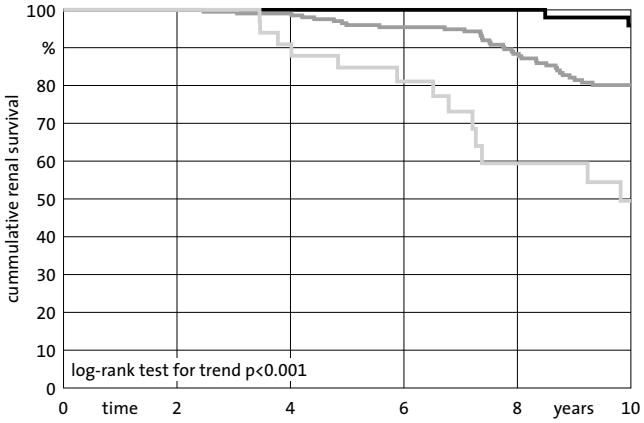
■ eGFR ≥60	73	70	67	63	58	48
■ eGFR 30–59	265	259	245	227	201	146
■ eGFR <30	39	37	34	26	18	14

SUPPLEMENTAL FIGURE 2B Kaplan-Meier curves for survival stratified by renal function (eGFR) at year one. Tacrolimus.



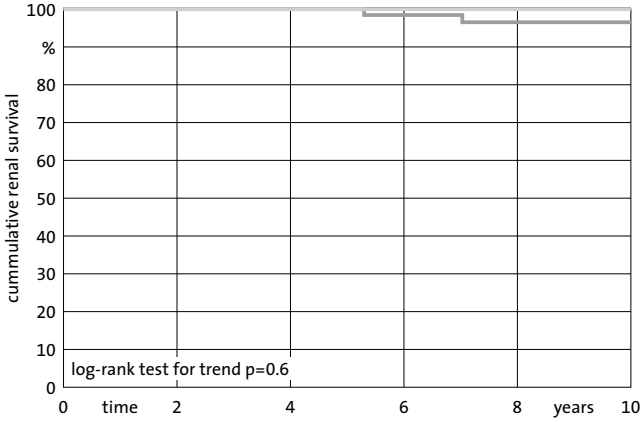
■ eGFR ≥60	29	25	19	10	4	1
■ eGFR 30–59	58	48	30	15	3	2
■ eGFR <30	7	6	3	3	1	1

SUPPLEMENTAL FIGURE 3A Kaplan-Meier curves for renal survival stratified by renal function (eGFR) at year one. Era < 2000.



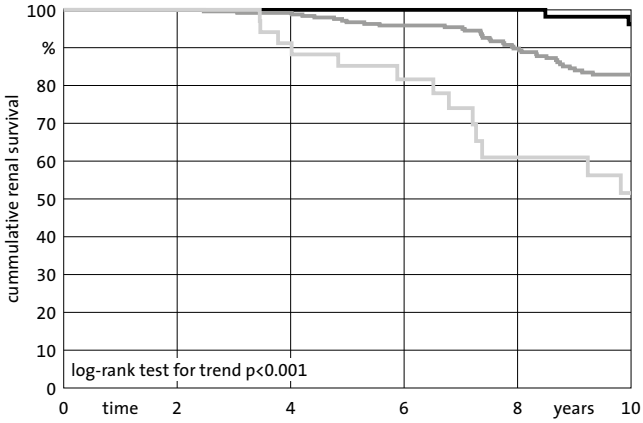
■ eGFR ≥60	60	58	55	53	51	45
■ eGFR 30–59	218	212	198	174	147	117
■ eGFR <30	35	33	30	22	13	10

SUPPLEMENTAL FIGURE 3B Kaplan-Meier curves for renal survival stratified by renal function (eGFR) at year one. Era ≥ 2000.



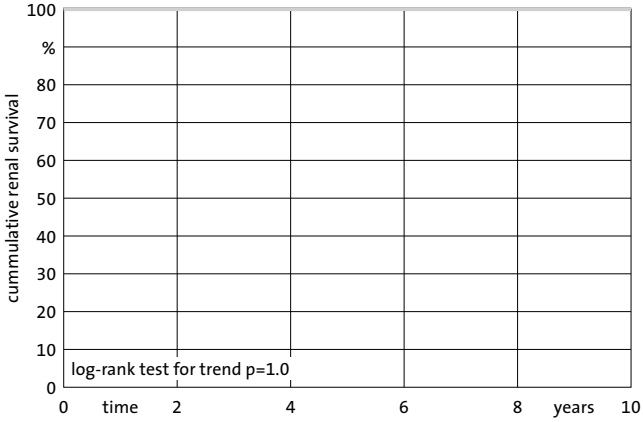
■ eGFR ≥60	42	37	31	20	11	4
■ eGFR 30–59	105	95	75	59	42	17
■ eGFR <30	8	7	3	3	2	2

SUPPLEMENTAL FIGURE 4A Kaplan-Meier curves for renal survival stratified by renal function (eGFR) at year one. Cyclosporine.



■ eGFR ≥60	73	70	67	63	58	47
■ eGFR 30–59	265	259	243	218	186	132
■ eGFR <30	37	35	31	23	14	11

SUPPLEMENTAL FIGURE 4B Kaplan-Meier curves for renal survival stratified by renal function (eGFR) at year one. Tacrolimus.



■ eGFR ≥60	29	25	19	10	4	2
■ eGFR 30–59	58	48	30	15	3	2
■ eGFR <30	6	5	2	2	1	1

Time of injury affects urinary biomarker predictive values for acute kidney injury in critically ill, non-septic patients

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Bmc Nephrology (2013) 14: 273-279

ABSTRACT

Background

The predictive value of acute kidney injury (AKI) urinary biomarkers may depend on the time interval following tubular injury, thereby explaining in part the heterogeneous performance of these markers that has been reported in the literature. We studied the influence of timing on the predictive values of tubular proteins, measured before the rise of serum creatinine (SCr) in critically ill, non-septic patients.

Methods

Seven hundred adult critically ill patients were prospectively included for urine measurements at four time-points prior to the rise in serum creatinine (T = 0, -16, -20 and −24 h). Patients with sepsis and or AKI at ICU entry were excluded. The urinary excretion of the proteins, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), which are up-regulated in the distal and proximal tubules, respectively, were measured as well as the constitutive cytoplasmatic enzymes, π- and α-glutathione-S-transferase (GST), which are released by the distal and proximal tubules, respectively.

Results

Five hundred and forty-three subjects were eligible for further analyses; however, 49 developed AKI in the first 48 h. Both NGAL ($P = 0.001$ at $T = -24$ vs. non-AKI patients) and KIM-1 ($P < 0.0001$ at $T = 0$ vs. non-AKI patients) concentrations gradually increased until AKI diagnosis, whereas π- and α-GST peaked at $T = -24$ before AKI ($P = 0.006$ and $P = 0.002$, respectively vs. non-AKI patients) and showed a rapid decline afterwards. The predictive values at $T = -24$ prior to AKI were modest for π- and α-GST, whereas NGAL sufficiently predicted AKI at $T = -24$ and its predictive power improved as the time interval to AKI presentation decreased (area under the receiver operating characteristic curve; AUC = 0.79, $P < 0.0001$). KIM-1 was a good discriminator at $T = 0$ only (AUC = 0.73, $P < 0.0001$).

Conclusions

NGAL, KIM-1, π- and α-GST displayed unique and mutually incomparable time dependent characteristics during the development of non-sepsis related AKI. Therefore, the time-relationship between the biomarker measurements and the injurious event influences the individual test results.

INTRODUCTION

There is an on-going search for biomarkers for AKI prediction. These biomarkers, may help, in the future, to guide preventive and therapeutic measures to benefit patients [1-13]. The AKI-induced up regulation of low molecular weight proteins, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), and their subsequent release and excretion into the urine have been studied in AKI patients and patients who are at risk for the condition [6-9,11,13-18]. Currently, NGAL, presumably from distal tubular origins at least in experimental AKI [19], is the most frequently described human AKI biomarker, although it is not perfect, and NGAL is considered as a reference standard [3,5,6,8-13,20,21]. Nevertheless, the literature possesses a marked heterogeneity in its reported AKI predictive power. The clinical value of KIM-1, a predominantly ischaemic proximal tubular injury marker [1,4,5], remains uncertain, with reports suggesting superiority [1,4] or inferiority [3,5,13] compared with other markers. The constitutive cytoplasmatic enzymes, π- and α-glutathione-S-transferase (GST), are detectable in the urine when the cell wall integrity of the distal and the proximal tubules are damaged, respectively [22]. However, the few clinical studies regarding the AKI predictive value of these enzymatic markers are conflicting [2,3,9,23] and the only comparison evaluating urinary NGAL was limited to a post cardiac surgery study [9]. Additionally, the available literature reports heterogeneous predictive performances for AKI biomarkers in different patient populations and conditions, such as adult vs. pediatric patients, sepsis vs. non-sepsis states, surgical vs. non-surgical conditions, developing vs. established AKI and fixed vs. non-fixed intervals between injury and sampling.

In this study we aimed to evaluate the predictive performance variation of urinary AKI biomarkers that precede the rise in serum creatinine (SCr). Additionally, we sought to study their individual kinetics as a function of time in non-septic patients, because predictive values and optimal cut-off levels for AKI markers may differ between septic and non-septic AKI [24]. In contrast to our previous study, which included AKI at ICU entry [11], the primary endpoint for the current study was AKI development within 48 h following ICU admission. Indeed, AKI prediction is more useful than confirming established AKI; however, many previous studies grouped together developing and established AKI, thereby potentially leading to predictive value overestimation [1-6,8-10,12,13,21].

METHODS

Setting

This was a prospective single center cohort study in a 30-bed closed format university hospital intensive care unit (ICU) in which general surgical, trauma, medical, neurological and neurosurgical, but not cardiac surgery, patients were treated. All consecutively admitted adult critically ill patients, between September 1, 2007, and April 1, 2008, were considered eligible. Exclusion criteria included the following: patients under 18 years of age, readmissions during the inclusion period, refusal of informed consent, a history of nephrectomy, documented chronic kidney disease (CKD) (> stage 3) or kidney transplantation and a sepsis diagnosis at the time of ICU entry. Sepsis and CKD were applied as exclusion criteria to avoid their confounding roles in biomarker expression. The study was approved by the Erasmus MC University Medical Centre Institutional review board (Rotterdam, the Netherlands). Deferred patient consent was used in combination with written informed consent that was obtained from the participants or their health care proxy within 48 h following ICU admission. In the consent refusal cases (n = 6, 0.9%), the collected urine specimens were appropriately destroyed. This study was a sub-study of a previously reported study [11].

Protocol, sample collection and processing

Demographic data were recorded, including the severity of illness scores, several renal and outcome parameters (such as the hospital discharge serum creatinine levels), the duration of ICU stay and the 28-day and in-hospital mortality rates. Serum creatinine values were available at the time of admission and at 6:00 am daily thereafter, until 72 h after entry. AKI diagnoses were approximated and calculated during admission and as close as possible 24 and 48 hours after admission. The serum creatinine levels were measured in the hospital's clinical chemical laboratory with a Roche enzymatic kit, (which provided similar results to a well-regarded reference method) based on isotope dilution mass spectrometry. Urinary output and fluid balances were also recorded. At ICU admission (T = 0), and at T = 4, 8, 24 hrs thereafter, urine samples were collected using a urine catheter. The samples were processed in the hospital's laboratory and the supernatants were stored at −80°C. NGAL (Triage® immunoassay, Biosite Inc. Alere, San Diego, CA, USA), KIM-1, π-GST, and α-GST (Argutus Medical, Dublin, Ireland) concentrations were measured using research-based immunoassays. The detection limits for the urine NGAL assays

were 2.6-4100 ng/ml. The assays' coefficient of variation was 13.9%. The π-GST, α-GST and KIM-1 assay detection limits were 3.12-100 ng/ml, 6.25-200 ng/ml and 0–10 ng/ml, respectively. These assays average coefficient of variation in this study were 4%, 3% and 1%, respectively.

Definitions

The baseline serum creatinine levels were defined as the steady state levels four weeks to six months prior to ICU admission. If these values were not available, the admission value was applied as the baseline. The sepsis criteria were a clinically suspected or confirmed infection, a temperature above 38.5°C or below 36.0°C, tachycardia (> 90 beats/min) and tachypnea (> 20/min) or necessity for mechanical ventilation, and leukocytosis > 12 $x10^9$/L or >10% bands, or leukopenia < 4 x109/L. AKI was defined using the acute kidney injury network (AKIN) classification for serum creatinine changes relative to a steady state baseline value (AKIN 0 = no-AKI, AKIN 1 = serum creatinine increase > 50% or an absolute serum creatinine rise of 0.3 mg/dL (= 26.5 μmol/L) compared to baseline, AKIN 2 = serum creatinine increase > 100% and AKIN 3 = serum creatinine increase > 200%) without using the urine output (UP) criteria. To plot the biomarker expression levels that preceded AKI, the time-points following ICU admission were recoded as the time-points preceding AKI. AKI occurred either at T = 24 or T = 48 following ICU admission. The initial AKI time-point was recoded as T = 0 and the available measurements preceding this time point were recoded relative to T = 0 (including T = −48, T = −44, T = −40, T = −24, T = −20 and T = −16 hrs). Fifty-six patients had more than one ICU admission; therefore, only the data from their first admission were used.

Statistical analysis

Patients were grouped according to whether they lacked AKI or had a developing AKI within the first 48 h of admission. Most continuous data were distributed non-normally (Kolmogorov-Smirnov test $P < 0.05$). We compared developing AKI patients and non-AKI patients using univariate analyses for continuous variables (Mann–Whitney U test) and categorical variables (using the $\chi 2$ or Fisher exact test). Two-tailed tests were used throughout. Receiver operating characteristics curve (ROC) analyses were used to assess the predictive value of biomarkers in developing AKI patients. The area under the curve (AUC), with 95% confidence intervals [95%-CI], was calculated and compared. Statistical analyses were performed with

the SPSS statistical software package, version 16.0 (SPSS, Chicago, IL, USA) for windows as well as MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium). The data were reported as numbers (percentages) or as medians (with interquartile ranges), where appropriate. Means and standard errors of the mean (SEM), however, were used in the time course graphs for the sake of clarity. A $P \leq 0.05$ was considered statistically significant, and exact values are presented throughout.

RESULTS

Patient characteristics

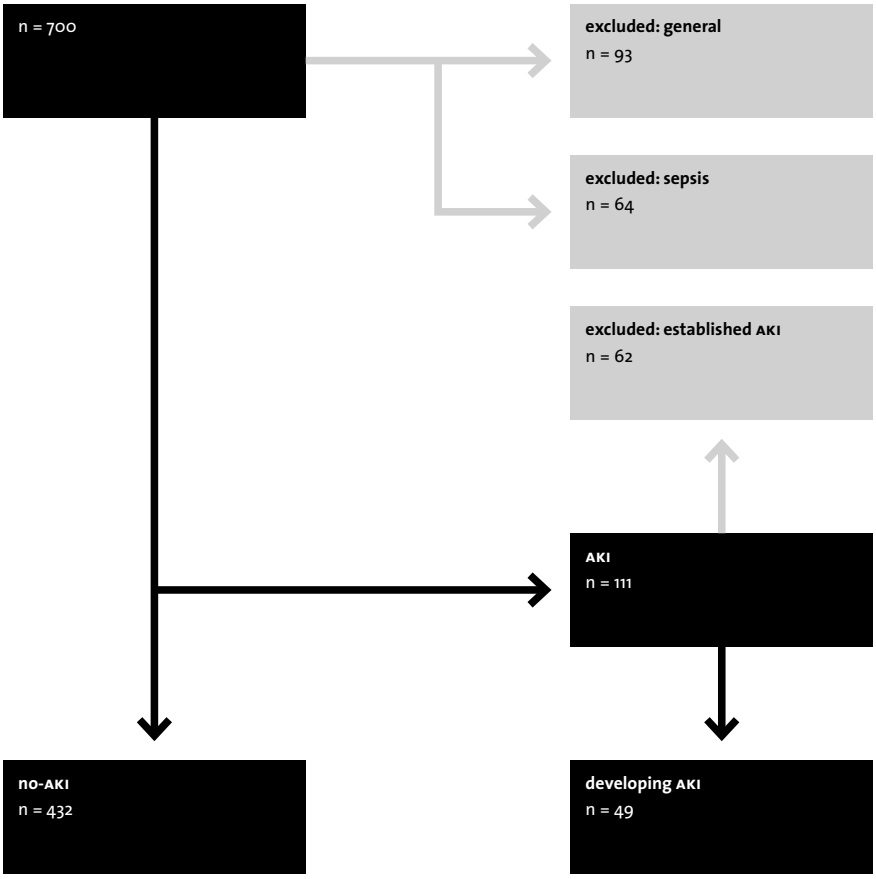
Seven hundred consecutive ICU admissions were included in the study. Six patients refused consent (0.9%), 6 patients had previously undergone a nephrectomy (0.9%), 56 admissions were counted as readmissions during the study period (8%) and 25 patients had chronic kidney disease (CKD) stage 3 or a kidney transplant (4%). Of the remaining 607 patients, 64 subjects were diagnosed with sepsis; therefore these patients were also excluded, leaving 543 cases for the final analysis. Out of the 111 patients with AKI within the first 48 hours of admission, 62 of these patients (56%) had already met the AKI criteria at the time of ICU entry, leaving 49 developing AKI subjects (figure 1). The admission diagnoses were subdivided into non-cardiac postoperative (n = 185), respiratory insufficiency (n = 110), subarachnoid or intracerebral bleeding (n = 99), multi-trauma (n = 42), isolated neurotrauma (n = 29), liver transplantation (n = 28), cardio pulmonary resuscitation (n = 26), haemorrhagic shock (n = 20), multi organ failure (n = 2) and lung transplantation cases (n = 1) with one missing diagnosis.

The developing AKI patients were older, more severely ill and more often male (table 1). Furthermore, the developing AKI patients had higher pre-admission baseline serum creatinine levels and a higher cumulative fluid balance within the first 24 h of ICU admission. At hospital discharge, SCr values were higher in patients who had an AKI episode compared with the non-AKI patients. Additionally, the 28-day and hospital mortality rates were higher as well in the AKI patients.

The biomarker patterns following ICU admission

The biomarker levels following ICU admission for the developing AKI patients and those without AKI are shown in figure 2A. This panel represents the not-recoded data. The up-regulated NGAL and KIM-1 protein concen-

FIGURE 1 Study cohort flow chart.



established AKI = AKI at the time of ICU admission
developing AKI = AKI developing at or 24 hours following admission

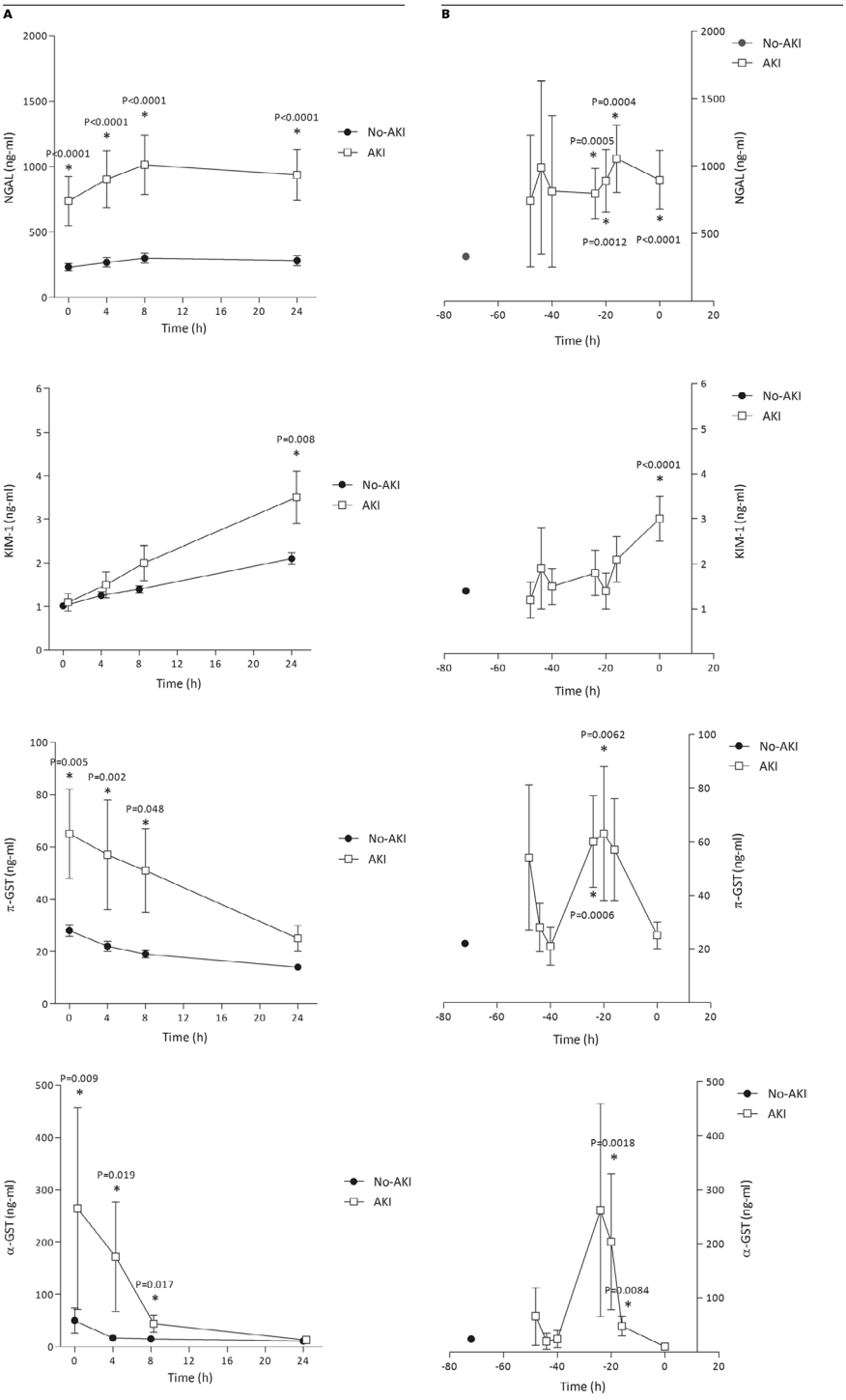
trations increased over the time following ICU admission, whereby NGAL increased right from the time of admission ($P < 0.0001$); the KIM-1 levels differentiated between the non-AKI and AKI at the T = 24 hour time point for the first time ($P = 0.008$). The KIM-1 concentrations in the non-AKI patients increased over the time following ICU admission. The constitutive enzyme concentrations, π- and α-GST, both decreased but remained higher up until 8 hours after admission in the AKI compared to the non-AKI patients ($P \leq 0.048$ and $P \leq 0.017$ respectively).

TABLE 1 Patient characteristics.

	non AKI (n = 432)	developing AKI (n = 49)	P-value
age, years	57 (25)	61 (25)	0.04
gender male, n (%)	243 (56)	38 (77)	0.004
BMI (kg/m²)	24.6 (4.8)	25.1 (4.4)	0.67
APACHE II	16 (9)	23 (11)	<0.001
SOFA	4 (4)	9 (6)	<0.001
admission diagnosis, n (%)			
medical	100 (23)	18 (36)	
surgical	215 (49)	20 (40)	
neurological	117 (27)	11 (22)	
renal characteristics			
baseline SCr (mg/dl)	0.74 (0.3)	0.85 (0.3)	0.002
UP (ml/kg/h)	1.1 (0.8)	0.9 (0.9)	0.32
FB (l)	1.9 (3.0)	4.3 (4.4)	<0.001
AKIN-stages, n (%)			
AKIN-1	–	34 (69)	
AKIN-2	–	11 (22)	
AKIN-3	–	4 (8)	
patients with CVVH, n (%)	–	3 (6)	
outcome			
SCr at hospital discharge	0.68 (0.2)	0.77 (0.6)	0.002
ICU days	3 (5)	7 (11)	<0.001
28-day mortality (%)	53 (12)	15 (30)	0.002
hospital mortality (%)	59 (13)	17 (34)	0.001

Median (IQR) or number of patients (percentage) where appropriate.

FIGURE 2 Biomarker patterns after ICU admission (A) and preceding AKI (B). Biomarker concentrations are expressed in ng/ml and data represent the mean (standard error of the mean; SEM). Mean biomarker concentrations in AKI patients vs. non-AKI patients at each time-point were compared using the Mann–Whitney U test (A) and the mean biomarker concentrations in AKI patients were compared to the pooled mean value of all available non-AKI measurements using the Mann–Whitney U test (B). Panel A represents the un-recoded data plotted against the time following ICU admission. Panel B represents the recoded data prior to the rise in SCr.


A
B
NGAL (ng-ml)
Time (h)
No-AKI
AKI
P<0.0001
P<0.0001
P<0.0001
P<0.0001
P=0.0004
P=0.0005
P=0.0012
P<0.0001
KIM-1 (ng-ml)
P=0.008
P<0.0001
π-GST (ng-ml)
P=0.005
P=0.002
P=0.048
P=0.0062
P=0.0006
α-GST (ng-ml)
P=0.009
P=0.019
P=0.017
P=0.0018
P=0.0084

The biomarker patterns preceding AKI

Figure 2B shows the pre-AKI biomarker patterns. All available non-AKI biomarker values were pooled to represent the non-AKI concentration in the graph represented at T = −72. The up-regulated proteins KIM-1 and NGAL gradual increased in concentration prior to the SCr increase. KIM-1, however, was different in the AKI patients compared with the non-AKI patients right at the time of AKI presentation (T = 0, P < 0.0001). This contrasted with NGAL, which displayed a quicker response with different concentrations in the AKI compared with the non-AKI patients, starting at 24 hours prior to the AKI presentation time (P = 0.0005). The constitutive enzyme concentrations, π- and α-GST, peaked at 24 and 20 hours prior to the times SCr rose (T = 0), respectively, compared with the non-AKI patients (P = 0.006 and P = 0.0018). After a sudden peak, the biomarker concentrations declined quickly prior to AKI presentation times.

AKI prediction

Table 2 shows the area under de curves (AUC's) for the prediction of developing AKI for each individual biomarker at the different time points. NGAL displayed the most consistent predictive performance, starting 24 hours prior to AKI presentation (AUC = 0.66, P = 0.0005) and increased closer to the AKI endpoint (AUC = 0.79, P < 0.0001). In contrast, KIM-1 only "predicted" AKI at the same time when the rise in SCr levels occurred for the first time (AUC = 0.73 P < 0.0001). However, the π- and α-GST predictive power was modest (AUC = 0.65 for both) even at their peak concentrations (24 and 20 hours prior to AKI, respectively).

TABLE 2 ROC curves for developing AKI predictions vs non-AKI patients.

biomarkers	time	AUC (95%-CI)	P-value
NGAL	T = −24	0.66 (0.57–0.75)	0.0005
	T = −20	0.66 (0.57–0.75)	0.001
	T = −16	0.68 (0.57–0.78)	0.0004
	T = 0	0.79 (0.73–0.85)	<0.0001
KIM-1	T = 0	0.73 (0.64–0.83)	<0.0001
π-GST	T = −24	0.65 (0.56–0.75)	0.0006
	T = −20	0.64 (0.54–0.73)	0.006
α-GST	T = −20	0.65 (0.56–0.75)	0.002

Median (IQR) or number of patients (percentage) where appropriate.

DISCUSSION

The present study shows that NGAL, KIM-1, π- and α-GST show unique and mutually incomparable time dependent characteristics during the development of non-sepsis related AKI. The time-relationships between the biomarker measurements and the injurious renal hit therefore influenced the individual predictive test results. The constitutive enzymes displayed a narrow time window of expression, whereas NGAL outperformed KIM-1 in its early expression levels prior to an AKI diagnosis.

The NGAL predictive value for (non-septic) AKI in this study is in accordance with other work [3,5,6,8-13,20,21,25]. The expression pattern of NGAL prior to the rise in SCr is early and its predictive power also increases closer to the AKI presentation time. This latter observation suggests that the time-to-injury relationship is important and should be obtained for a correct interpretation of its AKI predictive value. KIM-1's expression was less accurate and late (in relation to the time of SCr increase) compared with NGAL in the current study. This confirms the work by others who also evaluated adult critically ill patients [1,3,4,7,9]. Moreover, the predictive value of KIM-1, which only slowly increased in the time following renal injury, as our data suggest, is higher if the AKI has already developed, as in cardiac surgery, rather than if the AKI develops over the course of time, as in our study [1,4,5,9]. The rise in KIM-1 over time even when AKI (defined as a rise in SCr) does not develop can perhaps be explained by subclinical injury, because KIM-1 is a transmembrane glycoprotein exclusively present in the epithelial cells that survive after injury and facilitate necrotic cell debris phagocytosis [1,9]. This may look, at first sight, like a clinically irrelevant observation without direct implications. We believe, however, that this might imply the loss of renal reserve, which will most likely become relevant when the kidney suffers new injurious hits.

π- and α-GST were only modest AKI predictors in this population with slightly better or similar results compared with those reported in adult cardiac surgery patients (AUC = 0.54 [95% CI 0.42-0.66]) [9,26]. These data, however, were similar in another cohort of general critically ill patients [25]. In an older study, the markers were suggested to be superior to other enzymes AUC = 0.93 [0.74-0.99] and 0.89 [0.69-0.98] respectively [23]; however, these results were not reproduced in subsequent studies. Several other studies described their diagnostic performances in established AKI [2,26,27].

These results, however, are incomparable to the present data for these enzymatic markers, the sampling time in relation to the injurious hit seems to be especially critical for their ability to predict a rise in SCr at a later time point. This might make this category of biomarkers less well applicable in patients without a circumscribed time point of renal injury, such as is the case in general ICU patients. However, due to their sudden urine concentration changes, their applicability might be more appropriate in a setting of that monitors the renal toxic effects of drugs and contrast agents in the kidneys.

There are several limitations to the current results. Despite the large initial number of included patients, the developing AKI patient subset was relatively small, because 64% of the AKI patients had AKI at ICU entry and were thus excluded from the current analysis. The subset of patients with developing septic AKI was even smaller and did not allow for sufficient data analyses, although it would have been interesting to study the possible differences in biomarker expression between both septic related and non-septic related AKI. Despite the recognition that serum creatinine is a poor indicator of renal injury, (based on its varying tubular secretion levels among other reasons), it is still used in many studies [3,12,28]. Therefore, the usefulness of potentially more sensitive markers might be underestimated. We believe this phenomenon is reflected by our data, which indicate the presence of subclinical tubular injury in non-AKI patients (i.e., the increase in KIM-1 levels in non-AKI patients according to the AKIN classification). Urinary biomarkers can be used in non-anuric AKI only, therefore, narrowing their clinical applicability. Controversy exists on whether the correction for urinary creatinine concentrations is necessary for the interpretation of the results. We believe that normalization to urine creatinine concentration poses a unique limitation because AKI patients are not in a steady state of creatinine turnover. Furthermore, several authors have shown that this effort does not contribute much to the final outcomes [1,2,5,6,9,13,23].

CONCLUSIONS

Our current data suggest that the different biomarker expression patterns, such as up-regulated proteins and constitutive enzymes, and the time of sampling with respect to the actual time of cellular injury may partially explain the previously observed predictive value heterogeneity. These factors should be taken into account in future studies.

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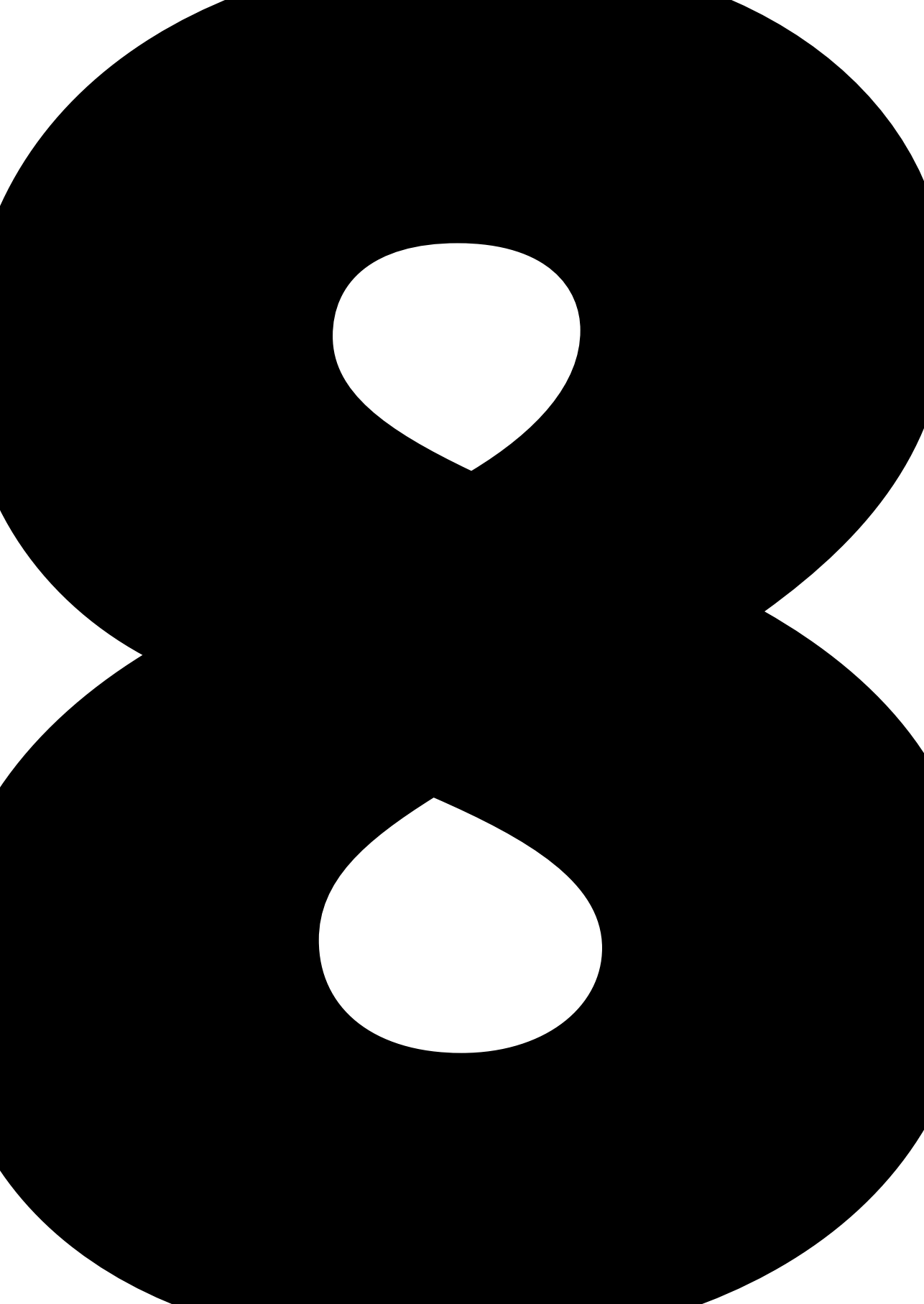

Summary and discussion

SUMMARY

Acute kidney injury (AKI) is a frequent complication of hospitalization and associated with an increased risk for mortality and chronic deterioration in renal function, leading to chronic kidney disease (CKD) and eventually end-stage renal disease (ESRD), respectively [1-4]. With a globally increasing prevalence, AKI has significant impact on healthcare. This has led to an increased awareness for AKI, which is reflected by the exponential rise in publications during the last decades [5, 6]. Unfortunately, despite this increased effort, there are still no therapeutic options available and current treatment strategies focus on the prevention of AKI.

As described in **chapter 1**, the general goal of this thesis was to gain more insight in the development of acute kidney injury (AKI) and its long-term sequelae. In particular, we aimed to identify potential risk factors associated with AKI and subsequent increased risk for morbidity and mortality. With this information, appropriate primary as well as secondary preventive measurements can be applied to patients with a high risk for AKI or an impaired prognosis. In **chapter 2** we evaluated potential risk factors associated with impaired renal function at hospital discharge in the critically ill that survived an episode of AKI requiring renal replacement therapy (RRT). We demonstrated that higher age and pre-existing CKD were the key players in predicting poor renal function at hospital discharge. In continuation of this study, **chapter 3** demonstrates that an impaired renal function at hospital discharge has important prognostic value for long-term mortality and progression towards ESRD. While AKI is considered an independent risk factor for morbidity and mortality, the magnitude of this risk seems to be determined by comorbid conditions present prior to hospital admission. For this reason we evaluated the impact of AKI stratified by the presence of comorbidity in **chapter 4**. We hypothesized that, in patients without pre-existing comorbidity, the prognostic value of AKI is limited. Unexpectedly, we found that the in-hospital mortality rate was equally high in those with or without comorbidity. However, in line with our hypothesis, patients without comorbidity that survived an episode of AKI had a favorable long-term prognosis, with a mortality risk that was similar to the general Dutch population.

Although AKI is a frequent complication of hospitalization, little is known about AKI in the cardiac transplantation population. However, cardi-

ac transplantation recipients are particularly prone for developing AKI due to early postoperative complications, altered hemodynamics and the use of nephrotoxic medication. In **chapter 5** we evaluate the incidence and impact of AKI after cardiac transplantation, which occurred in 76% of the transplant recipients. We demonstrated that AKI requiring RRT was associated with an increased risk for mortality, while even a minor episode of AKI was associated with an impaired renal function one year following transplantation. In continuation to the previous study, **chapter 6** offers an overview on the long-term sequelae of AKI following cardiac transplantation. Contrary to what we expected, AKI did not play an important role in the long-term prognosis of the transplant recipient. Only AKI requiring RRT was associated with an increased risk for long-term mortality and progressive deterioration in renal function. Unlike AKI, renal function at one year following transplantation was of prognostic value and an increasing degree of eGFR loss was associated with an increased risk for mortality and ESRD.

In **chapter 7** we evaluate the time dependent characteristics of biomarkers during the development of AKI. We demonstrated that urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), π- and α-glutathione-S-transferase (GST) all had unique time dependent characteristics during the development of AKI. While all biomarkers were significantly associated with an increased risk for developing AKI, these biomarkers only had limited predictive value for AKI of which NGAL had the best predictive value.

DISCUSSION

AKI requiring RRT and the prognostic value of renal function at hospital discharge

As therapeutic options in the treatment of AKI are still lacking, it is of great importance to identify specific patient populations that bear the greatest risk for an impaired long-term prognosis. Especially when temporary RRT is required, AKI is considered a serious complication of hospitalization and it is associated with a high hospital mortality risk and impaired long-term prognosis [7, 8]. Whereas multiple clinical and demographic characteristics are associated with the development of AKI, as well as on-going deterioration in renal function, pre-existing CKD seems to be the strongest risk factor for an impaired prognosis [9-11]. However, little is known about the prog-

nostic value of renal function at hospital discharge following an episode of AKI. Therefore, we evaluated the predictive ability of renal function at hospital discharge in the critically ill that survived an episode of AKI requiring RRT.

At first we identified potential risk factors associated with an impaired renal function at hospital discharge. In **chapter 2** we demonstrated that only a minority of patients leave the hospital with a normal renal function, defined as an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m². Higher age and serum creatinine at start of RRT were independently associated with impaired renal function at hospital discharge. Furthermore, pre-existing CKD was an independent risk factor for RRT dependence at hospital discharge and more than one fifth of the patients with pre-existing CKD needed chronic RRT. In **chapter 3** we demonstrated that, besides higher age, an eGFR < 30 ml/min/1.73m² at discharge was associated with impaired long-term renal and overall survival, whereas an eGFR between 30 and 59 ml/min/1.73m² was only associated with impaired renal survival. Whether these associations imply causality cannot be concluded from these results because of the retrospective study design. However, the results are in accordance with the results of previous large cohort studies that demonstrated that (pre-existing) renal impairment is associated with worse long-term outcome following AKI [9-11]. Furthermore, these findings are in line with the well-established association between progressive CKD and increased risk for morbidity and mortality [12]. In conclusion, renal function at hospital discharge has important prognostic value with regard to the long-term consequences of AKI. Furthermore, especially the elderly and those with pre-existing CKD have the greatest risk for impaired long-term renal and overall survival.

The role of comorbidity in the long-term sequelae of AKI

Besides the role of pre-existing CKD, there are multiple comorbid conditions associated with an impaired long-term prognosis after AKI, including higher age, hypertension, chronic heart failure, diabetes mellitus, sepsis and recurrent episodes of AKI [7, 9, 13-17]. Furthermore, most of these comorbid conditions itself constitute independent risk factors for the development of AKI, as well as for CKD [18-20]. Therefore, we believe that the long-term prognosis of an AKI survivor is strongly correlated to the individual pa-

tient's pre-existing condition, which can have important implications for clinical practice. As most large studies on AKI are performed in populations with a high burden of comorbidity, this may lead to overestimation of the risk for morbidity and mortality in those with limited or no comorbid conditions. In **chapter 4** we found that the presence of comorbidity significantly alters the long-term prognosis of the critically ill patient with AKI requiring RRT. We demonstrated that the in-hospital mortality risk was equally high in those with and without any comorbid condition. However, those without comorbidity that survived hospital admission had a significantly improved long-term prognosis compared to those with comorbidity. In addition, long-term survival seemed to correspond to the predicted survival in the average Dutch population (matched for age and sex). However, a trend towards a higher mortality risk was found and the lack of statistical significance could be the result of small sample size. Only a small proportion of patients without comorbidity left the hospital with an impaired renal function, which resulted in only one patient that became chronic dialysis dependent after discharge. These results are in line with the conclusions from **chapter 3**.

Interestingly, these results support the opinion that AKI and CKD cannot be considered two separate static entities, but are part of a complex continuum where comorbidity and susceptibility for renal injury play an important role [18]. In other words, the magnitude of the impact of AKI on long-term outcome depends on the residual renal capacity and ability to repair after renal stress [21, 22]. Furthermore, as described in **chapter 1**, the ability for hyperfiltration can camouflage structural renal damage of a previously healthy kidney, because the GFR can be preserved for a long time. As a result, manifest CKD may occur after a very long-time in these patients. Naturally, the degree of structural renal damage will be dependent of the duration and severity of AKI [2]. Additionally, a healthy kidney has, to a certain extent, the capacity to repair transient episodes of AKI [22, 23]. However, in patients with pre-existing CKD, these self-repair mechanisms will fail and an episode of AKI further accelerates the deterioration in renal function. Therefore, those most susceptible for AKI and on-going deterioration in renal function deserve close hemodynamic monitoring during hospital admission and subsequent follow-up in the outpatient clinic by a nephrologist seems warranted [24].

Incidence and impact of AKI after cardiac transplantation

While AKI has been extensively studied in the critically ill, as well in patients that underwent general or cardiac surgery, little is known about AKI following cardiac transplantation. However, due to cardiac failure before transplantation, perioperative complications, hemodynamic alterations and the use of nephrotoxic calcineurine inhibitors, cardiac transplantation recipients are prone to renal damage [25-27]. In **chapter 5** we demonstrated that AKI is a highly frequent complication of cardiac transplantation, which occurred in 76% of the cardiac transplantation recipients. However, compared to previous studies in various clinical settings, the proportion of patients with AKI requiring RRT (5%) was remarkably low [28-32]. Independent predictors for post-operative AKI included an impaired baseline renal function as well as a medical history of diabetes mellitus. Interestingly, we demonstrated that a higher BMI was also associated with an increased risk for AKI. However, little is known about the causal relationship between obesity and AKI. Hypothetically, this association could be the result of an constant inflammatory state driven by increased pro-inflammatory cytokines, oxidative stress, differences hemodynamic regulation and intravascular volume assessment, and altered pharmacokinetics [33].

AKI was associated with an increased risk for mortality during hospitalization, with increasing risk in more severe stages of AKI. However, during the first postoperative year AKI had no prognostic value and only AKI requiring RRT was independently associated with an increased mortality risk. While this association is supported by the results of other studies [28-32], data on the association between less severe episodes of AKI and mortality are conflicting. Two studies found a crude association between AKI and mortality following transplantation [29, 32], of which only one found an independent association between AKI and mortality after adjustment for multiple confounders [29]. However, in the latter study no adjustment was made for post-operative complications, which may have resulted in overestimation of the impact of AKI.

While the long-term impact of AKI on mortality seems limited to AKI requiring RRT, we demonstrated that even a minor episode AKI, was associated with a more pronounced deterioration in renal function during the first post-operative year. However, the magnitude of this deterioration seemed to decrease towards the end of the first postoperative year. This may be

partly explained by the fact that patients that experienced a more severe episode of AKI were more likely to receive a lower dosage of tacrolimus during de first post-operative year. These results are in accordance with the results of a previous study that demonstrated AKI was associated with an impaired renal function 6 months after transplantation, while this association was no longer present after two years of follow-up [31]. Furthermore, a subgroup of patients without AKI had a remarkable improvement in renal function during the first post-operative month after heart transplantation, when compared to renal function before transplantation. This is most likely the result of improved cardiac output and thereby better renal perfusion. While the improvement in renal function was just a temporary effect, patients with renal improvement during the first month were more likely to have a better renal function 1 year thereafter.

Chapter 6 evaluates the long-term sequelae of AKI following cardiac transplantation and the results of this study are in continuation to the results presented in **chapter 5**. In contrast to the latter chapter, no association was found between AKI stages I, II or III and an impaired long-term prognosis. These findings are contrary to the results of previous studies, performed in a variety of clinical settings, that demonstrated the opposite [2, 3]. It is possible that this discrepancy is partly the result of the smaller sample size of our study. However, another explanation might be that, in contrast to the previous studies, we excluded all patients deceased during the first post-operative year. We chose this particular study design because the greatest difference in survival in patients with or without AKI is observed within the first year following transplantation [28-32], which may lead to overestimation of the impact of AKI during longer follow-up. Furthermore, our study population had a distinctly lower median age and was less likely to suffer from comorbidity, such as diabetes and hypertension. However, in line with the aforementioned studies, AKI requiring RRT was independently associated with long-term mortality and renal impairment.

While AKI had limited prognostic value, a strong association was found between an impaired renal function at one year following transplantation and an increased risk for mortality, deterioration in renal function and chronic dialysis dependency. As described in **chapter 5** the development of AKI was independently associated with a decreased renal function during the first postoperative year creating a paradox, as renal function at year

one, but not the occurrence AKI, was associated with overall and renal long-term survival. These findings suggest that there is an indirect relationship between AKI and an impaired long-term prognosis, whereas the decline in renal function during the first-postoperative year is directly related to long-term outcome. As mentioned earlier, we believe that an episode of AKI accelerates deterioration in renal function in those most susceptible for on-going damage, whereas the degree of deterioration has the greatest prognostic value. Furthermore, the lack of prognostic value of AKI itself in cardiac transplantation recipients may be partly explained by the fact that those that experienced an episode of AKI were more likely to receive a lower dosage of CNIs, in an effort to preserve postoperative renal function.

The role of biomarkers in the prediction of AKI

While the previous chapters focussed mainly on the outcome of AKI, **chapter 7** evaluates the role of biomarkers as potential predictors for AKI. In current clinical practice, an acute rise in SCr levels or a decrease in urine output is used as a marker for AKI [34]. However, for accurate estimation of renal function (glomerular filtration rate) the SCr concentration requires a steady state, which is not the case during an episode of AKI [35]. Furthermore, while the SCr concentration can be used for estimation of the glomerular filtration rate, it is a poor indicator of structural renal damage [36-38]. This has resulted in an on-going search for biomarkers that reflect renal damage and can be used for early detection of AKI preceding the rise in SCr levels. This has led to the discovery of several novel biomarkers including NGAL, KIM-1, π- and α-GST [39-41]. Unfortunately, the role of biomarkers in the clinical setting remains unclear, because large prospective multicenter trials failed to demonstrate superior predictive value [42, 43]. This may be the result from the fact that AKI is a complex multifactorial clinical syndrome, in which renal damage can be the result of a variety of pathophysiological mechanisms [44]. For instance, there is a substantial difference between the pathophysiology of septic AKI versus non-septic AKI [45, 46]. In **chapter 7** we demonstrated that, in non-septic AKI patients without established AKI at ICU admission, urinary NGAL, KIM-1, π- and α-GST levels all had different time dependent characteristics during the development of AKI. The urinary levels of KIM-1 and NGAL gradually increased preceding AKI presentation defined by the AKIN criteria. However, the difference in KIM-1 between AKI

and non-AKI patients only became significant at the time SCr levels started to rise. In contrast, the urinary π- and α-GST levels peaked 24 and 20 hours preceding the rise in SCr. After the sudden peak, the π- and α-GST concentrations quickly declined prior to AKI presentation. While a significant difference was demonstrated for all urinary biomarkers between AKI and non-AKI patient, these biomarkers only had limited predictive value. Urinary NGAL had the greatest predictive value, starting at 24 hours prior to AKI presentation (T = -24, AUC = 0.66) and increased towards the AKI endpoint (T = 0, AUC = 0.79). Therefore, the timing of sampling is of critical importance for the interpretation and usability of the aforementioned biomarkers.

Future perspectives

We acknowledge that the results of this thesis constitute only "a small piece of the puzzle" in unravelling such a complex clinical syndrome as AKI and more clinical research is warranted. However, we believe that this thesis does offer new insights in the development of AKI and it's long-term sequelae. The current treatment regime for AKI hasn't changed in the last decades and we stress the initiation of preventive measures. However, multiple studies that evaluated potential therapeutic options have failed to demonstrate benefit of any preventive treatment for AKI, including ischemic preconditioning and several pharmacologic interventions [47]. Therefore, it is of great importance that future research will focus on prevention, early detection and treatment of AKI. With regard to early detection, the use of biomarkers may play a role in the future diagnostic approach of AKI. However, the currently available biomarkers do not demonstrate superior prognostic value compared to the standard diagnostic approach. Furthermore, early detection of AKI is only clinically relevant when early therapeutic interventions that improve outcome are available [48]. The increased knowledge on the pathophysiology of AKI offers new leads on potential therapeutic targets, which is reflected by the great number of registered clinical trails that evaluate possible therapeutic options for AKI. Until then, it is of pivotal importance that those that survive an episode of AKI and are most susceptible for long-term complications are offered adequate outpatient follow-up. Unfortunately, only a limited proportion of patients are offered follow-up by a nephrologist following AKI, even though the risk for complications is high during the first consecutive year [49]. Therefore, we advocate that patients

with substantial comorbidity or impaired renal function following AKI are offered follow-up by a nephrologist in the outpatient clinic. Those without pre-existing medical conditions that are associated with impaired renal recovery can be referred back to their general practitioner.

In conclusion, we believe that the results of this thesis will contribute to the increased awareness for AKI and that it is of great importance to identify those individuals most susceptible for the development of AKI and on-going renal damage thereafter. These individuals will benefit the most from possible interventions and adequate follow-up, in order to preserve renal function and to prevent adverse long-term complications such as increased risk for cardiovascular disease. Furthermore, while the last decades were dominated by research that mainly focussed on gaining more knowledge, we are hopeful that preventive and therapeutic options for AKI will follow in the near future.

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Appendices

Samenvatting
PhD portfolio
Publications
About the author
Dankwoord

SAMENVATTING

Acute nierinsufficiëntie (AKI) is een frequente complicatie gedurende een ziekenhuisopname en is geassocieerd met een verhoogd sterfterisico en achteruitgang in nierfunctie, wat kan leiden tot chronische nierfunctiestoornissen en uiteindelijk permanente afhankelijkheid van nierfunctie vervangende therapie. Wereldwijd neemt de incidentie van AKI nog steeds toe met grote gevolgen voor de huidige gezondheidszorg. Dit heeft de laatste decennia geleid tot een exponentiele toename in publicaties met betrekking tot de pathofysiologie en eventuele behandeling van AKI. Helaas is er tot op de dag van vandaag geen succesvolle behandeling en zijn de negatieve gevolgen van AKI nog onverminderd zichtbaar in de dagelijkse praktijk.

Zoals beschreven in **hoofdstuk 1** biedt dit proefschrift meer inzicht in de ontwikkeling van AKI en het beloop na het doormaken van een AKI episode. In het bijzonder hebben we ons gericht op het identificeren van potentiele risicofactoren voor het ontwikkelen van AKI en in hoeverre deze factoren van invloed zijn op de lange termijn prognose. Deze informatie is van groot belang aangezien het tijdig identificeren van patiënten met een hoog risicoprofiel de mogelijkheid biedt om deze patiënten intensiever te monitoren en indien mogelijk preventieve maatregelen toe te passen. In **hoofdstuk 2** hebben we beschreven welke factoren geassocieerd zijn met nierfunctiestoornissen ten tijde van ziekenhuisontslag. Dit hebben we onderzocht in een cohort van patiënten die op de intensive care een episode van AKI hadden doorgemaakt, waarvoor tijdelijke nierfunctie vervangende therapie noodzakelijk was. Uiteindelijk blijkt de nierfunctie bij ziekenhuisontslag met name bepaald te worden door de leeftijd van patiënt en is een pre-existent gestoorde nierfunctie een belangrijke voorspeller voor blijvende afhankelijkheid van nierfunctie vervangende therapie aansluitend aan de ziekenhuisopname. In **hoofdstuk 3** laten we zien dat nierfunctie bij ontslag een belangrijke prognostische waarde heeft op de lange termijn. Patiënten met een verminderde nierfunctie bij ontslag hadden een verhoogd risico op overlijden alsmede blijvende afhankelijkheid van nierfunctie vervangende therapie.

Echter de prognostische waarde van AKI lijkt sterk beïnvloed te worden door de fysieke conditie en reeds bekende chronische ziekten van het individu. In **hoofdstuk 4** hebben we een subgroep analyse uitgevoerd waarbij

we gestratificeerd hebben naar de aan- of afwezigheid van onderliggende chronische ziekten. Onze hypothese was dat patiënten zonder onderliggende chronische ziekten een betere prognose hebben ten opzichte van hun tegenhangers. Onverwacht bleek het risico op overlijden in het ziekenhuis na een episode van AKI net zo hoog in patiënten met als zonder chronische ziekten. Echter, in overeenkomst met onze hypothese, hadden patiënten zonder chronische ziekten op de lange termijn een relatief goede prognose. Het overlijdensrisico lijkt zelfs overeen te komen met het risico in de algemene Nederlandse populatie.

Terwijl er veel onderzoek is gedaan naar AKI op de intensive care, is er weinig bekend over de incidentie en de gevolgen van AKI na harttransplantatie. Echter, gezien het risico op postoperatieve complicaties, veranderingen in hemodynamiek en het gebruik van nefrotoxische medicatie, hebben patiënten die een harttransplantatie ondergaan juist een hoog risico op AKI. In **hoofdstuk 5** laten we zien dat AKI optrad in 76% van de patiënten gedurende de eerste week na harttransplantatie. In totaal had 5% van de patiënten tijdelijk nierfunctie vervangende therapie nodig kort na de ingreep. Met betrekking tot mortaliteit was alleen ernstig AKI met nierfunctie vervangende therapie geassocieerd met een verhoogd mortaliteitsrisico gedurende het eerste postoperatieve jaar. Daarentegen was zelfs een minimale acute verslechtering in nierfunctie geassocieerd met een progressieve verslechtering in nierfunctie gedurende het eerste postoperatieve jaar.
In aanvulling op deze resultaten beschrijft **hoofdstuk 6** de lange termijn gevolgen van AKI na harttransplantatie. Overeenkomstig **hoofdstuk 5** bleef de associatie tussen AKI waarbij dialyse noodzakelijk was en mortaliteit bestaan. Echter bleek er geen associatie aantoonbaar tussen AKI en achteruitgang in nierfunctie op de lange termijn. Een verslechterde nierfunctie 1 jaar na transplantatie bleek wel belangrijke prognostische waarde te hebben en is geassocieerd met een verhoogd risico op overlijden en blijvende afhankelijkheid van nierfunctie vervangende therapie in de opeenvolgende jaren.

Hoofdstuk 7 beschrijft de rol van alternatieve biomarkers welke ingezet kunnen worden voor de vroege opsporing van AKI. In het bijzonder geeft dit hoofdstuk het tijdsbeloop van de biomarkers gedurende het ontstaan van AKI in niet-septische patiënten opgenomen op de intensive care weer. In deze studie laten we zien dat de urine spiegels van “neutrophil gelatinase-associated lipocalin” (NGAL), “kidney injury molecule 1” (KIM-1)

en “π- and α-glutathione-S-transferase” (GST) allemaal een uniek tijdverloop hebben gedurende de ontwikkeling van AKI. Terwijl toename van alle schade markers een significante associatie hadden met een verhoogd risico op AKI was de predictieve waarde beperkt en lijkt NGAL het best te presteren als marker voor AKI.

Concluderend, biedt dit proefschrift meer inzicht in de ontwikkeling van AKI en de consequenties op de lange termijn. Het is van groot belang dat de patiënten die het meeste risico lopen op een episode van AKI alsmede een gecompliceerd beloop te identificeren. Juist deze patiënten zullen het meeste baat hebben bij optimale zorg met betrekking tot het behoud van nierfunctie en preventie van eventuele nadelige consequenties van chronisch nierfalen op de lange termijn.

PHD PORTFOLIO

A summary of PhD training and teaching activities

name PhD student	G. Fortrie
Erasmus mc department	Nephrology and transplantation
PhD period	2012-2017
promotor	Prof. R. Zietse
co-promotor	Dr. M.G.H. Betjes

PhD training	year	workload (ECTS)
general courses		
AMIE course: from man to mouse	2010	1.4
Rotterdam course in electrolyte and acid-base disorders	2011	0.5
De Baar: basic course kidney diseases	2016	0.8
specific courses		
NIHES summerschool: linear regression	2012	1.9
NIHES summerschool: logistic regression	2012	1.4
presentations		
poster presentation (2x), Dutch Nephrology Days	2012	0.6
poster presentation, NVIC congress	2012	0.3
poster presentation (2x), ASN congress	2013	0.6
oral presentation, Erasmus MC: science day	2013	0.5
poster (2x) and oral presentation, Dutch Nephrology Days	2013	1.1
poster (2x) and oral presentation, ERA-EDTA congress	2013	1.1
oral presentation, ECTTA congress	2014	0.5
oral presentation, NVC congress	2014	0.5
oral presentation, Joint BTS and NVT congress	2015	0.5
poster presentation, ATC congress	2015	0.3
oral presentation, ESOT congress	2015	0.5
poster presentation, ISHLT congress	2016	0.3
oral presentation, Annual Eurotransplant Meeting	2018	0.5
conferences		
Dutch Nephrology Days, Veldhoven, The Netherlands	2012, 2013	1.5
ASN Kidney Week, San Diego, USA	2012	1.5
ERA-EDTA congress, Istanbul, Turkey	2013	1.2
ECTTA congress, Budapest, Hungary	2014	1
Joint BTS and NVT congress, Bournemouth, England	2015	1
ATC congress, Philadelphia, USA	2015	1.5
ESOT congress, Brussels, Belgium	2015	1.2
ISHLT congress, Washington, USA	2016	1.2
annual Eurotransplant Meeting, Leiden, The Netherlands	2018	1
seminars, workshops and other		
Erasmus MC: science day, Antwerp, Belgium	2013	0.5
regional training kidney transplantation	2013	0.5
journal club nephrology	2013, 2014	0.5
local pathology meeting	2013, 2014	0.5
regional kidney pathology meeting	2011–2015	1.5

teaching		
supervision of two master thesis students	2014	2
local lectures at dept. of nephrology and ICU	2012–2014	0.5
grants		
Kolff scholarship by Dutch Kidney Foundation	2012–2015	
best poster presentation, NVIC congress	2012	
young investigator travel grant, ERA-EDTA	2013	
young investigator award, ATC	2015	
young investigator award, ESOT	2015	

LIST OF PUBLICATIONS

1 H.R.H. de Geus, **G. Fortrie**, M.G.H. Betjes, R.H.N. van Schaik RH and A.B.J. Groeneveld, Time of injury affects urinary biomarker predictive values for acute kidney injury in critically ill, non-septic patients. *Bmc Nephrol*, 2013. 14: p. 273-279

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8 **G. Fortrie**, H.R.H. de Geus and M.G.H. Betjes, The aftermath of acute kidney injury: a review of long-term mortality and renal function. *Crit Care*, 2019. 23(1): e-publication.

ABOUT THE AUTHOR

Gijs Fortrie was born on April 26th in 1986 in Heinkenszand, the Netherlands. After primary school he attended the St. Willebrord College in Goes, where he obtained his Atheneum degree in 2005. After his graduation, Gijs was not yet ready for college and needed more time to think about his future. He decided to take a sabbatical year and got a job at the call center department of the Uitvoeringsinstituut werknemersverzekeringen (UWV). In 2006, Gijs followed in his father's footsteps (a general practitioner) and started his medical education at the Erasmus University of Rotterdam. During the second year of college he got a side job at the hemodialysis department, which triggered his interest in nephrology. In 2012, Gijs started the PhD project presented in this thesis under the supervision of Dr. M.G.H. Betjes and Prof. dr. R. Zietse. Besides the PhD project he obtained his qualification as Medical Doctor in 2015 and in January 2016 he started working as a resident in Internal Medicine at the Franciscus Gasthuis in Rotterdam under the inspiring supervision of A.P. Rietveld. Currently, Gijs serves as a resident in the Erasmus Medical Center and in 2020 he will begin his extended specialty in Nephrology.

DANKWOORD

Eindelijk mag ik het zeggen. Het is af, klaar, voltooid, afgerond! Ik kan me nog goed herinneren dat ik in de keuken van de afdeling hemodialyse koffie aan het zetten was en dat Dr. Betjes binnenstapte. Hij had een voorstel. *"Heb jij misschien interesse in data onderzoek voor een IC arts in opleiding? Het levert je een auteurschap op en je kan dit mooi gebruiken voor je keuze onderzoek"*. Zonder na te denken heb ik deze kans gegrepen, niet wetende waar ik aan begon en wat dit me allemaal zou brengen. Het is een fantastisch avontuur geweest, wat uiteindelijk heeft geleid tot dit proefschrift.

Beste Michiel, Dr. Betjes, ik had me geen betere copromotor kunnen wensen. Vanaf dag één heb je mij altijd gestimuleerd en het beste in mij naar boven gehaald. Ik kan me geen moment herinneren dat je ooit negatieve kritiek hebt gegeven. Uiteraard was je wel kritisch, maar wist je de feedback altijd zo te verpakken dat dit voelde als een positieve stimulans. Dit zal met mij vast niet altijd makkelijk zijn geweest. Ik heb grote bewondering voor je kennis, inzicht en geduld. Bovenal heb ik grote bewondering voor je veerkracht, want de laatste jaren zijn verre van makkelijk geweest. Desondanks kon ik "gewoon" bij je terecht en was er altijd ruimte om te sparren. Ik ben je zeer dankbaar voor het vertrouwen en de kans die je mij hebt geboden. Dit heeft niet alleen geresulteerd in dit proefschrift, maar het heeft mij ook de mogelijkheid gegeven om me te ontwikkelen tot de persoon die ik nu ben. Ik kijk er naar uit om de komende jaren, als nefroloog in opleiding, met je te mogen samenwerken.

Professor Zietse, beste Bob, gedurende mijn eerste jaar van geneeskunde was ik nog van mening dat de nier een tamelijk saai en stoffig orgaan was. Jouw colleges, vaak doordrenkt met gortdroge humor, deden mij echter realiseren dat ik er niet verder naast had kunnen zitten. In het oude ziekenhuis kwam ik af en toe even langs op de D-vleugel om onder het genot van een kopje Nespresso de voortgang te bespreken. Ik heb daar niet alleen geleerd dat Arpeggio de beste koffie smaak is, maar ook dat er een belangrijke maas in het Nespresso ordersysteem zat. Dit resulteerde vaak in 2 dozen koffie voor de prijs van één. Bob, ik wil je bedanken voor je kennis, advies en niet in de laatste plaats het feit dat je het "*nefrovirus*" op mij hebt kunnen overbrengen.

Ook wil ik de overige leden van de kleine commissie, professor Jan van Saase, professor Diederik Gommers en professor Can Ince, bedanken voor het beoordelen van dit proefschrift. Ik ben trots dat jullie de harde kern van mijn commissie vormen. Tevens wil ik professor Hoorn, professor Oudemans-van Straaten en professor Pickkers bedanken voor de bereidheid om zitting te nemen in de grote commissie. Jullie gaan het mij vast niet makkelijk maken tijdens de verdediging.

Suzanne, zonder jou was dit proefschrift er nooit gekomen. Je kan uiteindelijk wel stellen dat het onderzoek wat wij hebben gestart behoorlijk uit de hand is gelopen. Dit heeft dan ook geresulteerd in niet 1, maar 2 proefschriften. Bedankt dat je me wegwijs hebt gemaakt in de wereld van het onderzoek. Ik wens je heel veel succes met je eigen verdediging!

Beste Hilde, ik kan me jouw promotie nog goed herinneren. Het was een van de eerste promoties die ik heb bezocht en het is mij daarom altijd bijgebleven. Ondanks de zware delegatie die je tegenover je had, wist je elke "aanval" goed te pareren. In het bijzonder kan ik me nog herinneren dat je de rollen zelfs even omdraaide en een wedervraag stelde aan een van de commissie leden. Het was een groot plezier om met je samen te werken. Bedankt dat je altijd bereid was om even mee te denken en je kennis op het gebied van AKI met mij te delen. Dat heeft het proefschrift zeker naar een hoger niveau getild.

Ik wil alle ex-NIOs, in het bijzonder Ewout, Albert-Jan, Annelies en Jeroen, bedanken voor de tijd dat ik met jullie de kamer mocht delen. Een betere werkplek kon ik me niet wensen. Er was altijd een super goede sfeer en ik kon op jullie terugvallen als ik weer eens vast liep. Ook zal ik jullie fenomenale belichaming van "rejectie" nooit vergeten.

Marike en Olivier, zonder jullie was dit proefschrift eveneens niet tot stand gekomen. Marike, jij hield, als "moeder de gans" met een hart van goud, haar kroost (Meelad en ik) altijd goed in de gaten. Als je het idee had dat we tekort kwamen werden we gewoon uitgenodigd om thuis bij jullie te komen eten. Olivier, zonder jou was dit boekje slechts voor de helft gevuld geweest. Via jou mocht ik op audiëntie komen bij Aggie Balk om toegang te verkrijgen tot de best bewaakte lijst van Nederland. Na een vlekkeloos verlopen gesprek was ik in het bezit van het fundament voor

ons onderzoek. Echter, bij mijn vertrek werd ik er nog wel fijntjes op gewezen dat ik de volgende keer geen spijkerbroek meer mocht aantrekken. Marike en Olivier, bedankt voor jullie humor, warmte en gezelligheid, zowel op de werkvloer als buiten het ziekenhuis.

Meelad, mijn genetische tegenpool, als iemand ons 10 jaar geleden naast elkaar had gezet, had niemand gedacht dat wij zo'n goede match zouden zijn. Wat hebben we veel mooie dingen meegemaakt en wat is er in de tussentijd veel veranderd. Ik kwam steevast naar werk in m'n versleten kloffie en jij altijd tot in de puntjes gestyled. Ik kan me nog goed herinneren dat ik voor het eerst naar een groot congres mocht in San Diego. Er was geen sprake van dat ik me daar zou vertonen in mijn alledaagse kleding. We gingen samen naar de Bijenkorf en voor ik het goed en wel in gaten had, onderging ik binnen een uur een volledige metamorfose. Ik durf stellig te beweren dat dit een van je grootste prestaties is die je in de laatste jaren hebt geleverd. Bedankt voor als je hulp en je vriendschap. Ik vind het een eer dat je na al die jaren nu mijn paranimf bent.

Cagri, Mr. Gungor, zonder jou was de studie geneeskunde een ondraaglijke lijdensweg geweest. Ik denk dat we elkaar in de eerste week al tegenkwamen en sindsdien zijn we onafscheidelijk geweest. Ik zou kunnen zeggen dat we vanaf dag 1 altijd het beste in elkaar naar boven haalden. Echter, niets is minder waar. Het was soms alsof jij het duiveltje was op mijn schouder en ik op de jouwe. De eerste jaren van onze vriendschap stonden dan ook niet in het teken van studeren, maar van "extra-curriculaire activiteiten". We hebben zo veel avonturen beleeft dat het er te veel zijn om op te noemen. Ook zijn vele hiervan ongeschikt om in dit dankwoord te beschrijven. Wie had gedacht dat we het zo ver zouden schoppen. Ik in opleiding tot internist en jij tot psychiater. Uiteindelijk ben je een van mijn allerbeste vrienden geworden en het is dan ook vanzelfsprekend dat jij als paranimf aan mijn zijde zal staan. Bedankt voor je onvoorwaardelijke vriendschap.

Arie, bedankt voor de kans die je me hebt geboden en de fantastische jaren in het Franciscus Gasthuis. Je bent als opleider en als mens vanaf dag één een enorme inspiratie bron voor mij geweest. Ik ben dan ook trots dat ik nauw met je hebt mogen samenwerken in je laatste jaren als opleider.

John, Jin en Michel aka “The Wolfpack”, bedankt voor de legendarische samenwerking. Ondanks dat iedereen nu zijn weg gaat, weet ik zeker dat dit de basis is voor een lange vriendschap. En jullie weten het, “Don Papa maakt geen grappen”.

Ron, Jesse, Mike, Ed, Pieter en alle supporters van “The Firm”, bedankt voor alle memorabele momenten, de biertjes, de muziek en de mogelijkheden om even stoom af te blazen wanneer dit nodig was.

Jan, Els, Melanie en Kim, bedankt voor jullie steun in de periode toen ik die het hardst nodig had.

Tim, het is je gelukt, je staat nu officieel in een proefschrift. Bedankt voor je vaak absurde humor en je interesse in de academische wereld.

Stephan, inmiddels ben je naast een goede vriend ook mijn broer geworden. Een beloning op de jarenlange vriendschap.

Leen, Janny, Wouter, Karen, de drie donderstenen en oma, bedankt voor de warme ontvangst in de familie Kleijn.

Jesse, als oudste en trouwste vriend ben jij altijd de wetenschapper van ons twee geweest. Van kleins af aan was ik steevast de dromer, terwijl jij altijd al bezig was met de meest ingewikkelde experimenten en ontwerpen. Ik tekende misvormde kabouters terwijl jij in perspectief een gebouw aan het ontwerpen was. Ik heb enorm veel bewondering en respect voor de manier waarop jij elke uitdaging aan gaat. Jij hebt me laten zien dat geluk in het leven niet verbonden is aan materie, een diploma of een titel.

Lieve Geert en Joris, ondanks dat we vroeger het bloed onder elkaars nagels vandaan konden halen, zijn jullie uiteraard de beste broers die ik mij kan wensen. We hebben het vroeger lang niet altijd makkelijk gehad, maar dat heeft ons uiteindelijk alleen maar dichter bij elkaar gebracht. Ik spreek het niet zo vaak uit, maar ik ben enorm trots op wat jullie bereikt hebben in het leven. Zoals Joris zou zeggen “doorzettingsvermogen is een van de kernkwaliteiten van een Fortrie”. Dat heeft er uiteindelijk dan ook tot geleid dat ik toch geen putjesschepper ben geworden. Walter, Nathalie en kleine Jim, ook jullie mogen hier uiteraard niet ontbreken aangezien jullie inmiddels een onmiskenbaar deel zijn van de familie. Ik wil jullie allemaal bedanken voor alle liefde, warmte en support.

Lieve mam, bedankt dat je me altijd door weer en wind gesteund hebt. Ook in de jaren dat anderen misschien minder vertrouwen hadden in een goede afloop, ben jij achter mij blijven staan. Ik ben blij dat je me uiteindelijk de ruimte hebt gegeven om mijn eigen fouten te maken en hier van te leren. Je was het lang niet altijd met me eens, maar je was er van overtuigd dat ik mijn keuzes altijd met de beste intenties maakte. Hierdoor heb ik altijd mijn eigen plan kunnen trekken en weet ik zeker dat dit me heeft gebracht op het punt waar ik nu sta. Lieve mam, ik wens je nog veel gezonde en liefdevolle jaren toe.

Lieve pap, zonder jou geen dokter Gijs. Als huisarts ben je altijd mijn grote voorbeeld geweest. De passie voor je vak, je humor en je enorme betrokkenheid bij alle patiënten heeft diepe indruk op me gemaakt. Ik kan me de dag nog herinneren dat je met pensioen ging en afscheid nam. Het hele dorp was uitgelopen, van piepjong tot hoogbejaard. De mensen stonden rijen dik tot ver buiten het gebouw te wachten om je te bedanken voor al de jaren trouwe dienst. Sommige patiënten waren tot tranen geroerd. Pap, ik ben super trots dat ik in jouw voetsporen mag treden. Ik hoop dat je samen met Elly nog vele jaren mag genieten van je pensioen.

Lieve Anne, zonder jou zou dit proefschrift geen enkele waarde hebben. Ik kan me nog goed herinneren dat ik je voor het eerst tegenkwam bij het verdelen van de coschappen. Ik wist het gelijk, die moet ik hebben en dat stak ik niet onder stoelen of banken. Een neurochirurge in wording die er ook nog leuk uit ziet, dat hield ik niet voor mogelijk. Je hebt me er uiteindelijk hard voor laten werken. Dit resulteerde dan ook in een wat ongemakkelijke start van de coschappen. Zeker toen je bij PKV van de docent moest komen om mijn fantastische buikhuidreflex te testen. Een stoplicht zou naast je verbleken. Inmiddels zijn we onafscheidelijk en hoop ik nog ontelbaar veel avonturen met je te beleven. Je bent mijn maatje, mijn aapie en bovenal de liefde van mijn leven. Dit houdt wel in dat je voor de rest van je leven moet horen dat mijn proefschrift eerder af was.

acute dialysis quality initiative	ADQI
acute kidney injury	AKI
acute kidney injury network	AKIN
acute physiology and chronic health evaluation	APACHE
acute renal failure	ARF
anti-thymocyte globulins	ATG
acute tubulus necrosis	ATN
area under the curve	AUC
body-mass index	BMI
coronary artery bypass grafting	CABG
continuous arteriovenous haemodialysis	CAVHD
chronic kidney disease	CKD
calcineurin inhibitor(s)	CNI(s)
chronic obstructive pulmonary disease	COPD
continuous renal replacement therapu	CRRT
continuous venovenous hemofiltration	CVVH
cerebrovascular accident	CVA
extracorporeal membrane oxygenation	ECMO
estimated glomerular filtration rate	eGFR
end-stage renal disease	ESRD
fluid balance	FB
glutathione-S-transferase	GST
hemolysis elevated liver enzymes and low platelets	HELLP
hazard ratio	HR
intra-aortic balloon pump	IABP
intermitted haemodialysis	IHD
intensive care unit	ICU
interquartile range	IQR
kidney disease outcomes quality initiative	K/DOQI
kidney disease improving global outcome	KDIGO
kidney injury molecule-1	KIM-1
kidney transplant	KT
left ventricular assist device	LVAD
modification of diet in renal disease	MDRD
neutrophil gelatinase-associated lipocalin	NGAL
odds ratio	OR
peritoneal dialysis	PD
registratie nierfunctievervanging Nederland	RENINE
risk injury failure loss end-stage renal disease	RIFLE
receiver operating characteristic	ROC
renal replacement therapy	RRT
right ventricle	RV
subarachnoid bleeding	SAB
sequential organ failure assessment score	SOFA
serum creatine concentration	SCr
standard error of mean	SEM
standard mortality rate	SMR
urine output	UP
95% confidence interval	95%-CI