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EDITORIAL

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Defining renal recovery: pitfalls to be avoided

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Long-term mortality and sequelae have become a leading issue in the growing number of ICU survivors. Renal outcome after an episode of acute kidney injury (AKI) illustrates the significant risk of non-recovery of organ function after discharge. AKI and chronic kidney disease (CKD) are now recognized as an interconnected syndrome. Epidemiologic evidence shows that AKI is an independent risk for the occurrence or the progression of CKD, and joint physiopathological mechanisms have been described [1]. Today, studies on AKI recovery suffer from the same issue as research on AKI several years ago, when a consensual definition was lacking. The use of different definitions of AKI recovery (Table 1) precludes any synthetic analysis of the literature and a wide range of post-AKI non-recovery has been reported, from 0.03 to 72 cases per 100 person-years [2–4]. This heterogeneity not only depends on the definition used but also on case-mix. Important risk factors of AKI non-recovery have been identified such as pre-existing CKD, age and AKI severity [2, 3, 5].

It is intuitive to define recovery by the disappearance of a disease. Because AKI stages are defined by a percentage of serum creatinine (Screat) increase, such a simple definition would not correspond to complete recovery. A patient with a baseline Screat of 1.5 mg/dL and a maximal Screat of 2.5 mg/dL (AKI stage 1 [6]) would be considered as reaching renal recovery if his/her Screat return below 2.25 mg/dL. Defining partial and complete recovery appears, therefore, necessary. In the most severe cases, recovery of a sufficient renal function allowing renal replacement therapy (RRT) independency is also a pertinent outcome that should be included.

In a recent issue of *Intensive Care Medicine*, Schetz and collaborators provide useful information on the impact of the criteria used to define AKI recovery [7]. In the subgroup of 1310 patients randomized in the "early versus late parenteral nutrition in critically ill adults" study [8] who developed AKI, they compared AKI recovery rate at hospital discharge, according to different

Table 1 Common criteria used to define renal recovery

Renal function
Discontinuation of dialysis
eGFR >60 mL/min
Disappearance of AKI criteria
Return to ±10 or 20 % of baseline Screat/eGFR
Return to baseline Screat/eGFR
Time point
ICU discharge
Hospital discharge
30 days
3 months
>3 months
Population
Patients with AKI
Patients with AKI requiring RRT
Survivors from AKI

definitions. The severity of the creatinine-based definition strongly affected the complete recovery rate. The least severe tested definition was the disappearance of AKI criteria [6] and yield for 79 % of recovery. When using the most stringent threshold corresponding to the return of Screat to baseline, recovery rate was only 42 %. Baseline Screat is, however, frequently unknown [2]. The authors compared recovery rate in patients in whom pre-existing renal function was available using either the true or the calculated Screat value obtained from the Modification of Diet in Renal Disease formula [6]. A large difference was found in the recovery rate which was significantly lower when using the calculated Screat. This difference was mainly related to the patients with pre-existing CKD in whom the calculated Screat underestimated baseline Screat. In the absence of known baseline renal function, it is impossible to differentiate de novo CKD and pre-existing unknown CKD. In any case, de novo CKD diagnosis or the detection of unknown pre-existing CKD will require similar management with a referral to nephrologists when needed.

A definition of AKI recovery based on Screat evolution is hampered by the decrease in the creatinine production rate during an ICU stay [9, 10]. Schetz and collaborators observed that, at hospital discharge, 40 % of the patients had a Screat lower than baseline and 20 % of CKD patients had a paradoxical normalization of their renal function. Many factors affect muscle wasting in critical illness and, therefore, can influence Screat. This is particularly true for older patients in whom a definition based on Screat overestimates the recovery rate [3]. In the Schetz study, a similar overestimation was found in CKD patients in whom recovery was paradoxically higher than in patients without CKD, except when RRT independency was considered in the definition. A higher muscle wasting in CKD patients might explain this observation. Another important factor affecting muscle wasting is the length of stay (LOS). Unsurprisingly, patients "healed" from their CKD at hospital discharge had a longer LOS. For all these reasons, a definition of short-term AKI recovery based on Screat will always overestimate the glomerular filtration rate. In critically ill patients, complete AKI recovery should result in a post-AKI Screat lower than baseline. A stringent threshold for the decrease in Screat after an AKI episode should therefore be chosen. As for defining AKI, it appears uncertain that the use of biomarkers could overcome the limitations of Screat [11].

The renal recovery definition should include a standardized time point (Table 1). While a short period of time seems sufficient to become independent from RRT [12], different patterns of glomerular filtration rate evolution have been described after AKI and its stabilization may require up to 1 year [5]. While not studied by Schetz and collaborators, it is likely that the time point for renal function assessment influences the recovery rate for two main reasons. First, the longer the delay, the higher the odds of recovery. A systematic review found that AKI recovery was 67 % at hospital discharge and 76 % when a delayed time point was used [3]. The odds of late recovery may, however, depend on the baseline renal reserve [3]. Conversely, delayed assessment may increase the probability of new renal insults and post-discharge AKI episodes that could decrease the odds of recovery [13]. Second, a longer LOS will result in a more pronounced artificial decrease in Screat. While it seems preferable to define a fixed time point, assessing renal recovery "at least" at hospital discharge may correspond to a pragmatic time point at which patients with non- or partial recovery can be detected.

Patient evolution after AKI corresponds to a multistate model that must be considered. Death, dialysis dependency, partial and complete recovery are all possible outcomes. Schetz and collaborators addressed the question of studying recovery in survivors only. This point appears crucial because the absence of recovery was twofold higher in non-survivors. To determine the volume of patients who will require a nephrological follow-up, AKI recovery should be assessed in survivors only. When testing interventions, death that precludes new or worsening CKD must be considered as a competing risk, and specific statistical methodologies are required to avoid wrong conclusions [14]. For instance, in some studies showing a better renal outcome with continuous RRT, the significant difference was merely explained by a higher mortality in patients managed with continuous rather than intermittent RRT. When using a composite end point (death and/or renal recovery), the difference was no longer significant [15].

Unfortunately, a validation of the definitions tested by Schetz and collaborators is lacking. Such validation could be based on the risk of long-term death or end stage renal disease (ESRD) [16]. Pannu and collaborators tested different thresholds of recovery from within 5 % of baseline Screat to >55 %, and found that the adjusted risk was significant for a threshold >55 % for death and >25 % for ESRD [16].

Schetz and collaborators clearly demonstrated that the use of different definitions leads for strong differences in the epidemiology of AKI recovery. Although a definition is never perfect, it is urgently needed. This definition should facilitate the estimate of the exact burden of post-AKI non-recovery and the assessment of preventive measures of long-term renal sequelae. In clinical practice, such a definition should help to detect patients with persistent renal dysfunction who could benefit from referral to nephrologists [17, 18].

Compliance with ethical standards

Conflicts of interest None.

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ORIGINAL

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Recovery from AKI in the critically ill: potential confounders in the evaluation

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Take-home message: Reports on recovery from AKI should clearly describe the applied definitions, AKI severity, the study population, and the proportion of patients with imputed baseline.

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Abstract *Purpose:* Studies on recovery from acute kidney injury (AKI) in ICU patients yield variable results. We assessed the impact of different recovery definitions, of different exclusion criteria, and of imputing missing baseline creatinine on AKI recovery in a heterogeneous ICU population. *Methods:* Secondary analysis of the EPaNIC database. Recovery of kidney function in patients who developed AKI in ICU was assessed at hospital discharge. We studied recovery rates of different AKI stages with different definitions of recovery after inclusion or exclusion of non-survivors and in patients with or without chronic kidney disease (CKD). In addition, the impact of imputing missing baseline creatinine was investigated. *Results:* A total of 1310 AKI patients were studied of which 977 were discharged alive from hospital. Rate of complete recovery (absence of KDIGO criteria) was markedly higher in survivors than in all AKI patients (79.5 vs 67.0 %), especially for more severe forms of AKI. For patients with CKD, only the need for renal replacement therapy worsened kidney outcome as compared with no-CKD patients. Using stricter definitions of complete recovery significantly reduced its occurrence. New or worsening CKD occurred in 30 % of AKI survivors. In no-CKD patients with available baseline creatinine, using an imputed baseline did not affect recovery. Patients with unavailable baseline creatinine were different from those with known baseline and revealed different recovery patterns. *Conclusion:* These results indicate the need for rigorous description of AKI severity, the included population, definitions, and baseline creatinine handling in reports on AKI recovery.

Keywords AKI · Recovery · Definition · Baseline imputation

Introduction

Several large observational studies have shown an association between acute kidney injury (AKI) and long-term mortality and the development of chronic kidney disease/end-stage renal disease (CKD/ESRD) [1, 2]. Even a complete recovery from AKI has been suggested to predispose to long-term adverse outcomes [3–8], whereas absent or only partial recovery further aggravates this predisposition [4, 9–12].

Most studies reporting short-term recovery from AKI used older definitions of AKI and/or focused on independence from dialysis in dialysis-requiring AKI [13, 14]. Data on the renal outcome of AKI in ICU patients defined by modern definitions (RIFLE, AKIN, KDIGO) that also include less severe forms are scarce [13–26]. In addition, available studies are often small and limited to specific surgical populations [19–21, 26, 27], used only administrative or laboratory databases [10, 11, 25], or also included non-ICU patients [10, 11, 15, 17, 22, 24, 25].

Evaluation of AKI recovery is hampered by the lack of a generally accepted definition. The available reports used definitions based on absence of RIFLE criteria [4, 17, 24], return to baseline serum creatinine (Screat) [11, 19, 27], or a discharge Screat that returned to a value below 1.1 or 1.25 times baseline [7, 10, 16, 20]. Few studies reported recovery according to AKI severity [4, 11, 15] and none of these studies used the KDIGO criteria [28] for both diagnosis of AKI and for assessment of recovery. Using new-onset CKD or worsening of pre-existing CKD to define absence of recovery may be more clinically relevant in determining the need for nephrological follow-up [29].

The optimal timing to evaluate recovery is also unclear. The majority of the available studies reported recovery at hospital discharge [17, 19–25]. With the exception of studies focusing on long-term follow-up [4, 5, 10], recovery is mostly reported for all AKI patients (survivors and non-survivors) [15, 16, 18, 19, 21–23, 26]. Although inclusion of non-survivors is important from a pathophysiological point of view and essential for intervention trials, recovery of kidney function among survivors is probably more relevant from a patient's perspective and crucial for determining the burden of postdischarge nephrological follow-up. Including or excluding non-survivors is expected to have a pronounced effect on the degree of renal recovery, especially in the most severe forms of AKI with the highest risk of death.

Another complicating factor in determining AKI recovery is the fact that a baseline Screat is often missing. The available clinical trials either excluded patients with an unknown baseline Screat [9, 19], used an imputed baseline Screat based on the Modification of Diet in Renal Disease (MDRD) equation (as suggested by ADQI and KDIGO) [4, 16, 17, 23, 25], used the minimum Screat measured during hospitalization [5, 21], or did not mention how baseline Screat was determined [18, 24]. The impact of using an imputed instead of the observed baseline on the incidence of AKI has been reported [30–32]. However, the impact of baseline Screat imputation on AKI recovery has not been studied.

The aim of the current investigation was to compare the rate of complete, partial, or absent recovery from different stages of AKI, defined by KDIGO criteria, in a large heterogeneous ICU population using different definitions of renal recovery, with inclusion and exclusion of non-survivors and for patients with pre-existing CKD versus those without CKD. Our second aim was to assess the impact of using an imputed versus the true baseline Screat on the pattern of renal recovery.

Methods

Patients

This is a secondary analysis of the EPaNIC database [33]. EPaNIC was a prospective multicenter RCT of 4640 adult ICU patients who, between August 2007 and November 2010, were randomly assigned to early or late addition of parenteral nutrition to insufficient enteral nutrition. Written informed consent was obtained from all patients or their designated representatives. The institutional review board of the University Hospitals Leuven and the Belgian authorities approved the protocol. For the present analysis patients were excluded if they were on chronic dialysis, were admitted after kidney transplantation, or had incomplete data on kidney function during ICU stay. Baseline characteristics, including demographics, comorbidities, and clinical parameters of illness severity, were recorded. Daily clinical and biochemical data were entered in the study database.

Definition of AKI

AKI was classified according to the KDIGO criteria [28], however, not taking into account the urine output. The "0.3 mg/dL increase of Screat over 48 h" criterion was only applied during ICU stay. As baseline Screat, we used the lowest Screat during the 3 months prior to ICU admission for elective admissions and the lowest Screat from 3 months to 1 week before ICU admission for emergency admissions. Screat was searched for in the hospital database or manually retrieved by searching documents from referring hospitals/physicians. In case of missing values a baseline Screat was imputed from the MDRD formula assuming an estimated GFR of 75 ml/min per 1.73 m^2 [29]. The maximal AKI stage (AKI_{max}) during ICU stay was recorded.

Impact of the definition used to identify renal recovery at hospital discharge

Definitions using serum creatinine criteria

The first definition of recovery was based on the presence or absence of KDIGO criteria taking into account dialysis dependence and the percentage change of Screat compared with baseline. For patients with AKI stage 1 we separately evaluated the cohorts with 0.3 mg/dL increase of Screat in 48 h only and no other AKI criteria (further referred to as stage 1–0.3) and the cohort with 50 % increase (further referred to as stage 1–50 %). For patients with stage 3 we separated the threefold increase of serum creatinine and the need for renal replacement therapy (RRT) subcategories. Complete recovery from

AKI was defined as being discharged from hospital without AKI (Screat below 1.5 times the baseline value). A reduction in AKI stage compared with AKI_{max} was defined as partial recovery. Because of the important impact of dialysis need on health status, patients with AKI stage 3 with need for RRT that did not need dialysis at hospital discharge but still had AKI were also considered as partial recovery, even if they remained in stage 3. Absence of recovery was defined as persistent AKI_{max} (persistent need for RRT for stage 3 with RRT) or worsening of AKI stage after ICU discharge. Besides the KDIGO criteria we also assessed two stricter definitions defining complete recovery as a return to below 1.25 times baseline Screat or as a complete return to baseline Screat (without need for dialysis).

Definition using eGFR criteria

This definition of recovery was based on the eGFR (MDRD equation) at hospital discharge in AKI survivors. Patients with discharge eGFR below 60 ml/min/1.73 m^2 were considered as potential CKD, since CKD sensu stricto requires a GFR below 60 ml/min/1.73 m^2 for at least 3 months. We also determined the proportion of "new potential CKD" in patients without pre-existing CKD and the worsening of pre-existing CKD using the KDOQI classification [34].

Impact of the study population regarding survival status and pre-existing CKD

The renal recovery pattern of different stages of AKI_{max} in all AKI patients was compared with the subgroup of hospital survivors only. In addition, patients with pre-existing CKD were compared with those without CKD.

Impact of imputation for missing baseline serum creatinine values

For this analysis we excluded patients with stage 1-0.3 because this stage does not use a premorbid baseline creatinine. In AKI patients who survived to hospital discharge and for whom baseline Screat was available, we compared the pattern of recovery with the true or calculated baseline: the "true baseline group" comprised the patients where both development and recovery of AKI were assessed with the true baseline and the "calculated baseline group" comprised the patients where both development and recovery of AKI were assessed with the calculated baseline. This analysis was performed in all AKI survivors and in the subgroup without pre-existing CKD. The "imputed baseline group" comprised the patients where the baseline was actually missing and had to be calculated. Their baseline characteristics and pattern of recovery were compared with the "calculated baseline group" without CKD.

Statistical analyses

Continuous variables are expressed as medians and interquartile ranges (IQR) and compared with Wilcoxon or Kruskal–Wallis tests as appropriate. Categorical variables are expressed as frequencies and proportions and compared using the Chi-square test or Fisher's exact test. Agreement between two methods to evaluate recovery in the same population was assessed with kappa statistics and Bowker's test of symmetry. Statistical analysis was performed using JMP 10 software (SAS Institute, Cary, NC) and a two-tailed p value less than 0.05 was considered statistically significant, without correction for multiple testing.

Results

Patients

The EPaNIC study [33] included 4640 patients. The nutritional strategy itself had no significant impact on recovery from AKI [35]. From the original study population, 56 patients were excluded for ESRD, 15 for kidney transplantation, and 9 for missing data required for this study. AKI was diagnosed in 1310/4560 patients (28.7 %). A total of 160 patients (12.2 %) had stage 1–0.3 and 425 (32.4 %) had stage 1–50 %; 213 (16.3 %) had stage 2; 164 (12.5 %) had stage 3 without need for RRT and 348 (26.6 %) needed RRT. Baseline characteristics and outcomes are described in Table 1 of the electronic supplementary material. Baseline Screat was unavailable in 31 % of these AKI patients and this increased from 21 % in patients with AKI stage 1 to 43 % in patients with AKI stage 3. Pre-existing CKD was present in 24 %. Mortality, ICU and hospital stay increased with increasing AKI severity.

Impact of the definition and the study population

Kidney outcome with KDIGO definition in the whole population versus survivors only

Discharge KDIGO classification for the different levels of AKI_{max} is shown in Table 1, for all AKI patients and for survivors only. Survivors had 79.4 % complete recovery, 10.8 % partial recovery, and 9.8 % absent recovery; whereas these proportions were 30.6, 12.3, and 57.1 % for the non-survivors ($p < 0.0001$). Death or no recovery occurred in 429 (32.7 %). In comparison with the survivors the whole population had less complete recovery (67 %) and more absent recovery (21.8 %). This difference was

Table 1 Kidney outcome of different AKI_{max} stages in the total population and survivors only

AKI discharge	Frequency, *n* (%)	No AKI	Stage 1	Stage 2	Stage 3 no RRT	Stage 3 RRT
AKI max, total population						
Stage 1–0.3	160 (12.2)	154 (96.2)	*6 (3.8)*			
Stage 1–50 %	425 (34.4)	358 (84.2)	*54 (12.7)*	*9 (2.1)*	*4 (0.9)*	
Stage 2	213 (16.3)	151 (70.9)	**40 (18.8)**	*20 (9.4)*	*2 (0.9)*	
Stage 3 no RRT	164 (12.5)	87 (53)	**24 (14.6)**	**31 (18.9)**	*21 (12.8)*	*1 (0.6)*
Stage 3 RRT	348 (26.6)	128 (36.8)	**27 (7.8)**	**18 (5.2)**	**6 (1.7)**	*169 (48.6)*
	1310	878 (67)	151 (11.5)	78 (6)	33 (2.5)	170 (13)
AKI max, survivors only						
Stage 1–0.3	142 (14.5)	138 (97.2)	*4 (2.8)*			
Stage 1–50 %	372 (38)	320 (86)	*44 (11.8)*	*7 (1.9)*	*1 (0.3)*	
Stage 2	169 (17.3)	136 (80.5)	**25 (14.8)**	*7 (4.1)*	*1 (0.6)*	
Stage 3 no RRT	113 (11.6)	74 (65.5)	**20 (17.7)**	**16 (14.2)**	*2 (1.8)*	*1 (0.9)*
Stage 3 RRT	181 (18.5)	108 (59.6)	**24 (13.3)**	**17 (9.4)**	**3 (1.7)**	*29 (16)*
	977	776 (79.4)	117 (12)	47 (4.8)	7 (0.7)	30 (3.1)

Absent recovery shown in *italics*, partial recovery in **bold**

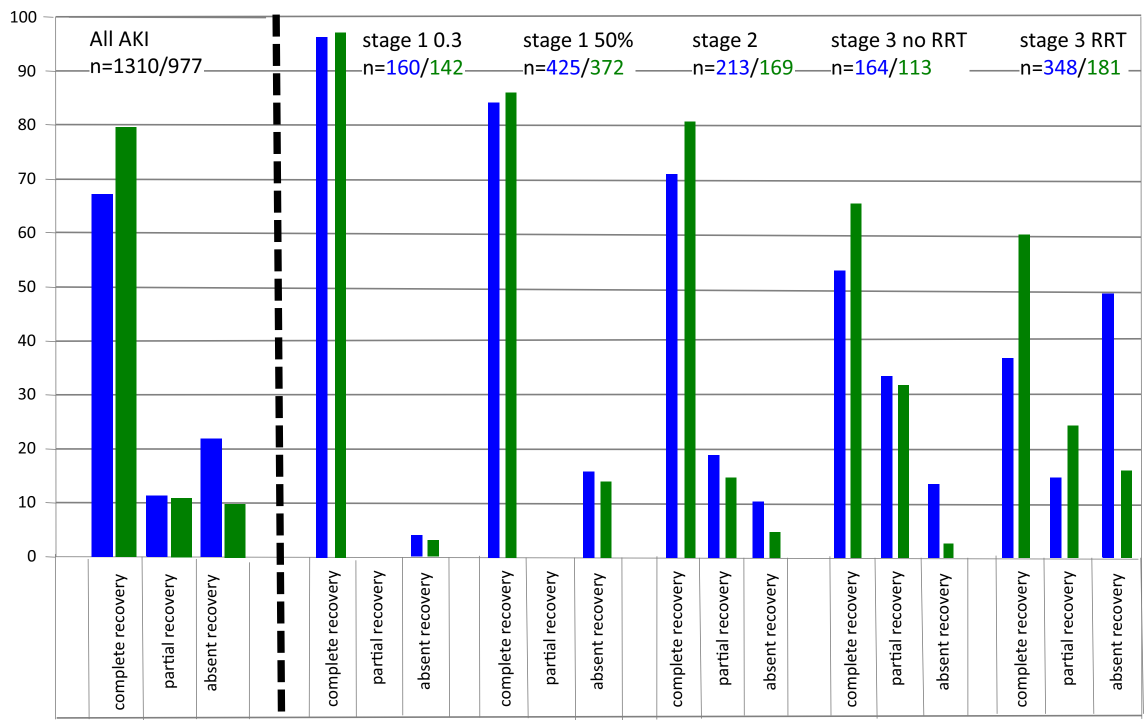

Fig. 1 Proportion of complete, partial, and absent recovery for the total AKI group and split by different stages of AKI_{max} in all AKI patients (*blue*) ($n = 1310$) and in hospital survivors only (*green*) ($n = 997$)

most pronounced for the more severe AKI stages (Fig. 1). In AKI stage 3 with need for RRT, complete recovery was 60 % in survivors and 37 % in the total population. The characteristics of non-surviving patients and of survivors with complete, partial, and absent recovery are shown in Table 2 of the electronic supplementary material. Important differences between the recovery groups existed with regard to baseline kidney function, emergency admission, APACHE II score, and AKI severity.

Kidney outcome according to AKI severity

As expected, complete recovery among survivors decreased substantially with increasing AKI severity (from 97.2 % in stage 1-0.3 to 59.7 % in stage 3 with RRT) ($p < 0.0001$). In patients with AKI stage 3, the recovery pattern also significantly differed between the subgroups with and without need for RRT ($p < 0.0001$) (Fig. 1).

Table 2 Frequency of complete recovery in AKI survivors assessed with different definitions

	All AKI	*P* value[a] Bowker's test	Kappa (CI)[a]	Stage 1–0.3	Stage 1–50 %	Stage 2	Stage 3 no RRT	Stage 3 RRT
KDIGO	776 (79.4)			138 (97.2)	320 (86)	136 (80.5)	74 (65.5)	108 (59.7)
Within 1.25 times baseline	646 (66.1)	<0.0001	0.67 (0.62–0.72)	133 (93.6)	262 (70.4)	104 (61.5)	60 (53.1)	87 (48.1)
Return to baseline	410 (42)	<0.0001	0.45 (0.41–0.50)	95 (66.9)	145 (39)	72 (42.6)	43 (38)	55 (30.4)
Absence of new or worsening CKD	687 (70.3)	<0.0001	0.58 (0.52–0.64)	130 (91.5)	285 (76.6)	121 (71.6)	63 (55.8)	88 (48.6)

Data are presented as *n* (%) unless indicated otherwise

[a] Comparison with KDIGO

Table 3 Kidney outcome of different AKI stages (with the exception of stage 1–0.3) in surviving patients

AKI discharge	Frequency, *n* (%)	No AKI	Stage 1	Stage 2	Stage 3 no RRT	Stage 3 RRT
AKI max A[a]						
Stage 1–50 %	231 (56.2)	193 (83.5)	*31 (13.4)*	*6 (2.6)*	*1 (0.4)*	
Stage 2	93 (22.6)	74 (79.6)	**15 (16.1)**	*3 (3.2)*	*1 (1.1)*	
Stage 3 no RRT	41 (10)	31 (75.6)	**8 (19.5)**	**1 (2.4)**	*1 (2.4)*	
Stage 3 RRT	46 (11.2)	30 (65.2)	**6 (13)**	**6 (13)**	**2 (4.3)**	*2 (4.3)*
	411	328 (79.8)	60 (14.6)	16 (3.9)	5 (1.2)	2 (0.5)
AKI max B[b]						
Stage 1–50 %	143 (49.1)	127 (88.8)	*13 (9.1)*	*2 (1.4)*	*1 (0.7)*	
Stage 2	85 (29.2)	70 (82.3)	**13 (15.3)**	*2 (2.4)*		
Stage 3 no RRT	17 (5.8)	15 (88.2)	**2 (11.8)**			
Stage 3 RRT	46 (15.8)	35 (76.1)	**5 (10.9)**	**3 (6.5)**	**1 (2.2)**	*2 (4.4)*
	291	247 (84.9)	33 (11.3)	7 (2.4)	2 (0.7)	2 (0.7)
AKI max C[c]						
Stage 1–50 %	72 (25.2)	62 (86.1)	*9 (12.5)*	*1 (1.4)*		
Stage 2	45 (15.7)	34 (75.6)	**7 (15.6)**	*4 (8.9)*		
Stage 3 no RRT	58 (20.3)	31 (53.4)	**12 (20.7)**	**13 (22.4)**	*1 (1.7)*	*1 (1.7)*
Stage 3 RRT	83 (29)	47 (56.6)	**15 (18.1)**	**9 (10.8)**	**1 (1.2)**	*11 (13.3)*
	258	174 (67.4)	43 (16.7)	27 (10.5)	2 (0.8)	12 (4.7)

Absent recovery shown in *italics*, partial recovery in **bold**. *p* values for the distribution between complete, partial, and no recovery are reported in Fig. 3b

[a] Patients with available baseline and without CKD and development and recovery assessed with the true baseline ($n = 411$)

[b] Patients with available baseline and without CKD and development and recovery assessed with the imputed baseline ($n = 291$)

[c] Patients with both development and recovery assessed with imputed baseline ($n = 258$)

Kidney outcome with KDIGO versus stricter definitions

Defining complete recovery as a complete return to baseline Screat or as a return to below 1.25 times the baseline Screat reduced the proportion of complete recovery in survivors from 79.4 % to 42 or 66 %, respectively, with a parallel increase of partial recovery ($p < 0.0001$) (Table 2).

Kidney outcome in patients with versus without CKD

Pre-existing CKD was present in 320 patients, of whom 81 (25.3 %) died. Surviving patients with pre-existing CKD appeared to have a better renal outcome than those without CKD with the exception of patients requiring RRT (Fig. 1 in the electronic supplementary material).

Kidney outcome with eGFR definition (new or worsening CKD)

Amongst the 977 AKI survivors, 420 (43 %) had potential CKD at hospital discharge, the largest proportion being seen in stage 3 with need for RRT (Table 2). New or worsening CKD was seen in 290 (29.6 %) survivors, including new potential CKD in 230 (31 %) of the 738 patients without pre-existing CKD and worsening CKD in 60 (25 %) of the 239 AKI survivors with pre-existing CKD. Somewhat surprisingly, 49 (20 %) of the CKD patients had an eGFR above 60 at hospital discharge. These patients had a higher baseline eGFR [50.8 (43–56.7) versus 39.4 (30.6–48.6); $p < 0.0001$] and a longer hospital stay compared with those with persistent CKD [29 (21–56) versus 22 (15–38); $p = 0.011$].

Table 4 Baseline characteristics and general outcome of surviving AKI patients with true (available) and imputed (unavailable) baseline

	Available baseline, $n = 577$	Available baseline no CKD, $n = 411$	Unavailable baseline, $n = 258$	p_1	p_2
Demographics					
Age (years), median (IQR)	67.9 (58.1–75.6)	65.1 (55.7–73.9)	66 (55.5–76.5)	0.56	0.25
Male gender, *n* (%)	347 (60.1)	260 (63.3)	157 (60.9)	0.84	0.53
Comorbidity					
Diabetes, *n* (%)	134 (23.2)	86 (20.9)	38 (14.7)	0.004	0.042
Malignancy, *n* (%)	183 (31.7)	145 (35.3)	28 (10.9)	<0.0001	<0.0001
Baseline Screat, mg/dL (median IQR)	0.88 (0.67–1.16)	0.76 (0.58–0.91)	0.97 (0.79–1.00)	0.21	<0.0001
Calculated baseline, mg/dL (median IQR), *p* value for difference true−calc	0.97 (0.78–1.00), 0.66	0.97 (0.79–1.00), <0.0001	0.97 (0.79–1.00)	0.53	0.40
Acute illness					
Emergency admission, *n* (%)	281 (48.7)	215 (52.3)	258 (100)	<0.0001	<0.0001
Surgical admission, *n* (%)	495 (85.8)	350 (85.2)	189 (73.3)	<0.0001	0.0002
Sepsis on admission, *n* (%)	200 (34.7)	160 (38.9)	137 (53.1)	<0.0001	0.0003
APACHE II score, (median IQR)	26 (20–35)	27 (18–35)	37 (32–40)	<0.0001	<0.0001
Max lactate d1, mmol/L (median IQR) ($n = 577$)	2.2 (1.6–3.3)	2.3 (1.7–3.6)	2.3 (1.4–3.7)	0.91	0.45
Need for HD support	522 (90.5)	365 (88.8	217 (84.1)	0.0094	0.08
Need for MV	539 (93.4)	386 (93.9)	238 (92.2)	0.54	0.40
Characteristics AKI					
Adm Screat, mg/dL median (IQR)	1.31 (0.93–1.86)	1.18 (0.84–1.57)	1.76 (1.27–2.89)	<0.0001	<0.0001
AKI on admission, *n* (% of all AKI)	285 (49.4)	235 (57.2)	193 (74.9)	<0.0001	<0.0001
Early AKI (within 48 h), *n* (% of all AKI)	461 (79.9)	343 (83.5)	224 (86.8)	0.014	0.23
AKI max				<0.0001	<0.0001
Stage 1–50 %	300 (52)	231 (56.2)	72 (27.9)		
Stage 2	124 (21.5)	93 (22.6)	45 (17.4)		
Stage 3	55 (9.5)	41 (10)	58 (22.5)		
Stage 3 RRT	98 (17)	46 (11.2)	83 (32.2)		
Outcome					
ICU stay	7 (4–15)	7 (4–15)	11 (5–23)	<0.0001	<0.0001
Hospital stay	27 (17–48)	28 (17–48)	35.5 (19–59)	0.0019	0.0029

Screat serum creatinine, *eGFR* estimated GFR, *CKD* chronic kidney disease, *HD* hemodynamic support, *MV* mechanical ventilation, p_1 for comparison of patients with available versus unavailable baseline, p_2 for comparison of no-CKD patients with available baseline versus patients with unavailable baseline

Impact of using imputation for missing baseline serum creatinine

Comparing recovery in the "true baseline group" ($n = 577$) with the "calculated baseline group" ($n = 725$) (Fig. 2a; Table 3 in the electronic supplementary material) showed less complete recovery with the calculated baseline (59.6 vs 80.4 %; $p < 0.0001$). However, repeating the same analysis in the subgroup of patients without CKD ($n = 411/291$) showed no difference in recovery pattern ($p = 0.3$). Compared with the "calculated baseline group" without CKD the "imputed baseline group" ($n = 258$) had worse recovery ($p < 0.0001$) (Fig. 2b; Table 3 in the electronic supplementary material). Even after correction for AKI severity, the unavailability of a true baseline remained associated with less complete recovery [OR 0.69 (0.47–0.97)]. Comparing baseline characteristics of survivors with available and unavailable baseline showed significant differences. The "obligatory imputed patients" had less comorbidity, more emergency admissions, more sepsis on admission, higher illness severity, more AKI on admission, and more severe AKI. They also had a longer ICU and hospital stay (Table 4).

Discussion

This analysis describing renal recovery from AKI in a heterogeneous ICU population showed that the pattern of recovery from AKI depends on the study population and on the definitions applied. AKI recovery, especially from the most severe forms, was markedly better when only survivors are considered. Pre-existing CKD only worsened renal outcome in stage 3 with need for RRT. Not unexpectedly, recovery decreased with increasing AKI severity, with worst kidney outcome for the subgroup of AKI stage 3 with the need for RRT. The use of a more strict definition of recovery substantially reduced the proportion of complete recovery at the expense of more partial recovery. New or worsening CKD was present in 30 % of the patients. Using a calculated versus a true baseline Screat in patients with available baseline did

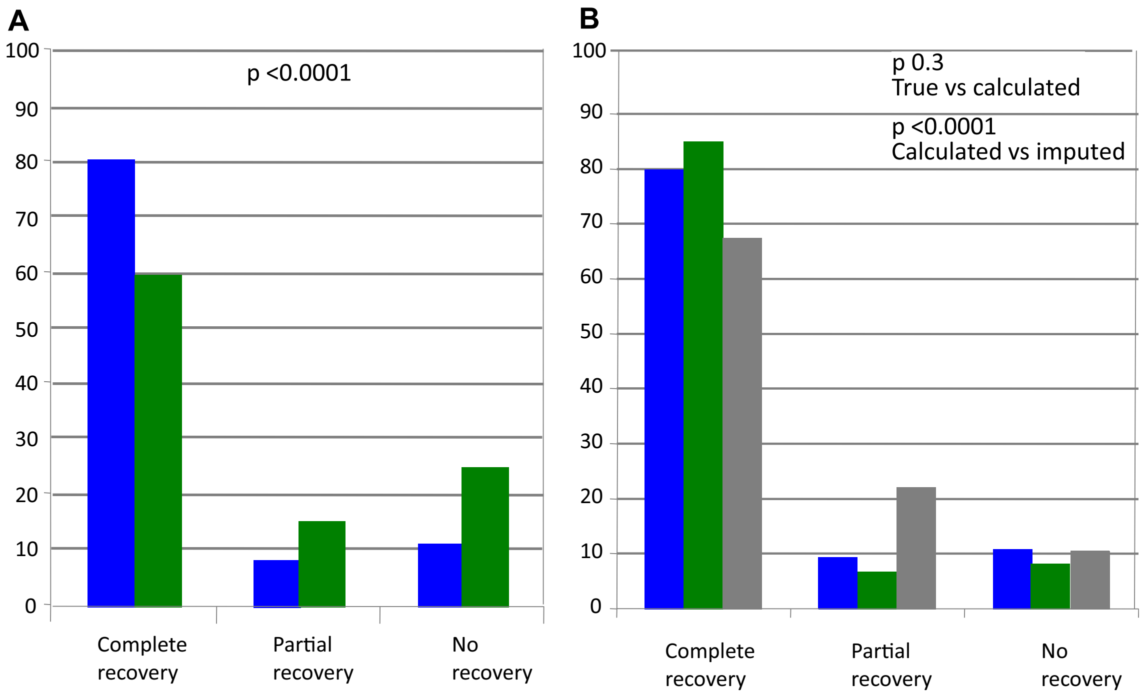

Fig. 2 **a** Recovery in the "true baseline group" ($n = 577$) (*blue bars*) and the "calculated baseline group ($n = 725$) (*green bars*). **b** Recovery in no-CKD patients in the "true baseline group ($n = 411$) (*blue bars*), the calculated baseline group ($n = 291$) (*green bars*), and in the "imputed baseline group ($n = 258$) (*gray bars*) (see text for explanation of group composition)

not affect recovery in patients without pre-existing CKD. However, patients with unavailable and thus obligatory imputed baseline creatinine had different baseline characteristics and a different recovery pattern when compared with those with available baseline Screat. These results highlight the need for a clear description of the included population (inclusion or exclusion of non-survivors, proportion of CKD, AKI severity, method used for baseline creatinine assessment, and proportion of patients with imputed baseline) in studies on this topic.

Although one could argue that kidney outcome should be assessed in all AKI patients, the inclusion of non-survivors (as in [16, 18, 19, 22–24, 26]) not only induces bias (as patients may not have had enough time to recover before they died) but being dead with recovered kidneys also has little significance from a patient's perspective. Since mortality increases with increasing AKI severity, exclusion of non-survivors mainly affects the recovery pattern of more severe forms of AKI. Worsening renal recovery with increasing severity of AKI confirms previous findings [4, 11, 15, 19, 20] and underscores the importance of clearly reporting AKI severity, including the need for RRT in stage 3.

The proportion of CKD patients included in the available studies on AKI recovery varies widely between 5 and 39 % [16, 20–23, 25, 26]. Renal outcome of AKI patients with pre-existing CKD has been reported to be worse [15, 19, 20, 36], similar [11, 22], or better [10] than in no-CKD patients. In our cohort the presence of CKD appeared to result in a better renal outcome for the less severe AKI forms. This may potentially be explained by selection bias, as comorbidity determines the indication for postoperative ICU admission. CKD patients indeed had more elective admissions, a lower APACHE II score, and a shorter hospital stay (data not shown). However, in those patients requiring RRT, the presence of CKD adversely affected recovery, as has been described previously [14, 20, 36].

An ideal definition of recovery from AKI would compare baseline, minimal, and final kidney function with a golden standard for GFR measurement such as inulin clearance. Since this is impossible in clinical practice clinicians will have to rely on the parameters that are available, i.e., serum creatinine and the derived eGFR and AKI staging. Serum creatinine is not an ideal parameter to assess kidney outcome in ICU patients that frequently develop muscle wasting. Indeed, others and we have previously shown decreases in serum creatinine during ICU stay in patients without AKI [37, 38]. Also in this analysis, 40 % of the AKI survivors with true baseline ($n = 673$) had a discharge creatinine lower than baseline (data not shown), suggesting that recovery may have been overestimated.

We primarily defined recovery of AKI as the absence of AKI by the same criteria that are used for its diagnosis. Defining recovery from a disease as absence of this disease seems the most logical approach. Many studies used more strict definitions [7, 10, 16, 19, 20, 22, 24], which, as we have shown, only caused a shift from complete to partial recovery. Whether the difference in complete recovery between KDIGO and more strict definitions has implications for long-term outcome remains to be investigated.

The most meaningful outcome from a patient's perspective and for determining the need for nephrological follow-up is the presence of new or worsening CKD, which predominantly occurs in the most severe stages of AKI. We recognize that eGFR at hospital discharge may not be an ideal method to estimate recovery. Indeed, we have previously shown that eGFR in comparison with 24-h creatinine clearance overestimates recovery at ICU discharge as a result of muscle wasting resulting in a reduced creatinine generation, especially in patients with prolonged ICU stay [37]. This phenomenon may also explain the 20 % of the CKD patients who were "healed" from their CKD after an episode of AKI. Compared with those with persistent CKD, these patients indeed had longer hospital stays and a baseline eGFR closer to the 60 ml/min/1.73 m^2 limit.

Which of the evaluated definitions should be recommended in clinical practice depends on the context and purpose. For determining the need for nephrological follow-up and from a patient's perspective, the CKD status in survivors is likely the most meaningful, whereas in an intervention trial targeted at renal recovery, recovery has to be defined in comparison with baseline kidney function and assessed in the whole population, taking into account the competing end-point of mortality. Whether the absence of AKI criteria or stricter definitions of recovery are more appropriate requires further investigation on the relationship of these definitions of recovery with long-term patient and kidney outcome.

Imputation of baseline Screat in patients with unavailable baseline is proposed by both ADQI and KDIGO [28] and was actually used in several clinical trials on AKI recovery [4, 16, 17, 23, 25]. We noted that patients with unknown baseline Screat had less complete recovery when compared with those with available baseline. This may be explained by the assumptions about the normality of kidney function prior to ICU admission that underlies this strategy and may thus result in underestimation of recovery in patients with "hidden" CKD. In addition, patients with unknown baseline showed different baseline characteristics, which may also explain their different recovery pattern. Exclusion of patients with unavailable baseline may therefore induce ascertainment bias. The proportion of patients with imputed baseline creatinine should be clearly reported, especially since the need for imputation was higher in the most severe forms of AKI.

Strengths of this study are the large sample size, the use of a consensus definition for AKI diagnosis, and active searching for baseline Screat, being available in the majority of the included patients, despite the high proportion of emergency admissions. On the other hand, this study also has limitations. We did not use the urine output criteria because these data were not available. It is possible that patients with both creatinine and urine output criteria or those reaching a higher AKI severity due to oliguria criteria may have different recovery patterns. This will require further investigation. A recent analysis showed that patients reaching stage 3 by both urine output and creatinine criteria have worse short- and long-term survival and dialysis need than those with either creatinine or oliguria alone [39]. The patient population was mainly surgical (79 % of AKI patients). However, more than 40 % had sepsis on admission and less than 50 % were elective postoperative admissions, suggesting that the majority of the surgical patients were admitted after emergency surgery or after postoperative complications had developed ("medical patients with a scar"). We did not use a fixed time point to assess recovery. Hospital discharge might be too early a time point to assess AKI recovery for two reasons: there is not enough time for recovery or patients may have developed muscle wasting resulting in decreased creatinine generation and thus overestimation of AKI recovery [37, 38]. Restoration of muscle mass with rehabilitation after hospital discharge may then result in an apparent deterioration of kidney function. This phenomenon may also result in overestimation of recovery when the minimum Screat during hospitalization is used as a surrogate for baseline Screat. On the other hand, most reports on AKI recovery have reported kidney outcome at hospital discharge [17, 19–25].

Reliable data on AKI recovery have significant implications for planning nephrological follow-up [40–42], for comparative research, and for power calculations in future intervention studies. Our analysis suggests that, in order to be comparable, reports on recovery from AKI should provide detailed data on the included population (inclusion or exclusion of non-survivors, proportion of CKD), on the definition and severity of AKI, on the definition used for and the timing of recovery assessment, and on the handling of missing baseline creatinine.

Conflicts of interest The authors declare that they have no conflicts of interest related to the subject of the study.

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