Incidence, clinical characteristics and outcomes of acute kidney injury in hospitalised patients – the relevance of presence on admission versus post-admission syndrome onset

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May 26, 2020

Abstract

Background and aims: Acute kidney injury (AKI) is a common clinical syndrome that has been consistently linked with increased morbidity and mortality risk. Prognosis, as well as incidence, varies depending on patients characteristics and health care setting. We aimed to evaluate the incidence of AKI and related outcomes in a population of hospitalised patients taking into account the time of onset and severity of the syndrome. Methods: This retrospective study included adult patients admitted to a tertiary care hospital between January 1, 2013, and December 31, 2015, who had at least one inpatient serum creatinine (SCr). We distinguished between AKI apparent at admission (CA-) and afterwards during hospitalisation (HA-AKI). Results: The incidence of AKI was 15.2 %, of which 68% of episodes developed during hospital care. Baseline characteristics of CA-AKI and HA-AKI were similar, but CA-AKI patients were more likely to have more severe episodes and shorter length of stay than patients with HA-AKI (30.9% vs 14.5% with AKI stage 3 and 8.1 vs 14.8 days, respectively). We found a strong, gradual association (after multivariate adjustment) between stage of AKI and mortality. Irrespective the type of AKI, stage 3 was related to the five-fold risk of in-hospital death and a two-fold risk of death at the 6th-month in comparison to No AKI. Conclusions: One in six of hospitalised patients experienced AKI, and almost two-thirds of events developed during the hospital stay. There were no differences in short-term mortality between AKI type, but the risk of death related to the severity of the syndrome.

What is known?

- AKI affects a large proportion of hospitalised patients and encompasses a variety of aetiologies and pathophysiologic pathways.
- An episode of AKI is associated with considerable mortality and other adverse outcomes, including cardiovascular complications, chronic kidney disease and end-stage renal disease.
- Prognosis worsens with increasing severity of AKI.

What is new

- Two-thirds of AKI episodes were detected after the first 24 hours of admission, which entails a window of opportunity for the prevention or mitigation of the syndrome.
- Each subsequent day, more than 1% of patients experienced hospital-acquired AKI

Introduction

AKI is recognised as one of the major complications in hospitalised individuals imposing a substantial burden on patients and health care systems. The syndrome is associated with an increased risk of morbidity and mortality [(1)], progressive deterioration of renal function [(2)] and reduced quality of life[(3-5)]. High costs of AKI-related inpatient care result from prolonged hospitalisations, additional examinations and complications such as the need for renal replacement therapy (RRT), and readmissions [(6, 7)]. Strata of AKI severity have significant prognostic implication [(2)]; however, the direct contribution of AKI to adverse events is difficult to establish. Studies over the last decade have identified complex and bidirectional interactions between the kidney and other remote organ systems, including heart, lungs, brain liver in the settings of AKI[(8)]. As a result, the syndrome is often seen as a proxy of the underlying severity of illness [(9)]involving a spectrum of differing etiologies, pathophysiologies and clinical scenarios [(10)]. Its epidemiological profile is highly dependent on patient characteristics and the setting in which occurs. Studies on AKI in specific clinical cohorts allow understanding the magnitude, clinical features and outcomes in local circumstances, thus providing essential information for prevention and treatment strategies. The objective of this study was to describe the occurrence of AKI in a general population of hospitalised patients and to characterise them with a distinction between AKI apparent at admission and acquired later during hospitalisation. We studied whether the two groups differed in baseline characteristics, AKI severity and short-term outcomes, namely the length of hospital stay, in-hospital and 6-month post-discharge mortality. Besides, in patients free of AKI at admission, we assessed how the risk of the development of the syndrome changes over hospital stay.

Methods

Study design and data collection.

All adult (18 years and more) admissions to a tertiary care university hospital (Centro Hospitalar Universitário de São João), in Porto, Portugal, between January 1, 2013, and December 31, 2015, were considered for this study (Figure 1). Admissions to maternity and gynaecological departments, patients with a history of renal transplant, on chronic renal replacement therapy (RRT) or hospitalised due to end-stage renal disease were excluded. We also eliminated admissions with no inpatient serum creatinine (SCr) measured. For patients with multiple hospitalisations during the study period, we included only one randomly selected admission.

Using institutional electronic medical records, we retrieved patients' demographics, admission and discharge data, discharge diagnoses and procedures coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification, and laboratory results, including SCr with the date and time of biological specimen sampling. All clinical routine SCr measurements were isotope-dilution mass spectrometry-aligned. Comorbidities were identified, and Charlson Index was automatically calculated on the basis of patients' diagnoses of hospitalisations in the previous five years and certain secondary diagnoses of the index hospitalisation. Patients' vital status after discharge was ascertained based on electronic medical records.

This study was approved by the institutional Ethics Committee (Comissão de Ética para a Saúde do Centro Hospitalar Universitário de São João, reference number 365-15 dated: 29-12-2015) with a waiver of informed consents obtained because of the observational nature of the study.

Definitions

The baseline SCr was defined as the median of ambulatory measurements at the same hospital between 7 and 365 days before admission[(11)]. When no preadmission SCr was available, missing values were imputed using random-forest model controlled for patients' age, sex, admission unit and type (medical, surgical and intensive care; emergency and elective), comorbid conditions (history of myocardial infarction, chronic heart

failure, cardiovascular disease, dementia, chronic liver disease, pulmonary disease, diabetes mellitus, chronic kidney disease (CKD), hypertension, cancer, peripheral vascular disease and rheumatologic disease), total Charlson Index and first inpatient SCr. To calculate the estimated glomerular filtration rate (eGFR), we used Chronic Kidney Disease Epidemiology Collaboration formula[12].

AKI was identified using the Kidney Disease: Improving Global Outcomes definition [13, 14] if at least one of the criteria was met: i) SCr [?] 1.5 times higher than the baseline SCr within first 7 days after admission; ii) SCr [?]1.5 times higher than the lowest inpatient SCr creatinine within 7 days and iii) SCr [?]0.3 mg /dL higher than the lowest value within 48 hours, and with the increase sustained for more than 24 hours. Urine output data were not available. We considered one AKI episode per admission and the time of first SCr measurement meeting the criteria was recorded as AKI onset. Patients with AKI apparent within 24 hours of admission were designated community-acquired AKI (CA-AKI), while patients in whom the syndrome developed afterwards were denoted as hospital-acquired AKI (HA-AKI). Based on the ratio of peak inpatient SCr relative to the baseline value, we categorised AKI severity into three stages: Stage 1 - ratio 1.5 to 2 or increase in SCr of 0.3 mg/dL; Stage 2 - ratio 2 to 3 and Stage 3 - ratio [?]3 or increase in SCr above [?]4.0 mg/dL or receipt of RRT.

Statistical analysis

Patients with CA-AKI and HA-AKI were compared with respect to baseline characteristics, clinical presentation and outcomes. Normally distributed continuous variables are reported as means and their standard deviations (SD) or as medians with 25^{th} and 75^{th} percentiles (P25, P75) otherwise. Categorical variables are presented as counts with percentages.

We estimated cumulative incidence functions for the length of hospital stay, in-hospital and 6^{th}-month mortalities and compared them among groups of patients with No AKI, CA-AKI and HA-AKI, and across severity stages, with differences being evaluated by log-rank tests. Discharge and in-hospital death were considered to be the competing risk outcomes, and time to these events was presented in days counted from the syndrome onset. We used multivariable Cox proportional hazard regression to examine the effect of the presence of CA- or HA-AKI and its' severity on the risk of outcomes. There were significant interactions between AKI type (CA- and HA-AKI) and AKI stage, therefore in the Cox model, we created dummies to treat each combination AKI type - AKI stage separately.

To estimate the hazard function for AKI incidence over time in patients free of AKI at admission, we tested two parametric survival regression models with:

exponential distribution of time to an event, T˜exp (λ), assuming constant hazard function over time and given by

$h\left(t\right) = \lambda$

where hazard function *h(t)* denotes the probability of AKI onset on day t , given that the patient remains AKI free to the beginning of day t and λ is a scale parameter,

Weibull distribution of time to an event, T˜Weibull (λ, p), allowing monotonic increase or decrease in hazards over time and given by

$$h\left(t\right) = \lambda\pi\tau^{p-1}$$

where p is the shape parameter (the hazard function is increasing when $p > 1$, and decreasing otherwise).

We plotted the survival functions of the two models against the Kaplan-Meier curve to determine the most suited distribution of time to AKI occurrence. We used Akaike's information criterion (AIC) to evaluate which model better fitted to our data.

All analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and packages: *'random forest'* , *'survival'* , *'survminer' and 'cmprsk'* .

Results

During the study period, there were 113, 723 adult admissions, of which 15,114 (13.3%) were not eligible for this analysis and a further 28,372 (25.9% of the total) were excluded because they had no data on SCr during hospitalisation (Figure 1). After a random selection of one admission per patient, the final study data set included 48,835 patients. Ambulatory preadmission SCr was ascertained in 20.7% of admissions; for the remaining the baseline SCr was imputed.

AKI incidence

AKI was identified in 7,427 patients giving an overall incidence of 15.2%. In 2,847 patients, criteria of AKI were fulfilled within the first 24 hours after admission, accounting for 5.8% of all hospital admissions and 38.3% of all AKI episodes. In 4,580 patients, AKI was not present within the first day, but developed later during their stay, with the earliest SCr keeping with the definition, on average, about five days after admission, irrespective the HA-AKI stage (p=0.05) (Figure 2).

Patients' characteristics

In comparison to No AKI patients, those with AKI were older, more likely to be admitted via the emergency room, had more comorbidities and more often required critical care (Table 1).

Patients with CA- and HA-AKI had a very similar distribution of comorbidities, except for CKD, which we found more prevalent in those with AKI at admission. The type of AKI also related to the principal diagnosis, with genitourinary system and infectious diseases being most frequent in CA-AKI and circulatory system disease in HA-AKI patients. Serum creatinine at admission was, on average, twice as high as the baseline value in patients with AKI at admission. These patients were also more likely to endure more severe AKI (23.2% stage 2 and 30.9% stage 3 in CA-AKI vs 21.4% and 14.5%, in HA-AKI, respectively).

Outcomes

Greater severity of AKI when apparent at admission translated into a higher number of patients requiring in-patient RRT and slightly higher in-hospital mortality (8.3% and 23.3%, respectively, vs 3.9% and 20.6% in HA-AKI) (Table 1). Patients with CA-AKI had a median length of hospital stay of 8.1 days (P25, P75: 4.8, 14.4) which was shorter, on average, almost seven days than a length of stay in HA-AKI group. In the latter, significant differences in the total length of stay between severity of AKI (p<0.001) arose from the number of days after, not the number of days before AKI detection (Figure 2). Among patients who survived hospitalisation, 6.4 % of CA-AKI and 5.3% of HA-AKI died up to 6^{th}-month after discharge.

Generally, the outcomes of our interest worsened according to staging, whether AKI was present at admission or acquired during hospital stay (Figure 3). One should notice that an initially low in-hospital mortality in HA-AKI stage 2 and 3 started steadily increasing and in the post-discharge period exceeded the mortality rate observed in the group of most severe CA-AKI.

After multivariable adjustment in the Cox model, the gradual relationship between the severity of AKI and the risk of the adverse outcome remained significant (Table 2). Patients with HA-AKI stage 1 were least likely to die during hospitalisation among all AKI patients, but still, over twice more likely than No AKI patients (hazard ratio (HR) 2.28, 95% confidence interval (CI): 2.03–2.56). Patients in stage 3 of both CA- and HA-AKI were in a much higher risk of death, either during hospital (HR 5.65, 95% CI: 4.81–6.63 and

HR 6.70, 95% CI: 5.84–7.68) or within six months of discharge (HR 2.50, 95% CI: 1.79–3.49 and HR 2.18, 95% CI: 1.53-3.11), than patients in other stages.

Hazard function

The survival regression with the Weibull distribution of time to AKI occurrence coincided better with the function determined by Kaplan-Meier curve and showed a better fit to our data in comparison to the model with an exponential distribution of time (AIC 47437 vs 47588) (Figure 4 A). The probability of AKI occurring in subsequent days decreased from 1.68 in the first day to 1.27 in the 30th day of hospitalisation (Figure 4 B).

Discussion

In this large cohort of hospitalised patients, AKI was detected in 15.2% of admissions, a proportion that agrees with other studies on general populations of inpatients in developed countries reporting the incidence ranging from 12% to 20% [7, 15, 16]. The variability in the incidence may depend on adopted definitions for AKI and baseline SCr, the frequency of creatinine measurements and clinical settings. Patients with AKI were relatively old, half of them had more than 72 years, with a high burden of comorbidities. This is consistent with the existing evidence of AKI being particularly common in the elderly [17]. Reduced renal reserve in older age[18] together with polypharmacy and greater susceptibility to nephrotoxic drugs, poses this population at high risk of AKI [19]. Furthermore, advanced age is a risk factor for impaired recovery from AKI [20], progression to CKD and it is still not conclusively proven that elderly fully benefit from RRT [21]. AKI development was related to a higher number of comorbidities, including but not limited to cardiovascular, diabetes, chronic pulmonary disease, hypertension and CKD, which confirms the conviction that AKI is a broad clinical syndrome of various etiologies more likely to occur in patients with a higher burden of comorbidities [10].

In epidemiological studies on AKI in hospital settings, the syndrome is often distinguished between community- and hospital-acquired assuming different causes and underlying pathophysiological processes. In our analysis, CA-AKI represented 38% of AKI population, which differs in comparison to previous investigations on AKI present at admission. In the study of Sawhney at el., the proportion was 27%[22]; nevertheless, AKI originates in the community has been consistently found to be more common than hospital-acquired accounting for about 70% of all AKI episodes. This could be explained by the adoption of different criteria to define AKI[23], the extension of the time window for CA-AKI detection up to 48 hours [24] or defining the baseline SCr as normal when the value was unknown [25].

We observed that the risk profile did not differ much between CA- and HA-AKI[22], however, our results confirmed that pre-existing CKD, liver diseases, dementia and history of cancer are more common among patients presenting AKI at admission to the hospital[24]. These patients also sustained more severe AKI than HA-AKI patients [23]. One explanation could be more prevalent or possibly more severe CKD in patients with CA-AKI since the incidence and the severity of AKI increase considerably with lower levels of baseline eGFR [26]. Besides, the high proportion of emergency admission and primary diagnoses in this group indicate that severe renal impairment could result indirectly from an acute condition that necessitated hospitalisation (for example severe infections) or directly from post-renal causes (urinary tract obstructions).

RRT during inpatient was required in 8.3% of CA- and 3.9% of HA-AKI and a large proportion of these patients died before discharge (30% and 50%, respectively) (data not shown) supporting the evidence that dialysis-requiring AKI is a strong predictor of mortality[17, 27]. Given such poor prognosis along with the rapidly escalating incidence of dialysis-requiring AKI[28], development of new instruments such as standardised management recommendations on RRT initiation and discontinuation may be a measure to improve outcomes[29].

Overall, one in five of AKI patients died during the hospital stay which corresponds to mortality rates seen in other studies[4, 22], while in the absence of AKI, mortality runs at 3.6%. When comparing outcomes between CA- and HA-AKI, conclusions of a recent meta-analysis pointed out less severe clinical manifestation and lower mortality in CA-AKI [30]. Higher risk of death in HA-AKI is commonly attributed to underlying chronic illness, specifically cardiovascular disease, increased incidence of complications during the hospital stay or iatrogenic origin of AKI (nephrotoxicity, surgeries) [24, 31], which are considered to do more harm to kidney than prerenal causes[32]. In contrary, we did not find differences in in-hospital and 6^{th}-month mortalities between CA- and HA-AKI in our cohort. These discordant conclusions cannot be explained by the time window we adopted to identify CA-AKI (first 24 hours), which differs from the criteria used by other authors; patients in whom AKI was detected in each of the first three consecutive days after admission had a comparable risk of death during hospitalisation (23.3%, 21.0 and 20% respectively). We suppose the reason for the discrepancy in findings may be dissimilarity in characteristics of underlying populations (age, prevalence of risk factors, in particular, CKD, socioeconomic status) and in settings, in which previous studies were conducted. Our hospital is a tertiary centre which provides specialist care, also for seriously ill patients transferred from smaller centres; therefore, the severity of AKI and mortality might have been affected.

Estimates of the regression model highlighted that severity of AKI, rather than its origin, is a strong and independent determinant of resource utilisation and mortality. It was particularly noticeable for AKI stage 3 but even mild episodes of kidney dysfunction also substantially impacted outcomes of the interest. It should be remembered; however, that reported causes of death are mostly related to coexisting conditions, including causes of AKI, rather than kidney injury[33, 34]. This reinforces the fact that AKI is not a single condition and points to a need for a detailed characterisation of affected patients encompassing etiology, adequacies in management and the level of recovery to improve individualised patient-centred care effectively.

Noteworthy, the risk of death for AKI stage 1 was found to be significantly different in the community- and in the hospital-acquired syndrome. Arguably, this resulted from variant criteria determining stage 1 in the two groups; 15% of all AKI episodes (in patients with SCr concentration above 1.0 mg/dL) was defined by an absolute increase of 0.3 mg/dL above the reference SCr without reaching a relative increase of [?] 50% within a week. Our observations of divergent prognosis are in line with the latest study of Sparrow et al. proving that in patients with AKI stage 1 defined as an absolute change in SCr concentration had shorter stays and were less likely to die in a hospital than those with a 50% relative increase[35].

Among HA-AKI, the highest instantaneously incidence was observed on the second day after admission. We suspect that part of these cases was community-acquired, with later manifestation due to the limited ability of SCr to timely reflect changes in kidney function. Nevertheless, whatever the origin, early risk assessment (for example, at the moment of hospital admission) and identification of high-risk patients provide the opportunity to intervene in the treatment and protect the kidneys from further damage. It is estimated that 20% of hospital-acquired AKI are avoidable[36]. Given that each day more than 1% of patients in our cohort developed AKI, the risk should be re-evaluated during the whole stay. In patients with AKI present at admission, sufficiently early recognition and accurate management have shown to have a positive impact on prognosis[37].

There are some limitations to our study. We did not apply urine criteria to define AKI, as data on urine output were not available, and this might decrease the overall incidence of AKI. Limitations in recording data in structured electronic records also relate to etiologies of the syndrome; therefore, future research into the causes of AKI must include other sources of information. Baseline SCr was known for 20% of patients and missing data were estimated using multiple imputations that showed to be more accurate than commonly used surrogate methods. Finally, this study was conducted at a single tertiary medical centre, and the epidemiological profile of AKI of this population may not be generalisable to patients in other centres or lower health care level settings.

Availability of electronic medical records improves our ability to report a comprehensive depiction of AKI occurrence and related outcomes in the real-life setting. Our study provided valuable insights into the

understanding of magnitude, complexity and strain of the syndrome in this population. There is a necessity for further efforts to increase the awareness of AKI among clinicians and health care professionals and to induce strategies for effective prevention, recognition and management of the syndrome.

Conclusions

The estimated incidence of AKI in this population was 15.2 %, of which 68% of episodes developed during hospital care providing a window of opportunity for changes in patients care and mitigation of AKI, if not prevention, in high-risk patients. CA-AKI and HA-AKI demonstrated similar in-hospital and 6-month mortality as well as demographics and risk factors. The prognosis, however, substantially worsens with the syndrome severity. Both preventive and management strategies to reduce the incidence and improve outcomes are highly warranted.

Funding:

This study was supported by FEDER through the Operational Programme Competitiveness and Internationalisation and national funding from the Foundation for Science and Technology (Portuguese Ministry of Science, Technology and Higher Education) under the Unidade de Investigação em Epidemiologia - Instituto de Saúde Pública da Universidade do Porto (EPIUnit) (POCI-01-0145-FEDER-006862; Ref. UID/DTP/04750/2019); the individual PhD Grant SFRH/BD/104037/2014 *("EMR (electronic medical record)-embedded predictive model for acute kidney injury in an acute care hospital"*) was co-founded by the FCT and POCH/FSE Program.

Acknowledgements

We thank Sofia Correia from Instituto de Saúde Pública, Universidade do Porto, for her exceptional work in data retrieval.

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Figure legends

Figure 1 Study sample selection

ESRD, end-stage renal disease, RRT, renal replacement therapy, SCr, serum creatinine.

Figure 2

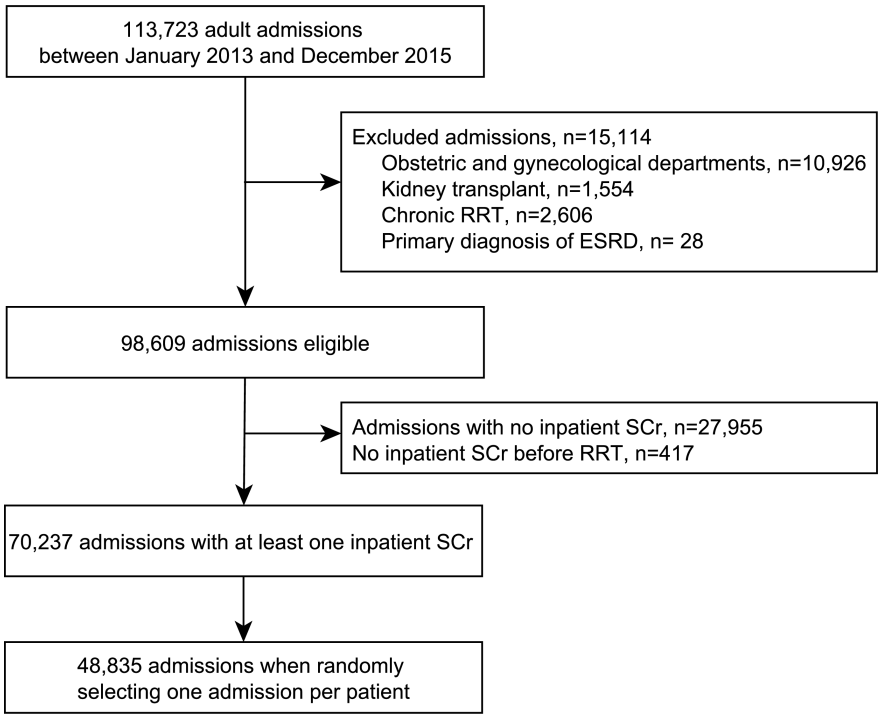
A median number of days of hospital care before and after detection of HA-AKI

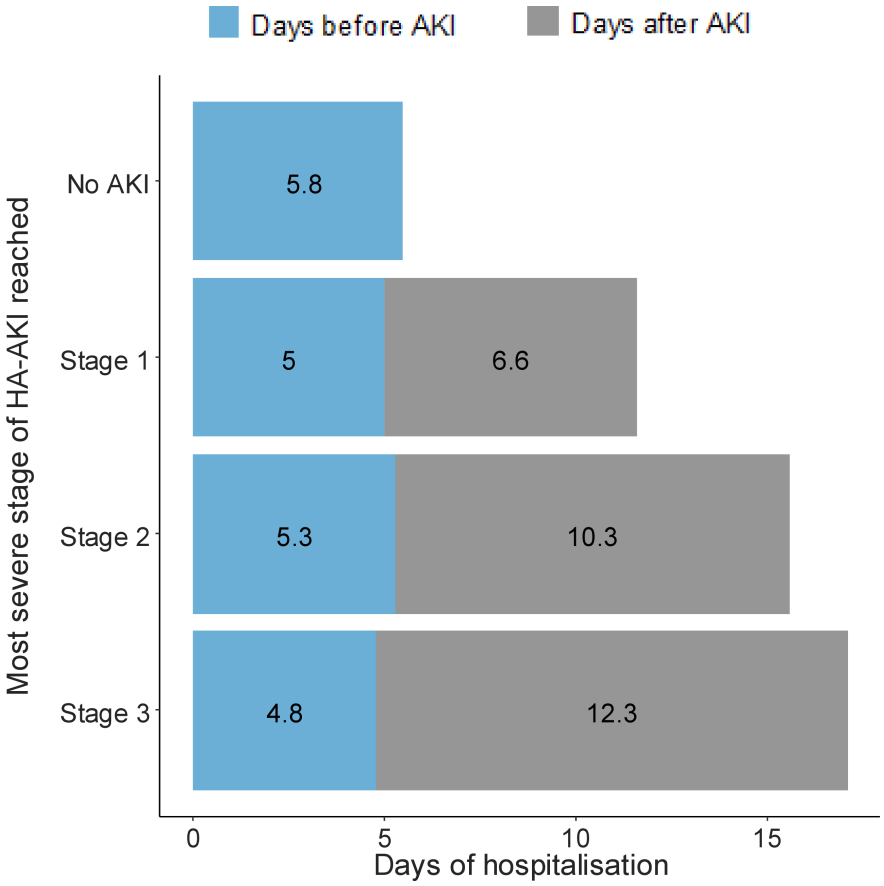
Days before AKI were calculated as the number of days from admission until the AKI criteria were met for the first time. p-value 0.05 and $p<0.001$ for differences between HA-AKI stages in the number of days before and the number of days after AKI, respectively. HA-AKI, hospital-acquired acute kidney injury

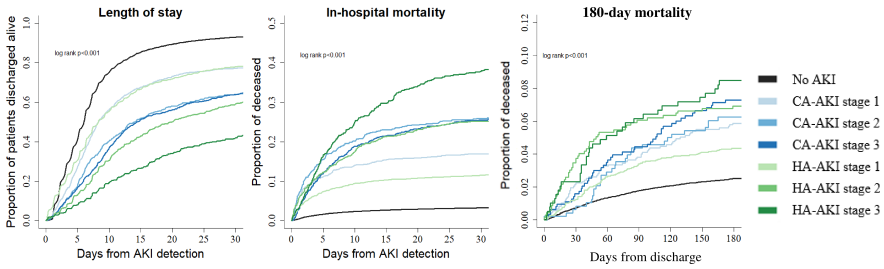
Figure 3 Cumulative hazard function curves comparing the length of stay, the risk of in-hospital and 180-day mortality in No AKI and AKI patients by AKI severity

When plotting hazard functions for the length of stay and the risk of in-hospital mortality, discharge and death were considered to be the competing risk outcomes. CA-AKI, community-acquired acute kidney injury; HA-AKI, hospital-acquired acute kidney injury.

Figure 4 (A) Survival functions estimated by Kaplan-Meier and parametric models (B) hazard function of AKI incidence corresponding to Weibull distribution







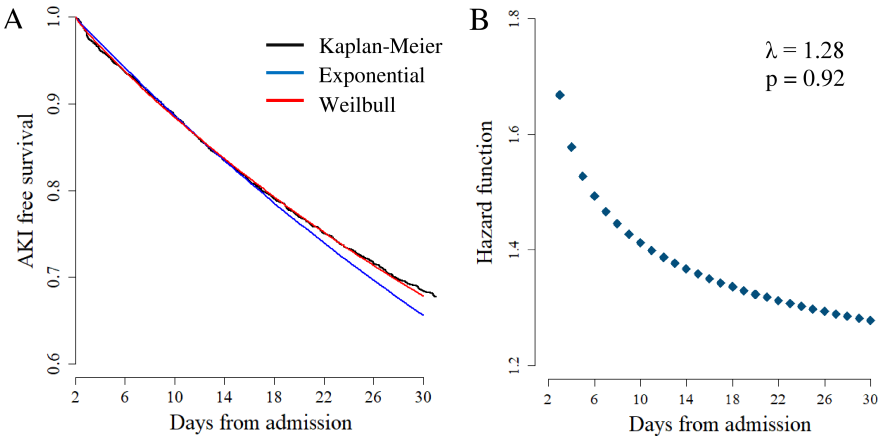


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Table 2.docx available at https://authorea.com/users/325549/articles/453536-incidence-clinical-characteristics-and-outcomes-of-acute-kidney-injury-in-hospitalised-patients-the-relevance-of-presence-on-admission-versus-post-admission-syndrome-onset