Journal of Nephrology (2022) 35:2087–2095
https://doi.org/10.1007/s40620-022-01323-y

ORIGINAL ARTICLE

The effect of different consensus definitions on diagnosing acute kidney injury events and their association with in-hospital mortality

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Received: 18 January 2022 / Accepted: 26 March 2022 / Published online: 20 April 2022

Abstract

Background Due to the existence of different AKI definitions, analyzing AKI incidence and associated outcomes is challenging. We investigated the incidence of AKI events defined by 4 different definitions (standard AKIN and KDIGO, and modified AKIN-4 and KDIGO-4) and its association with in-hospital mortality.

Methods A total of 7242 adult Greek subjects were investigated. To find the association between AKI stages and in-hospital mortality, we considered both the number of AKI events and the most severe stage of AKI reached by each patient, adjusted for age, sex, and AKI staging, using multivariable logistic regression. To predict mortality in AKI patients, as defined by the four definitions, a classification task with two prediction models (random forest and logistic regression) was also conducted.

Results The incidence of AKI using the KDIGO-4 was 6.72% for stage 1a, 15.71% for stage 1b, 8.06% for stage2, and 2.97% for stage3; however, these percentages for AKIN-4 were 11%, 5.83%, 1.75%, and 0.33% for stage 1a, stage 1b, stage 2, and stage 3, respectively. Results showed KDIGO-4 is more sensitive in detecting AKI events. In-hospital mortality increased as the stage of AKI events increased for both KDIGO-4 and AKIN-4; however, KDIGO-4 (KDIGO) had a higher odds ratio at a higher stage of AKI compared to AKIN-4 (AKIN). Lastly, when using KDIGO, random forest and logistic regression models performed almost equally with a c-statistic of 0.825 and 0.854, respectively.

Conclusion The present study confirms that within the KDIGO AKI stage 1, there are two sub-populations with different clinical outcomes (mortality).

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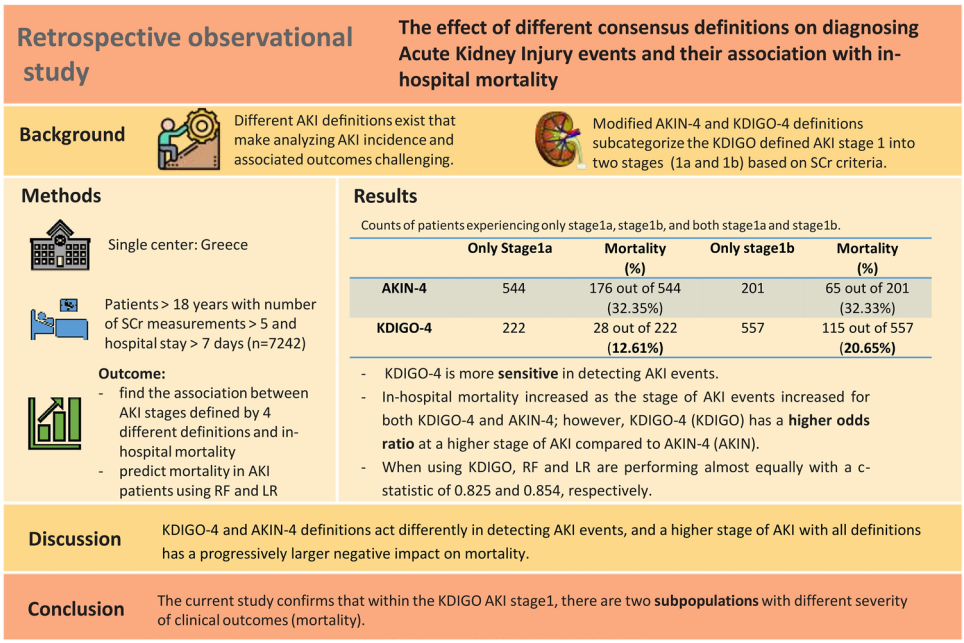
Graphical abstract



Keywords Acute kidney injury (AKI) · In-hospital mortality · Serum creatinine · Prediction model

Introduction

Acute kidney injury (AKI) is a heterogeneous clinical syndrome associated with various clinical presentations and characterized by a rapid deterioration of kidney function [1–5]. This syndrome is associated with considerable morbidity, mortality, and high healthcare costs [6]. AKI may also lead to the development of chronic kidney disease (CKD) or end-stage renal disease (ESRD) [7–9]. The incidence of AKI is increasing worldwide, particularly among hospitalized patients with acute illness and those undergoing major surgery [10–13]. The main causes for this increase could be attributed to the increase in the number of patients hospitalized who are susceptible to this disease: [aging population, increased incidence of cardiovascular disease, diabetes mellitus, and CKD], and to an expanding characterization of modifiable risk factors, such as sepsis, administration of contrast media and exposure to nephrotoxins and nephrotoxic medications [2, 14, 15].

However, the incidence of AKI varies widely in reported studies, which likely reflects differences in case ascertainment, and the location of patient care, but the choice of the definition retained for AKI could also impact this incidence [16–20].

Since 2002 when the first consensus criteria of AKI (known as Risk, Injury, Failure, Loss-of-kidney-function, and End-stage kidney disease or RIFLE) were proposed, a major step has been made towards a uniform diagnostic approach to AKI [21]. This definition required a pre-morbid serum creatinine (SCr) value which was lacking in many patients admitted with acute illness [22].

To address the limitations of RIFLE criteria, the Acute Kidney Injury Network suggested a modified definition, which focused on dynamic changes of SCr, more than on estimated GFR by equations, within a period of 48 h at any time during the patient's hospitalization [23]. In order to calculate absolute and relative increases of SCr within a period of 48 h the lowest SCr value during this period was used as the baseline for the calculations.

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) published a clinical guideline with the aim to harmonize AKIN and RIFLE diagnostic criteria into one universal diagnostic guideline [24]. The new criteria combined the absolute increase in SCr of 0.3 mg/dL over a 48-h period from the AKIN definition with the 50% relative increase in SCr over 7 days from the RIFLE definition into one set of criteria for AKI diagnosis. KDIGO also accepts the 3 stages model proposed by AKIN to categorize the severity of AKI.

These combined diagnostic criteria in the KDIGO definition mean that the absolute increase in SCr over 48 h and the relative increase over 7 days are equivalent criteria. However, several studies have questioned this equivalence as the relative increase criterion may overestimate the AKI diagnosis when the SCr baseline of the patient is low and

the absolute criterion may underestimate AKI and vice versa [16, 25–27]. Some even suggested that the use of relative criteria to diagnose AKI might be inappropriate in patients with low baseline SCr [16].

Recently Sparrow et al. evaluated the impact of further sub-categorizing the KDIGO-defined AKI stage 1 into two stages based on SCr criteria: stage 1a (an absolute increase of SCr of 0.3 mg/dL within 48 h) and stage 1b (a 50% relative increase in SCr within 7 days) and therefore creating a 4-stage KDIGO classification which they named KDIGO-4 (see Table 1). A similar analysis was carried out using the same modification for the AKIN criteria. The present study aimed to investigate the incidence of AKI events defined by 4 different definitions (standard AKIN and KDIGO, and modified AKIN-4 and KDIGO-4) and its association with in-hospital mortality.

Materials and methods

Study design-patient population

This study is a retrospective observational study where we used existing medical records data. The study was approved by the hospital's Ethical and scientific committee.

All patients admitted to KAT General Hospital of Attiki in Athens, Greece, from January 1, 2016, to June 30, 2019, were screened for inclusion. Exclusion criteria included age < 18 years, patients with fewer than five SCr measurements during hospitalization, and hospital stay less than seven days.

The time between admission and discharge was recorded as the actual hospitalization period. Any observation not falling within this period was discarded from the data. Patients with multiple admissions-discharges were included and were considered as separate cases. The hospital is a major trauma center, so neither a nephrology nor a gynecology clinic exist within it. As a result, no pregnant women or any CKD stage 5 or nephrectomized or kidney transplanted patients are admitted to this hospital. Hence, such patients are not included in the dataset.

Finally, of 11,382 hospital admissions, 7242 patients were included in this study (Fig. S1 in Supplementary Material).

Definitions—Acute kidney injury criteria and calculations

Only the creatinine-based criteria were considered because urine output information was not available for all patients according to AKIN score. AKI diagnosis can be made by either an absolute increase of 0.3 mg/dL (26 μmol/L) in SCr within 48 h or a 50% increase from baseline again within the same time frame.

On the other hand, for the KDIGO criteria, the window of observations for the 50% increase from baseline is established over 7 days. In this study, the minimum SCr value within a rolling 48-h window for each inpatient's SCr value defined a dynamic baseline surrogate [28].

Staging of AKI is carried out the same way in both definitions and three severity stages are also defined in both definitions. According to AKIN criteria, stage 2 is defined as an increase of ≥ 2–3 times from baseline, while an increase more than 3 times from baseline in SCr is classified as stage 3. On the other hand, KDIGO defines stage 2 as an increase in SCr of ≥ 2–3 times and stage 3 a rise > 3 times from baseline within7 days [2].

The primary focus of our study was to evaluate the equivalence of the absolute increase of 0.3 mg/dL (stage 1a) with the relative increase of 50% (stage 1b) in the KDIGO and AKIN criteria.

Outcomes: incidence of AKI, association with mortality, and mortality prediction

The primary outcome was to estimate the incidence of AKI events in our cohort and to evaluate the revision of KDIGO criteria into 4 stages as was proposed by Sparrow et al. [25].

We evaluated if there was any association between the number of AKI events and mortality, as well as the association between different stages of AKI and mortality.

We also tested the effect of the revised 4 stages criteria on the association with the selected clinical outcomes.

Table 1 KDIGO-4 and AKIN-4 definition of AKI [25]

	AKIN-4	KDIGO-4
Stage 1a	≥ 0.3 absolute SCr increase over a 48-h window of observation	≥ 0.3 absolute SCr increase over a 48-h window of observation
Stage 1b	≥ 50% relative SCr increase over a 48-h window of observation	≥ 50% relative SCr increase over a 7-day window of observation
Stage 2	≥ 100% relative SCr increase over a 48-h window of observation	≥ 100% relative SCr increase over a 7-day window of observation
Stage 3	≥ 200% relative SCr increase over a 48-h window of observation	≥ 200% relative SCr increase over a 7-day window of observation

As our secondary objective, we applied a machine-learning algorithm to predict mortality in AKI patients. For this purpose, we employed a random forest model [29]. The results of the random forest model were compared with the logistic regression model.

Statistical analyses

Descriptive statistics for the AKI incidence and in-hospital mortality, based on the different definitions AKIN, KDIGO, AKIN-4, and KDIGO-4 are used and presented as percentages. Comparison of percentages is done with the chi-square test.

To analyze the association between AKI events (as defined by the 4 different definitions) and mortality, we considered two different approaches. The first approach was to consider the number of AKI events/stages for each patient. The second approach was to consider only one AKI episode (the most severe). For the first approach, we used the variables age, gender, and the number of AKI events that patients experienced. The model for the second approach consisted of the variables age, gender, and the different stages of AKI.

We also cast a prediction task (classification) by classifying AKI patients based on the clinical outcome (mortality) using multivariable logistic regression and a random forest algorithm. In supervised learning, it is common to use at least two different models based on different mathematics, to confirm (or disprove) the results (and the interpretation concerning the AKI events definitions). Moreover, it will aid researchers in the selection of an appropriate supervised machine learning algorithm for their studies.

Random forest

Random forest is an ensemble-based learning algorithm introduced by Breiman in 2001 [29]. The ensemble technique used by random forests is called Bagging (also known as Bootstrap aggregating). Fig. S3 in Supplementary Material illustrates an example of an ensemble decision tree.

Results

Patients

Of the 11,382 hospital admissions with at least five SCr measurements, 7242 were included in the study after excluding patients who were under the age of 18 (n = 438) and those who had less than 7 days of hospitalization (n = 3702). Characteristics of patients are shown in Table 2. It is worth mentioning that the inclusion criteria were chosen to be able to fulfill the AKI criteria. Out of 7242 patients, 55% were females and the median (IQR) age of the cohort was 77 (18–102) years. The median length of stay was 16 (1–1171) days, and the mortality rate in the hospital was 9.5% (n = 689 patients). Moreover, the distribution of the GFR according to the CKD stages is presented in Table 2.

Table 2 Patient characteristics

Characteristics	All patients ($N = 7242$)
Female sex, *n* (%)	3986 (55.04%)
Median Age, years (IQR)	77 (18–102)
Median Length of stay (days), (IQR)	16 (1- 1171)
Admission department	
Orthopedic clinic	4076 (56.28%)
ICU	1096 (15.13%)
General surgery	1008 (13.92%)
Cardiology	605 (11.6%)
Other departments	457 (6.31%)
Median Creatinine (mg/dL) at admission	
Females	0.80 (0.26–9.95)
Males	0.93 (0.38–13.84)
EKFC-eGFR (mL/min/1.73m^2) at admission	
> 90 (CKD1)	1214 (16.76%)
60–89 (CKD2)	3103 (42.85%)
45–59 (CKD3A)	1271 (17.55%)
30–44 (CKD3B)	1006 (13.89%)
15–29 (CKD4)	531 (7.33%)
< 15 (CKD5)	117 (1.6%)

Values are median (IQR) or *n* (%)

ICU intensive care unit, *eGFR* estimated glomerular filtration rate, *EKFC* european kidney function consortium [30], *CKD* chronic kidney disease

AKI incidence

Patients had a mean age of 72 ± 17.4 years (range, 18–102). Forty-five percent of patients were male. The incidence of in-hospital AKI using KDIGO-4 was 6.72% for stage 1a, 15.71% for stage 1b, 8.06% for stage 2, and 2.97% for stage 3 (Table 3). Percentages for AKIN-4 were 11.5%, 5.83%, 1.75%, and 0.33% for stage 1a, stage 1b, stage 2, and stage 3, respectively. The incidence of in-hospital mortality is also shown for both KDIGO and AKIN definitions in Table 3.

Note that patients may experience multiple AKI events during their hospital stay, with different grades of severity. Consequently, the number of events does not necessarily add up to the total of 7242, as it is the number of AKI events that are counted. Fig. S2 in Supplementary Material illustrates the presence of multiple events with various grades of severity for two random patients.

Table 3 also shows that 5713 out of 7242 patients did not experience an AKI event according to KDIGO-4, while this number was 6172 out of 7242 according to AKIN-4.

Table 3 Incidence of AKI and in-hospital mortality according to KDIGO-4, AKIN-4, KDIGO, and AKIN

KDIGO-4	Proportion of total patients meeting criteria		Incidence of in-hospital mortality	
	n	%	*n*	%
No AKI	5713 out of 7242	78.56	145 out of 5713	2.54
Stage 1a	486 out of 7242	6.72	185 out of 486	38.06
Stage 1b	1138 out of 7242	15.71	448 out of 1138	39.35
Stage 2	584 out of 7242	8.06	327 out of 584	55.99
Stage 3	215 out of 7242	2.97	139 out of 215	64.65
Total AKI events	2423 out of 7242	33.45	1099 out of 2423	45.35”
AKIN-4				
No AKI	6172 out of 7242	85.22	246 out of 6172	3.98
Stage 1a	797 out of 7242	11.00	350 out of 797	43.91
Stage 1b	422 out of 7242	5.83	222 out of 422	52.61
Stage 2	127 out of 7242	1.75	68 out of 127	53.54
Stage 3	24 out of 7242	0.33	15 out of 24	62.5
Total AKI events	1370 out of 7242	18.92	655 out of 1370	47.81”
KDIGO				
No AKI	5708 out of 7242	78.82	145 out of 5708	2.54
Stage 1	1382 out of 7242	19.08	487 out of 1382	35.24
Stage 2	583 out of 7242	8.05	326 out of 583	55.92
Stage 3	217 out of 7242	2.99	140 out of 217	64.52
Total AKI events	2182 out of 7242	30.13	953 out of 2182	43.67”
AKIN				
No AKI	6165 out of 7242	85.13	244 out of 6165	3.96
Stage 1	1018 out of 7242	14.06	424 out of 1018	41.65
Stage 2	127 out of 7242	1.75	68 out of 127	53.54
Stage 3	24 out of 7242	0.33	15 out of 24	62.5
Total AKI events	1169 out of 7242	16.14	507 out of 1169	43.37”

Actually, 461 patients had no AKI events according to AKIN-4 but did have AKI-events according to KDIGO-4 (stage 1a was absent, but there were 634 stage 1b events, 156 stage 2, and 47 stage 3 events among these 461 patients), and 101 of these patients died (stage 1a was absent, but there were 173 stage 1b events, 53 stage 2, and 15 stage 3 events among these 101 patients), while only 2 patients had AKI-events defined according to AKIN-4 but not according to KDIGO-4, and neither of these two died.

AKIN-4 defines significantly more 1a events compared to KDIGO-4. This happens because of the different time windows for stage 1b KDIGO-4 (7 days) compared to stage 1b AKIN-4 (48 h).

More precisely, in order to find patients who are in stage 1a, we define a lower bound which is ≥ 0.3 absolute SCr increase over a 48-h window for both AKIN-4 and KDIGO-4; however, the upper bound is < 1.49 relative SCr increase over a 7-day window of observation for KDIGO-4 and < 1.49 relative SCr increase over a 48-h window of observation for AKIN-4. As a result, the exact same numbers for these definitions have not been calculated.

From Table 3, it can be seen that there are significantly more defined AKI events (overall) when KDIGO-4 (n = 2423) is compared to AKIN-4 (n = 1370), or when KDIGO (n = 2182) is compared to AKIN (n = 1169). The distribution over the different stages 1a, 1b, 2 and 3 also shows a significant difference ($p < 0.0001$): 20.1% (= 486/2423), 47.0% (= 1138/2423), 24.1% (= 584/2423) and 8.9% (= 215/2423) for KDIGO-4 compared to 58.2% (= 797/1370), 30.8% (= 422/1370), 9.3% (= 127/1370) and 1.8% (= 24/1370) for AKIN-4. Using the modified KDIGO-4 the incidence of AKI was significantly higher for stage 1b compared to stage 1a (47.0% vs 20.1%, $p < 0.0001$), while the opposite (30.8% vs 58.2%, $p < 0.0001$) was observed when we used the modified AKIN-4 criteria. AKI stages 1a and 1b detect two different subgroups although there are differences between AKIN-4 and KDIGO-4, with AKIN-4 classifying more patients as 1a (58.2%) whereas KDIGO-4 classified more as 1b (47.0%).

Based on KDIGO-4, there were only 145 deaths out of 5713 patients (2.54%) that experienced ‘no AKI’ event, compared to 246 deaths out of 6172 patients (3.99%) that experienced ‘no AKI’ event based on AKIN-4 ($p < 0.0001$). These 145 deaths (without AKI-events according to KDIGO-4) were all part of the 246 deaths (without AKI-events according to AKIN-4), meaning that 101 deaths (= 246–145) experienced AKI-events as defined by KDIGO-4, but not by AKIN-4, out of a total of 461 patients (21.9%). On the other hand, only 2 patients experienced AKI-events according to AKIN-4 but not according to KDIGO-4, and neither of them died. Both definitions defined AKI-events in 1068 patients, of whom 443 died (41.5%) (see Table S1 and Table S2 in Supplementary Material).

AKI stages 1a and 1b accounted for 1624 cases defined by KDIGO-4 and 1219 cases defined by AKIN-4, and the mortality rate was 39% (= 633/1624) and 47% (= 572/1219) ($p < 0.0001$), respectively. The mortality rate in stages 1a and 1b was 38% and 39% ($p = 0.622$), respectively, for KDIGO-4 while there was a substantial difference in mortality rate in stages 1a and 1b (43.9% vs 52.6%, $p = 0.004$) when based on AKIN-4. However, since, in Table 3, patients that experienced both stages 1a and 1b were registered in both categories we analyzed stage 1 cases as patients who experienced only stage 1a, only stage 1b and as patients who experienced

both stages 1a and 1b. The results are shown in Supplementary Table S3.

Although there are about 5 times fewer patients in stages 2 & 3 (even 9 times fewer in stage 3) based on AKIN-4 (n = 151 in stages 2 & 3, n = 24 in stage 3) compared to KDIGO-4 (n = 799 in stages 2 & 3, n = 215 in stage 3), the mortality rate was about the same (55% vs 58%).

Association between AKI events and mortality, based on multivariable models

Based on the number of AKI events/stages

Figure 1 shows the trend of mortality probability predicted by the logistic regression model with the number of AKI events for both KDIGO-4 and AKIN-4. There is a clear, increasing trend of in-hospital mortality with the number of AKI events.

If we use a probability of 0.50 as the threshold to define "alive/dead", then according to AKIN-4, 3 to 4 events, or more, predict mortality, while according to KDIGO-4, 5 events or more are predictive for death. This is also reflected in the higher odds ratio for the number of AKI events in the logistic regression model when AKI events are defined by AKIN-4. Remember however that there are fewer AKI events (n = 1370) based on the AKIN-4 definition compared to the KDIGO-4 definition (n = 2423). In other words, the probability of dying for a fixed number of events (e.g., 5) based on both definitions, will be higher when the events are based on the AKIN-4 definition (prob = 75–90%), than based on the KDIGO-4 definition (prob = 25–60%).

We also investigated if there is a relation between mortality and the AKI profile (= the number of AKI-events per stage, per patient).

Results show that in-hospital mortality increased as the number of AKI events increased for both KDIGO-4 ($p < 0.001$) and AKIN-4 ($p < 0.001$) (Table 4). For every year older there is a 1.016 higher chance of dying. Also, men have a 1.317 times higher chance of dying than women. Moreover, for every stage 1a AKI event, the risk of death increases by a factor of 1.555 (as compared to no AKI event).

Based on the most severe stage of AKI

To find the association between AKI stages using KDIGO-4 and AKIN-4 and in-hospital mortality, we considered the most severe stage of AKI reached by a patient in a new logistic regression model. Results show that in-hospital mortality increased as the severity of AKI events increased for both KDIGO-4 ($p < 0.001$) and AKIN-4 ($p < 0.001$) (Table 4). In addition, Fig. S4 in Supplementary Material shows the odds ratio of in-hospital mortality using logistic regression, stratified by the most severe stage of AKI-events according to AKIN-4 and KDIGO-4.

Finally, AKIN-4, overall, finds fewer AKI events based on the most severe stage, as seen in Table S4 in Supplementary Material, AKIN-4 (1070) has a smaller number compared to KDIGO-4 (1529).

Based on these results, we see that the mortality rate increases more gradually from stage 1a, 1b, 2, to 3 in the KDIGO-4 definition (12.6%, 24.6%, 50.7% to 64.7%) compared to the AKIN-4 definition (32.4%, 49.3%, 52.8% to 62.5%). Another fact is that the number of 'most severe AKI events' are very different between AKIN-4 and KDIGO-4, with far more events in stage 1a for AKIN-4 (n = 544) compared to KDIGO-4 (n = 222) while the inverse is true for stage 1b (n = 377 for AKIN-4 versus n = 667 for KDIGO-4). Finally, the events AKIN-4 detects for stage 2 and stage

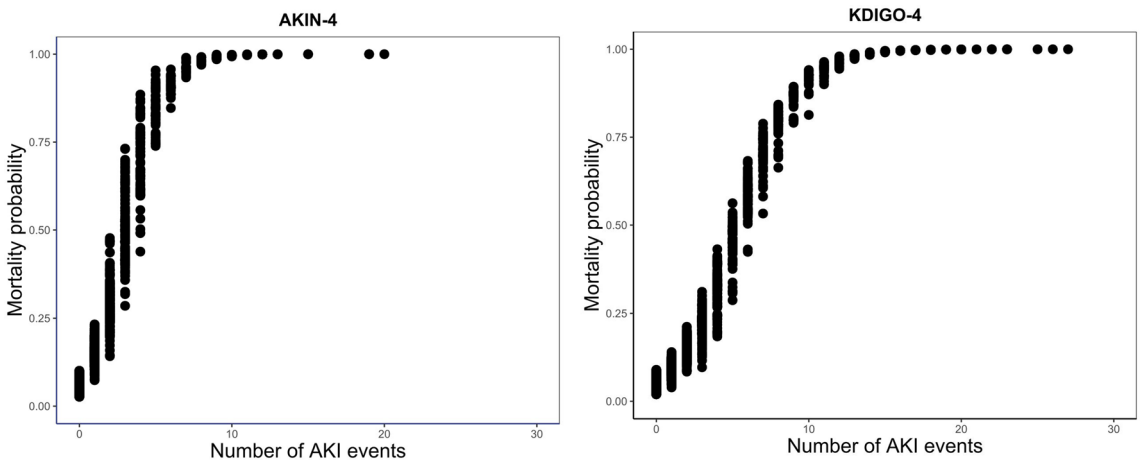


Fig. 1 Mortality prediction using Logistic regression plotted versus number of AKI-events

Table 4 Odds ratios (with 95% Confidence Interval) for the logistic regression models for in-hospital mortality

OR [95%CI]	Number of AKI Events		Number of AKI Stages		Most Severe AKI Stage			
	KDIGO-4	AKIN-4	KDIGO-4	AKIN-4	KDIGO-4	AKIN-4	KDIGO	AKIN
Age	1.016***[1.009–1.023]	1.014***[1.008–1.020]	1.016***[1.009–1.023]	1.015***[1.008–1.021]	1.006*[0.999–1.013]	1.006*[1.000–1.013]	1.006*[0.999–1.012]	1.005*[0.999–1.011]
Sex (Male)	1.288*[1.056–1.569]	1.205*[0.998–1.455]	1.317** [1.078–1.608]	1.225*[1.013–1.480]	1.272*[1.042–1.552]	1.298**[1.075–1.567]	1.220*[1.002–1.486]	1.248*[1.036–1.504]
Stage 1a	1.690*** [1.626–1.759]	2.385***[2.221–2.569]	1.555***[1.331–1.824]	2.165***[1.976–2.379]	4.689***[2.978–7.156]	10.38***[8.254–13.05]	9.725***[7.702–12.30]	14.67***[12.14–17.76]
Stage 1b			1.825[1.704–1.959]	3.093***[2.614–3.686]	11.86***[9.284–15.18]	22.75***[17.78–29.18]		
Stage 2			1.677***[1.522–1.855]	2.353[1.736–3.239]	39.79***[30.61–51.96]	24.28***[16.54–35.82]	39.72***[30.55–51.87]	24.48***[16.68–36.11]
Stage 3			1.405***[1.237–1.603]	2.572**[1.488–4.779]	62.88***[45.23–88.24]	37.45***[16.06–94.04]	62.68***[45.14–87.80]	37.59***[16.14–94.33]

Significance codes: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

3 are significantly lower compared to events detected by KDIGO-4. (125 vs 416 for stage 2 and 24 vs 215 for stage 3, respectively).

Comparing LR with RF for predicting mortality

Fig. S5 in Supplementary Material shows the ROC curve for using KDIGO-4 and AKIN-4, and KDIGO and AKIN for mortality prediction, respectively. By comparing ROC curves (or the AUCs from Table S5), we can conclude that using KDIGO-4 and AKIN-4 definitions have a slightly better (not significant) prediction compared to the original definitions (KDIGO and AKIN). Moreover, we found that logistic regression performs slightly better (not significant, $p < 0.005$) compared to random forest."

Discussion

AKI incidence by KDIGO-4 vs AKIN-4

The adoption of international criteria not only harmonized the definition of AKI, which is based on changes in SCr concentration and the degree of oliguria but also increased the awareness and standardized the diagnosis of AKI. However, our data show that the combined diagnostic criteria in the KDIGO definition for stage 1 are not equivalent and that they detect two distinct patient subgroups as AKI stage 1: one that is defined by an absolute increase of 0.3 mg/dL and one that is defined by the relative increase of 50% above the baseline.

In addition, our data show that KDIGO-4 and AKIN-4 definitions are very different, with KDIGO-4 being more sensitive compared to AKIN-4. These differences in the definitions clearly have consequences in terms of AKI incidence. For example, our analysis showed that a significant number of patients (461 patients) with AKI events defined by KDIGO-4 were classified as no-AKI according to AKIN-4 and only 2 patients were diagnosed with the inverse verdict. These extra "no-AKI" cases defined by AKIN-4 exhibited significantly higher in-hospital mortality.

The most relevant difference between KDIGO and AKIN (in both standard and modified definitions) is related to the conditions necessary to classify patients and is the criterion that requires SCr to increase > 50% from baseline. Whereas AKIN requires this increase to happen within 48 h the KDIGO requires this increase to happen within 7 days. It is obvious that in the strict time frame of 48 h fewer patients will meet the required increase by AKIN compared to KDIGO where the time frame is much broader. The longer we wait to observe the 50% increase in SCr, the more the sensitivity of the definition increases. This is also the case for stages 2 and 3 in both definitions where the incidence of AKI is significantly higher when the KDIGO definition is used compared to AKIN.

Moreover, based on our analysis the distribution of AKI events among the different stages (1a, 1b, 2, and 3) for both definitions are significantly different, with KDIGO-4 defining significantly more 1b events compared to AKIN-4 and AKIN-4 defining significantly more 1a events compared to KDIGO-4. This happens because of the different time windows for stage 1b KDIGO-4 (7 days) compared to stage 1b AKIN-4 (48 h). These findings support the conclusion that KDIGO-4 is more sensitive in detecting AKI events.

Impact of categorizing AKI stage 1 into stage 1a and stage 1b

AKI stage 1a represents patients whose reference SCr rises by 0.3 mg/dl, whereas AKI stage 1b represents patients whose reference SCr increases by 50%. Furthermore, our results show that these two criteria in KDIGO AKI stage

1 identify two different populations in terms of mortality. Table S3 in Supplementary Material shows the number of patients experiencing only stage 1a, 1b, and both. By using KDIGO-4, the mortality rate for these subcategories of patients is significant (13%, 21%, and 43%), while by using AKIN-4 there are no significant differences between patients who experience only stage 1a and only stage 1b (32.35% and 32.33%). Furthermore, to find differences between these two subcategories, we also classified the patients by the most severe stage of AKI reached during hospitalization (Table S4 in Supplementary Material). The results show that the mortality rate between patients who experience stage 1b as the most severe stage is two times higher than for the patients who experience stage 1a as the most severe stage. Consequently, the present study confirms that within the KDIGO AKI stage 1 classification, there are two subpopulations with different severity of clinical outcome (mortality). Additionally, patients with AKI stages 1a and 1b experienced clinically meaningful and statistically significant differences for outcomes of in-hospital mortality (Table 4). This analysis demonstrates how different both definitions are, and also exhibits that separating stage 1 into 1a and 1b shows a gradual increase in mortality rate.

Associations between AKI events and mortality

Based on the LR model, the odds for in-hospital mortality were progressively higher for patients with AKI compared to patients without AKI, and it was higher with higher stages. This was evident with both definitions: AKIN-4 and KDIGO-4. Moreover, the odds for in-hospital mortality were positively associated with the number of AKI events of the patient. Results show that when predicting adverse outcomes (in-hospital mortality in our case), classification seems better with the KDIGO and KDIGO-4 systems.

Additionally, our results show that due to poor sensitivity, the AKIN-4 definition classifies more cases as "no-AKI" compared to KDIGO-4. These "no-AKI" cases exhibited significantly higher mortality during the observation period (22.0% incidence of in-hospital mortality). This explains the increased overall incidence of mortality observed among "no-AKI" cases as defined by AKIN-4 compared to KDIGO-4. In addition, KDIGO (and KDIGO-4) classifies more patients as stage 2 and stage 3 than AKIN (and AKIN-4).

These findings support the conclusion that the classification of a patient at a higher stage of AKI with all definitions (in both standard and modified definitions) has a progressively greater negative impact on mortality. However, KDIGO-4 (KDIGO) has a higher odds ratio at a higher stage of AKI compared to AKIN-4 (AKIN). Moreover, this study demonstrates that KDIGO-4 and AKIN-4 definitions act differently in detecting AKI events, and also shows that separating stage 1 into 1a and 1b has clinically meaningful and statistically significant differences for the outcome of in-hospital mortality.

Conclusion

This study demonstrates that KDIGO-4 and AKIN-4 definitions act differently in detecting AKI events, and also shows that separating stage 1 into 1a and 1b has clinically meaningful and statistically significant differences for outcomes of in-hospital mortality. Repeated AKI episodes are also associated with mortality. In addition, results confirm that a higher stage of AKI with all definitions (in both standard and modified definitions) has a progressively broader negative impact on mortality.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-022-01323-y.

Acknowledgements The authors would like to thank the patients and staff of KAT General Hospital without whom this research would not have been possible.

Author contributions KM and MA designed the study. FNH and HP performed the statistical analysis. FNH and KM wrote the first draft of the manuscript with input from HP, PD, and EC. The manuscript was reviewed and approved by all authors before submission.

Funding The authors of this manuscript received no financial support for the research, authorship, or publication of this article. This research was not supported by any funding.

Data availability statement The data supporting the results of this study cannot be made publicly available due to the lack of approval from our ethics committee in this regard.

Declarations

Conflict of interest The authors of this paper have no conflicts of interest to disclose.

Ethical approval All strategies conducted in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later modifications or comparable ethical standards.

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