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Original Paper

Comparison of Three Methods Estimating Baseline Creatinine For Acute Kidney Injury in Hospitalized Patients: a Multicentre Survey in Third-Level Urban Hospitals of China

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Key Words
Acute kidney injury • Baseline creatinine • Imputation method • KDIGO classification • Early detection

Abstract
Background/Aims: A lack of baseline serum creatinine (SCr) data leads to underestimation of the burden caused by acute kidney injury (AKI) in developing countries. The goal of this study was to investigate the effects of various baseline SCr analysis methods on the current diagnosis of AKI in hospitalized patients. ***Methods:*** Patients with at least one SCr value during their hospital stay between January 1, 2011 and December 31, 2012 were retrospectively included in the study. The baseline SCr was determined either by the minimum SCr (SCr_{MIN}) or the estimated SCr using the MDRD formula (SCr_{GFR-75}). We also used the dynamic baseline SCr ($SCr_{dynamic}$) in accordance with the 7 day/48 hour time window. AKI was defined based on the KDIGO SCr criteria. ***Results:*** Of 562,733 hospitalized patients, 350,458 (62.3%) had at least one SCr determination, and 146,185 (26.0%) had repeat SCr tests. AKI was diagnosed in 13,883 (2.5%) patients using the SCr_{MIN}, 21,281 (3.8%) using the SCr_{GFR-75} and 9,288 (1.7%) using the $SCr_{dynamic}$. Compared with the non-AKI patients, AKI patients had a higher in-hospital mortality rate regardless of the baseline SCr analysis method. ***Conclusions:*** Because of the scarcity of SCr data, imputation of the baseline SCr is necessary to remedy the missing data.

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The detection rate of AKI varies depending on the different imputation methods. SCr_{GFR-75} can identify more AKI cases than the other two methods.

Introduction

AKI is a common disease in hospitalized patients and has a high mortality due to the severity of injury associated with poor outcomes [1-5]. The awareness of the importance of AKI makes clinicians strive for epidemiological research. Previous data have shown that the incidence of AKI in hospitalized patients varied between 1% and 21.6% [6, 7]; the differences mainly reflect the different clinical settings and definitions. However, the burden of AKI in hospitalized patients is vastly underestimated, especially in developing countries [8]. Even though the process of data generation was detailed and reliable, the underestimation was obvious [9-12], let alone the diagnosis rate by disease code [13]. A nationwide cross-sectional survey of approximately 1.4 million patients reported that the detection rate of AKI in Chinese hospitalized adults was 1% according to the KDIGO criteria [9].

One possible reason for the underestimation might be the lack of serum creatinine (SCr) data because the present evaluation of AKI incidence is based on the changes of SCr. It has been reported that less than 30% patients had repeated SCr tests in China [10], while more than 60% patients had two or more SCr tests in developed countries [2, 14]. Therefore, it was difficult to determine the baseline SCr especially when the data retrieved from the hospital database was lacking.

There are several ways to define the baseline SCr. The most widely used, which was recommended by KDIGO in 2012, is utilizing the lowest SCr value during hospitalization as the baseline SCr to define AKI [15]. Some investigators also thought that it may be better to measure SCr over a longer time-frame between 7 and 365 days before hospital admission [16]. When the SCr result is lacking, an "imputation" value becomes important. There are two methods of "imputation". In 2004, the Acute Dialysis Quality Initiative (ADQI) suggested the use of the estimation of baseline creatinine by solving the Modification of Diet in Renal Disease (MDRD) equation assuming a glomerular filtration rate of 75 ml/min/1.73 m^2 as the baseline SCr, and it has been widely used [17, 18]. However, the specificity of this method for AKI diagnosis was questioned, especially in patients with chronic kidney diseases (CKD). Siew [19] has recently demonstrated that the combination of multiple imputation methods can improve the accuracy in estimating lacking baseline SCr values and reduce misclassification of AKI, which was validated by several studies [10] and thought to be a suitable approach [10].

To our knowledge, no multicentre study so far has validated these different methods in one cohort of patients in China, as a developing country short of repeated SCr data in hospitalized patients. Concerning the situation in developing countries, it is more important to address the lacking data by means of epidemiological studies. We designed a multicentre, retrospective cohort epidemiological survey of AKI in hospitalized patients to compare three different methods of analysis of baseline SCr and to determine the accuracy of AKI diagnosis. The study was conducted in four Grade 3, Class A hospitals representing the east, west and south regions of China.

Materials and Methods

Study population

Four hospitals from Zhejiang, Shanghai, Chongqing and Fujian participated in the study. All of the hospitals were comprehensive Grade 3, Class A government-funded public hospitals. Detailed information is presented in Table 1. Since it was a retrospective study and no intervention was conducted, the ethics committees waived the need for informed consent.

Table 1. Detailed information of the participated hospitals

Hospital	Number of beds	Grade	Province	ICU beds	Number of Patients in 2011-2012
The First Affiliated Hospital of Zhejiang University	2500	Grade III Class A Hospital in China	Zhejiang	58	175967
Third Military Medical University,People's Liveration Army of China	2500	Grade III Class A Hospital in China	Chongqing	50	171322
The First Affiliated hospital of Fujian Medical University	2800	Grade III Class A Hospital in China	Fujian	12	116640
Changzheng Hospital, Second Military Medical University	980	Grade III Class A Hospital in China	Shanghai	49	98804

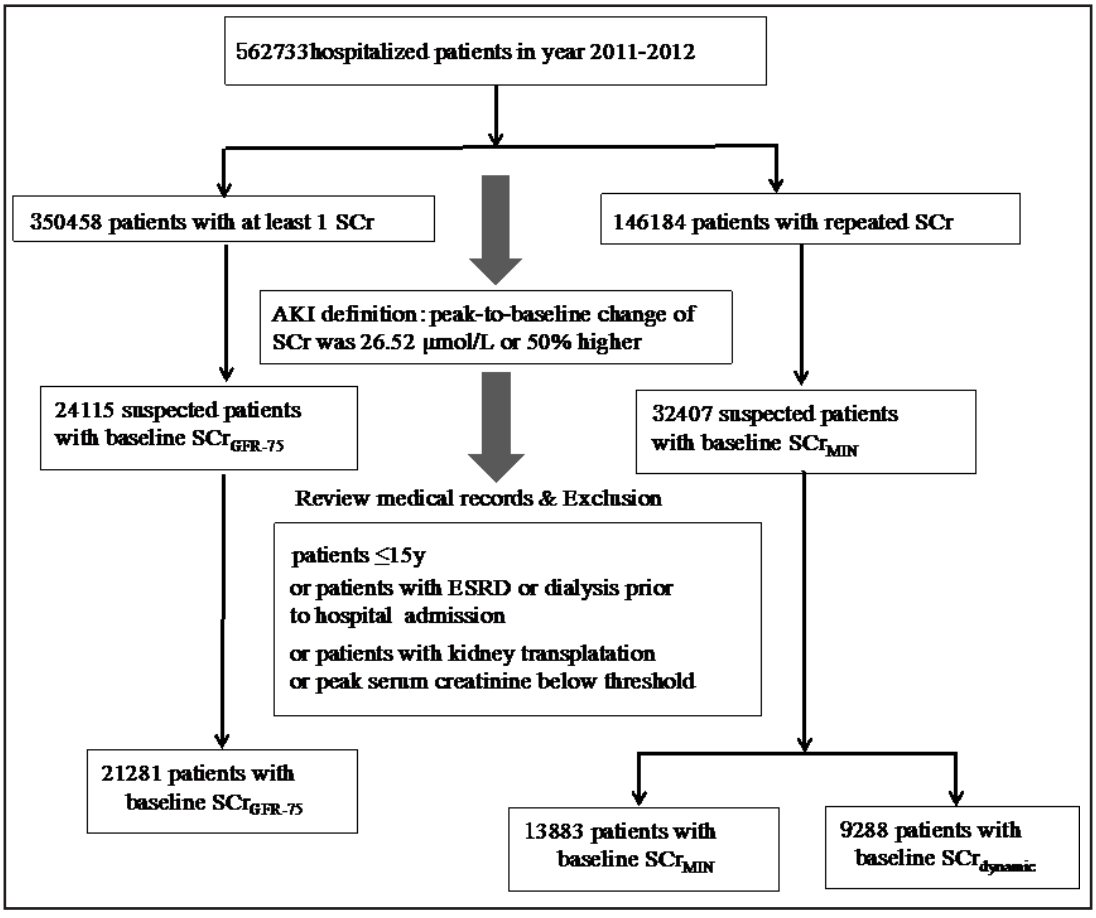

Fig. 1. Study inclusion and exclusion flow diagram.

Data collection

The hospital medical records (including age, sex, admission and discharge data, in-hospital death, SCr data and test time) of all the hospitalized patients were exported from an electronic medical records system. The statistical analyst screened out AKI patients according to the AKI definition. Detailed information of the preliminary selected AKI patients was further inspected by clinicians, including the basic demographic data, comorbidities, date of hospitalization and ICU discharge, survival at ICU and hospital discharge, and need for RRT in hospital. The presence of comorbidities was determined by the diagnosis codes at admission and discharge. For certain conditions, the comorbidities were defined according to the vital signs such as the blood pressure. Nephrologists reviewed the cases in accordance with specific standards. All centres were asked to complete a questionnaire for each AKI patient, and the data were screened in detail by experienced nephrologists.

Identification and Classification of AKI

The screening process was conducted using the laboratory information system. All patients above 15 years old who had at least one SCr were selected and recorded with SCr values between January 1, 2011 and December 31, 2012. If a patient had multiple hospital or ICU admissions, only the first hospital admission was considered. We retrieved the AKI patients by different strategies. Patients with pre-existing end-stage kidney disease (ESRD), prior kidney transplant or hospitalized for less than 24 hours were excluded. The study inclusion and exclusion flow diagram is shown in Fig. 1.

The assays for SCr were the creatinine enzyme method or alkaline picric acid method (Jaff method). The different assays for SCr were calibrated. The mean frequency of Cr testing was defined as the number of Cr tests/length of stay. The baseline SCr was determined three different ways. First, we defined the lowest value during hospitalization as the baseline SCr_{MIN}. Meanwhile, the baseline SCr_{GFR-75} was calculated from the Modification of Diet in Renal Disease (MDRD) study equation assuming an eGFR of 75 mL/min/1.73 m^2 for patients. This method was recommended by the ADQI in 2004 as the single imputation of eGFR75 and is still widely used currently. AKI was defined by the peak-to-baseline change of SCr. If the difference was 26.52 μmol/L or 50% higher, the patients were selected for further investigation. The hospital medical records of suspected patients were further screened case-by-case for re-determination. If a patient had a previous history of CKD and no record of SCr before hospital admission, the lowest value during the hospitalization was recorded as the baseline SCr. If the patients fulfilled the time window of 7 days or 48 hours according to KDIGO criteria, we recorded the baseline SCr as the baseline $SCr_{dynamic.}$

Statistical Analyses

Continuous variables were presented as the means ± SD and categorical variables were presented as percentages (95% confidence intervals [CIs]). Student's t and χ2 test were used for comparing two groups; one-way ANOVA or Wilcoxon rank-sum test was used for comparing multiple groups. Multivariate logistic regression analysis was conducted to investigate risk factors associated with hospital mortality and renal recovery, and the results were presented as odds ratios (ORs) with 95% CIs. We also calculated inter-rater agreement using the weighted k statistic to assess the agreement between three AKI diagnoses based on $SCr_{GFR-75,}$ SCr_{MIN} and $SCr_{dynamic}$. All the analyses were performed using the SPSS Statistics 20.0, and $p \leq 0.05$ was considered statistically significant.

Results

In 562, 733 hospital patients between January 1, 2011 and December 31, 2012, 350, 458 (62.3%) had at least one SCr determination, and 146, 185 (26.0%) had more than one SCr. Among those who had more than one SCr, the mean frequency of SCr tests was 0.5. Those patients with repeated SCr measurements during hospitalization were older (55.5±16.1 vs 49.3±18.2, $p<0.001$), and had a longer hospital stay (16.0±16.4 vs 8.3±14.9, $p<0.001$) compared to the patients with only one SCr.

AKI occurred in 21, 281 (3.8%) patients using baseline SCr_{GFR-75}, 13, 883 (2.5%) patients using baseline SCr_{MIN}, and 9, 288 (1.7%) patients using baseline $SCr_{dynamic}$. The average in-hospital mortality of AKI patients was 11.5%, 8.2% or 11.5% when using the SCr_{GFR-75}, SCr_{MIN} or $SCr_{dynamic}$ methods, respectively. Detailed information is presented in Table 2. Compared with non-AKI patients, AKI patients using any of the three baseline SCrs showed a significant association with in-hospital mortality. The odds ratio was 15.8 using the SCr_{GFR-75} (95% CI 6.2-16.0, $p<0.05$), 9.9 using the SCr_{MIN} (95% CI 9.8-25.4, $p<0.05$), and 24.3 using the $SCr_{dynamic}$ (95% CI 14.9-39.5, $p<0.05$).

We compared across the three definitions of AKI. The percentage agreement for AKI diagnosis based on SCr_{MIN} and $SCr_{dynamic}$ was 98.5% with a kappa of 0.8 (95% CI, 0.8–0.8). There were 297, 146 non-AKI cases and 6, 968 AKI cases that met both AKI definitions. The percentage agreement for AKI diagnosis based on $SCr_{dynamic}$ and SCr_{GFR-75} was 94.7% with a kappa of 0.4 (95% CI, 0.4-0.5). There were 307, 010 non-AKI cases and 9288 AKI cases that

Table 2. Characteristic of AKI patients. Abbreviation: AKI, acute kidney injury; SCr, serum creatinine

Characteristics	Baseline SCr (imputation of GFR 75 ml/min/1.73 m²)	Baseline SCr (min)	Baseline SCr (dynamic)
AKI Patients	21281 (3.8%)	13883 (2.5%)	9288 (1.7%)
Age (years)	63.7±16.2	60.4±16.6	60.4±16.4
Male sex (%)	65.6%	71.4%	45.3%
Baseline SCr (umol/L)	86.9±11.3	90.1±58.4	89.8±62.2
In-hospital mortality (%)	11.5%	8.2%	11.5%
Length of stay (days)	14.6±12.5	18.2±16.1	18.8±16.1
AKI stage			
1	10172 (47.8%)	6786 (48.9%)	4019 (43.3%)
2	5124 (24.1%)	3578 (25.8%)	2450 (26.4%)
3	5984 (28.1%)	3519 (25.4%)	2819 (30.4%)

Table 3. Different outcomes among every AKI stage. Abbreviation: ICU, intensive care unit

AKI Stage	1	2	3	Total	p
ICU	291 (9.5%)	187 (10.3%)	354 (16.9%)	832 (11.9%)	<0.001
Length of ICU stay (d)	11.9±19.1	12.3±17.5	16.5±31.0	14.0±24.9	0.042
Length of Hospital stay (d)	18.5±18.6	17.6±18.7	18.8±20.9	18.4±19.4	0.151
Mortality	223 (7.3%)	241 (13.2%)	432 (20.7%)	896 (12.8%)	<0.001
Complete renal recovery	1570 (51.0%)	838 (46.0%)	785 (37.6%)	3193 (45.7%)	<0.001

met both AKI definitions. The percentage agreement for AKI diagnosis based on SCr_{GFR-75} and SCr_{MIN} was 95.4% with a kappa of 0.6 (95% CI, 0.6-0.6). There were 295, 812 non-AKI cases and 10, 526 AKI cases that met both AKI definitions.

To get a better understanding of the prognosis and risk factors of AKI, we screened the detailed records of AKI patients between January and December 2011 using the SCr_{GFR-75} as the reference SCr in the medical record system. The in-hospital mortality of AKI patients was 12.8% (896 of 6989). When discharged from the hospital, 45.7% achieved complete renal recovery and 2.6% required renal replacement therapy (RRT). The different outcomes among every AKI stage are summarized in Table 3. The in-hospital mortality increased, and the complete renal recovery rate decreased significantly along with the AKI stage. The likelihood of admission to ICU and the ICU duration time were different as well.

Multivariate logistic regression was conducted to explore independent risks of in-hospital mortality. Important risk factors for in-hospital mortality included AKI stage (p<0.001), comorbidity with chronic liver disease (p<0.001), cancer (p=0.004), infection (p<0.001), use of diuretics (p<0.001), renal hypoperfusion during hospitalization (p<0.001), need for RRT (p=0.024), trauma (p<0.001) and the history of admission to ICU (p<0.001). These results are shown in Table 4.

Discussion

It is inevitable that the incidence of AKI varies a lot in different studies [2, 9, 10, 20, 21]. The reported incidence of AKI in developing countries is much lower than that in developed countries [6]. The huge difference may mainly come from the different AKI definitions and study strategies. A standard definition of AKI is important in both clinical and research settings, but the AKI definition has been controversial for a long time. Since the RIFLE classification was proposed in 2004 [22], this controversy has continued to evolve rapidly. The AKI Network (AKIN) [23], and the Kidney Disease Improving Global Outcomes (KDIGO) [15] classifications revised the definitions and have been validated in a growing number of populations. Nevertheless, the extensive use of accepted KDIGO or other definition did not eliminate the heterogenicity of the AKI definition.

Table 4. Multivariable Logistic regression analysis on patient mortality. Abbreviation: AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; RRT, renal replacement therapy

Variable	P value	OR	95% CI
AKI stage	<0.001	1.8	1.6-2.0
History of CKD	0.002	0.6	0.4-0.8
History of Chronic liver disease	<0.001	2.0	1.6-2.5
Cancer	0.004	1.6	1.2-2.1
Infection	<0.001	2.8	2.3-3.3
Application of diuretics	<0.001	1.9	1.6-2.3
Hypotension	<0.001	4.1	3.2-5.3
Trauma	<0.001	3.0	1.8-5.0
Urinary tract obstruction	<0.001	0.3	0.2-0.6
ICU	<0.001	2.2	1.8-2.7
RRT	0.024	1.4	1.1-1.9

Previous studies have shown that the AKI prevalence in China varied from 0.14% to 3.19% [11, 12]. Lately, the nationwide data showed the detection rate of AKI was 0.99% according to the KDIGO criteria and 2.03% according to the expanded criteria [9]. The age and sex of the patients in our study and other Chinese studies seemed to be similar [9]. We noticed that the burden of AKI has been underestimated due to the lack of adequate SCr measurements, especially in less economically developed areas. It was reported that less than 30% patients had repeated SCr tests in China [10], while in developed countries more than 60% had two or more SCr tests [2, 14]. Since most of the present AKI detection criteria are based on the changes of SCr, it is important and necessary to find a solution to the missing data in epidemiological studies. A similar situation also exists in other developing countries. To the best of our knowledge, this study is the first multi-centre, retrospective cohort epidemiological survey of AKI in hospitalized patients, validating three different methods of baseline SCr definition in one cohort in China, a developing country short of repeated SCr data.

We found that 62.3% of hospitalized patients had at least one SCr value, and 26.0% had repeated SCr. This finding was similar to previous studies [9, 10]. Given that most patients did not have repeated SCr, we included the patients who had at least one SCr into our further screen. The baseline SCr of these patients was calculated based on the MDRD equation assuming an eGFR of 75 mL/min/1.73 m^2. A previous study has shown that an MDRD-derived baseline serum creatinine leads to increased detection of AKI [24]. More recently, a definition using 48-hour window resulted in a more limited AKI diagnosis. However, Zavada J et al. found that this definition could lead to some misclassification, especially with the more severe stages [25]. The consensus opinion was that different methods may cause some false-positive detection of AKI, but remain necessary [18]. Our results were as expected. Among the three methods, the SCr_{GFR-75} classified more patients into AKI than the other two methods. However, the OR value of in-hospital mortality was the lowest. The SCr_{MIN} method got a better agreement with $SCr_{dynamic}$ compared to $SCr_{GFR-75.}$ However, we have to face the problem that in China, less than 30% patients admitted to hospital have repeated Scr determinations, which might lead to a considerable underestimation of mild cases. To get closer to the goal of "n missed diagnosis", we chose this definition. Moreover, the misclassification may occur primarily in patients with eGFR less than 60 ml/min [19]. Patients with CKD may be subject to more SCr measurements and in the further screen process, it is more likely to reach the correct diagnosis.

Other methods to estimate the baseline SCr include the long time window between 7 and 365 days before hospitalization, the short time frame within 7 d/48 h and the multi-imputation value when SCr is lacking [26]. A previous study has suggested that using the mean outpatient SCr might be the best method if outpatient and inpatient results could be distinguished automatically [16]. However, concerning the lacking data, it was difficult to obtain long time frame SCr data. Using the lowest inpatient SCr method could allow the

most sensitive result. The multi-imputation methods seemed to be the most comprehensive method, but its use in routine practice was impractical.

The awareness of AKI has been raising as a result of its global perspective as a silent killer, since it can be easily ignored by clinicians and is associated with poor patient outcomes [27]. Over the past years, the mortality of AKI patients has not decreased [28, 29]. Our study suggests that the poor prognosis is associated with its severity, which is consistent with previous studies [21, 30]. The in-hospital mortality increased, and the complete renal recovery decreased as the AKI staging went worse. Same trends were significant in the rate of ICU admission and the duration of ICU and hospital stay. Other risk factors include comorbidity with CKD, chronic liver disease, cancer, infection, use of diuretics, renal hypoperfusion during hospital period, need for RRT, trauma and the history of ICU admission. In addition to renal injury, these patients also had other extra-renal organ damages, leading to further kidney destruction [31]. The interactions between the kidneys and other organs (heart, liver, lung) form a vicious cycle, ultimately affecting the prognosis of patients.

Our study has certain limitations. First, it was a medical record database study. All the data used for establishing AKI, including the SCr data and the existence of CKD were derived from the medical records system. However, the patients' data were limited and incomplete. Thus, we could not validate the long time frame baseline SCr, which might reduce the reliability and accuracy AKI diagnosis. Additionally, we did not use urinary output as a criterion. In fact, less than 20% patients had urinary sample record. This was also an alert to clinicians. Third, we did not perform an aetiological analysis. Since our study was a brief screening, it was difficult to distinguish the exact causes of AKI from the existence of complex comorbidities according to the dataset.

Conclusion

Sufficient SCr data was still lacking in most patients in China. Imputation of the baseline SCr was necessary to remedy the lacking data. $SCr_{GFR\text{-}75}$ classified more patients into AKI than the other two methods. It might be a good approach to implement the $SCr_{GFR\text{-}75}$ imputation method automatically using computerization to detect AKI patients. Actually, in some hospitals, the GFR value calculated according to serum creatinine using MDRD formula is reported in the laboratory records. However, its accuracy and reliability still need to be validated. Mild AKI could be easily ignored, especially by non-nephrologists. Many clinical comorbidities and the widespread use of nephrotoxic drugs are related to both overall and renal outcomes. Thus, it is essential to improve the awareness of AKI and adopt special diagnostic protocols for the care of patients who develop AKI.

Disclosure Statement

The authors declare that they have no conflicts of interest regarding the publication of this article.

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