European Journal of Internal Medicine 60 (2019) 78–82

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Computerized algorithms compared with a nephrologist's diagnosis of acute kidney injury in the emergency department

Arnar Jan Jonsson[a,b], Ingibjorg Kristjansdottir[b], Sigrun Helga Lund[a], Runolfur Palsson[a,c], Olafur S. Indridason[c,*]

[a] University of Iceland, Reykjavik, Iceland
[b] Internal Medicine Services, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland
[c] Division of Nephrology, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland

ARTICLE INFO

Keywords:
Acute kidney injury
Serum creatinine
Diagnosis
Computer algorithms
KDIGO criteria

ABSTRACT

Background: The aim of this study was to examine acute kidney injury (AKI) diagnosis based on different computerized algorithms compared with a nephrologist's diagnosis in patients visiting an emergency department (ED) of a university hospital.

Methods: In this retrospective study, we used electronic medical records at the University Hospital in Reykjavik to identify all patients aged ≥18 years, who presented to the ED in the year 2010 with an elevated serum creatinine (SCr) level. All SCr values were reviewed and a nephrologist determined whether AKI was present using the KDIGO SCr criteria and clinical data. Computerized algorithms based on the KDIGO SCr criteria, accounting for various time intervals for baseline SCr and changes in follow-up SCr, were constructed using the statiscal software R.

Results: At 53,816 ED visits, SCr was measured in 15,588 patients for a total of 21,559 measurements. Elevated SCr was observed in 2878 (18.4%) patients. Strict adherence to the KDIGO SCr criteria yielded a 79% sensitivity, 94% specificity, 68% positive predictive value (PPV) and 96% negative predictive value (NPV) for the diagnosis of AKI. Allowing for a longer time frame (> 365 days) for baseline SCr, resulted in 93% sensitivity, 96% specificity, 80% PPV and 99% NPV. The algorithms which included a decrease in SCr from the index ED value yielded a sensitivity of 97% but lower specificity, 74% and 80%.

Conclusions: The algorithms that perform best yield excellent sensitivity and specificity and could be used to identify patients with AKI in the ED to enhance early diagnosis and treatment.

1. Introduction

Acute kidney injury (AKI) is characterized by a sudden decrease in kidney function, manifested by a rise in serum creatinine (SCr) which frequently is not recognized in the early stages, delaying the institution of potentially effective intervention. Several diagnostic criteria have been developed to facilitate the diagnosis of AKI and the comparison of epidemiological studies performed in different clinical settings. The most recent and widely accepted diagnostic criteria were published as part of clinical practice guidelines on AKI by the Kidney disease: Improving Global Outcomes (KDIGO) work group in 2012 [1]. In the KDIGO guidelines, the RIFLE and AKIN criteria were combined to generate a new definition and classification system as numerous studies that used these criteria had showed a significant increase in hospital mortality and morbidity with increasing severity of AKI [2–8]. Accordingly, the diagnosis of AKI is based on both absolute and relative increase in serum creatinine (SCr) from a baseline value. Although this recent consensus definition of AKI is a step forward, both for clinical practice and research, limitations remain since determining the baseline kidney function can be challenging as recent SCr values may not be available.

Many studies of AKI in the hospital setting have concluded that preadmission SCr values provide the most accurate measure of baseline kidney function and that use of surrogate values may result in misclassification of AKI and inflation of the AKI incidence [9,10]. Conversely, there is lack of agreement on the optimal time frame of SCr values prior to hospitalization [9]. One study suggested that the mean outpatient SCr, measured between one week and one year prior to admission, corresponded best to the baseline level [11]. However, the results of another study suggested that although extending the

* Corresponding author at: Division of Nephrology, Office 11-H, Landspitali – The National University Hospital of Iceland, Hringbraut, 101 Reykjavik, Iceland.
E-mail address: olasi@landspitali.is (O.S. Indridason).

https://doi.org/10.1016/j.ejim.2018.11.013
Received 24 September 2018; Received in revised form 25 November 2018; Accepted 30 November 2018
Available online 11 December 2018

Table 1
Computerized algorithms for diagnosis of AKI based on changes in serum creatinine.

Algorithm	Changes in serum creatinine
A1	26.5 μmol/L (0.3 mg/dL) increase over 48 h and/or 50% increase over 7 days (KDIGO criteria)
A2	50% increase from a mean value within 7–365 days **or** > 365 days
A3	50% increase from a mean value > 365 days
A4	**A1 or** 50% increase from a mean value within the last 3 months
A5	**A1 or** 50% increase from a mean value within the last 6 months
A6	**A1 or** 50% increase from a mean value within the last 30 days **or** mean value within 3–12 months
A7	**A1 or** 50% increase from a mean value within the last 30 days **or** mean value within 3–12 months **or** mean value of SCr within > 365 days
A8	**A1 or** 50% increase from a mean value within 7–365 days **or** > 365 days
A9	**A7 or** decrease of > 50% over 30 days following index SCr[a]
A10	**A3 or** decrease of > 50% over 30 days following index SCr
A11	**A8 or** decrease of > 33% over 7 days following index SCr

[a] *Index SCr defined as the presenting SCr in the emergency department.*

assessment period to 12 months before admission improves the sensitivity of the definition used for diagnosing AKI, the inclusion of very mild cases will increase, resulting in a lower risk of in-hospital mortality compared with those diagnosed with AKI using baseline SCr from three months before admission [12].

Computerized algorithms have been successfully developed for detecting hospital-acquired AKI to facilitate prompt evaluation and treatment of the disorder [13]. Detecting AKI in the outpatient setting or emergency department is more challenging due to the common absence of baseline SCr. In 2014, NHS England introduced a national automated algorithm based on the KDIGO criteria for detection of AKI to support clinicians in early recognition of the disorder [14]. The algorithm consists of three criteria, one of which should be fulfilled for the diagnosis of AKI. The criteria differ with respect to the time period of SCr change. This algorithm has been partially validated in a Scottish cohort using ICD-10 codes for AKI as reference for the assessment of sensitivity [15]. However, diagnostic codes are not reliable enough to accurately determine the incidence of AKI [16], and in order to use algorithms based on such codes for early identification of AKI in the outpatient setting or in epidemiological studies, a favorable balance between sensitivity and specificity must be achieved.

The aim of this study was to examine the performance of eleven computerized algorithms, which included various criteria for baseline SCr determination, in establishing the diagnosis of AKI compared with a diagnosis determined by a nephrologist in patients visiting an emergency department (ED) of a university hospital.

2. Materials and methods

2.1. Ethical approval

The study was approved by the National Bioethics Committee of Iceland (NBC 12–066).

2.2. Study design

This retrospective study was conducted at Landspitali–the National University Hospital of Iceland in Reykjavik which serves as a general hospital for the Reykjavik area, where two-thirds of the population resides, and as a tertiary referral hospital for the entire nation which numbered 318,452 at the end of the year 2010. We used electronic medical records to identify all patients aged ≥18 years, who upon arrival to the Emergency Department (ED) of the University Hospital in the year 2010 had an elevated SCr level (> 90 μmol/L for women and > 100 μmol/L for men).

2.3. Data collection

For every patient with elevated SCr, all previous and subsequent SCr values were retrieved from the hospital's laboratory database to establish the baseline SCr and examine the course of kidney function. The CKD-EPI equation was used to calculate eGFR from standardized SCr. Information on whether SCr was measured during hospital admission or in the outpatient setting was also obtained. Data on age, sex and comorbid conditions were collected from medical records.

2.4. Diagnosis of acute kidney injury determined by a nephrologist

All cases of elevated SCr upon a visit to the ED in 2010 (index SCr) were reviewed by one of the authors (OSI), an American Board of Internal Medicine-certified nephrologist, for determination of whether AKI was present based on the SCr component of the KDIGO criteria. For the selection of the most representative baseline SCr, the nephrologist reviewed all SCr values from the previous year with emphasis on more recent measurements. If no SCr values were available from the previous year, more remote SCr values were reviewed as well as measurements immediately following the index SCr value. If no SCr values obtained before arrival were available or if the diagnosis of AKI remained unclear, the nephrologist carefully reviewed medical records to search for risk factors predisposing to AKI, such as evidence for volume depletion or acute illness, prescribed medications associated with AKI and urinary abnormalities indicating AKI. AKI episodes were staged based on the KDIGO classification system [1].

2.5. Diagnosis of acute kidney injury by computerized algorithms

Eleven computerized algorithms (A1-A11) to diagnose AKI were constructed using preexisting and/or follow-up SCr values. The algorithms are shown in Table 1. In addition to strict adherence to the KDIGO SCr criteria, the algorithms were based on older SCr values in the case of individuals presenting to the ED without having a recent SCr measurement available. In the design of each algorithm, the period of assessment was extended in a stepwise manner and longer periods were broken down into various shorter periods. For algorithms consisting of more than one time period for assessment of baseline SCr, the most recent period with available SCr was used. For example, if an individual who had a SCr measurement performed within 7 days that did not meet the KDIGO criteria for AKI, while an older measurement within the past 3 months did, the diagnosis of AKI was excluded. The algorithms were programmed to include exclusively outpatient SCr values unless only inpatient values were available. Moreover, for each algorithm the ED episode was excluded from analysis if no SCr values were available in the assessment period. For individuals with multiple SCr measurements available in each time period we assessed both the mean and median as well as the lowest SCr value. Finally, the performance of all algorithms was compared with the diagnosis of AKI determined by a nephrologist (gold standard).

2.6. Statistical analysis

We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each algorithm, compared with the "gold standard" determination by an experienced nephrologist. Groups were compared employing the *t*-test or chi-square as appropriate. All statistical analyses were performed using the statistical software R (www.r-project.org).

3. Results

At 53,816 ED visits by 36,895 patients in 2010, SCr was measured in 15,588 patients for a total of 21,559 measurements. A total of 2878 (18.4%) patients had elevated SCr on 4101 visits. For individuals with elevated SCr, 59.7% were men and the median age was 70.8 (interquartile range (IQR), 62.6–83.1) years. Among individuals with SCr within normal limits, 45.4% were men and the median age was 53.4 (35.8–70.0) years, while 52% of those without a SCr measurement were men and the median age was 42.8 (26.6–55.9) years.

3.1. Diagnosis of AKI determined by a nephrologist

Of the patients with elevated SCr, 586 had AKI as determined by the nephrologist upon 618 ED visits. Twenty-seven individuals had two visits, four individuals had three visits and one had four such visits. Compared with individuals with elevated SCr who were not deemed to have AKI, those with AKI were more likely to have ischemic heart disease (41.1% vs. 35.9%), hypertension (63.5% vs. 56.0%) and to have experienced AKI previously (12.5% vs. 9.6%) (Table 2).

3.2. Performance of computerized algorithms in the diagnosis of AKI

Algorithm A1, strictly defined according to the KDIGO SCr criteria, yielded a sensitivity of 79%, a specificity of 94%, a PPV of 68% and NPV of 96% for the diagnosis of AKI. However, only 726 (17.7%) of the 4101 visits with elevated SCr could be evaluated with this algorithm, since few patients had SCr available in the week prior to the ED visit (Table 3, Fig. 1).

Algorithms A2 and A3 were solely based on a 50% increase from either the mean SCr value within 7–365 days or > 365 days before the ED visit, or the mean of SCr values obtained > 365 days prior to arrival, respectively. A similar proportion of visits could be assessed using these algorithms or 71.2% and 74.3%, respectively, yielding comparable specificities although A2 resulted in a higher sensitivity of 89% (Table 3).

Algorithms A4–A8 were based on the KDIGO SCr criteria (A1) together with a 50% increase in SCr from the mean SCr value from various time intervals before arrival. While the specificity of these algorithms ranged from 95%–98%, algorithms A7 and A8 yielded the best sensitivity of 93%. Algorithm A8 resulted in the most favorable outcome, yielding a sensitivity of 93%, a specificity of 96%, a PPV of 80% and a NPV of 99%. In addition to the KDIGO SCr criteria, this algorithm allowed the use of a continuous time frame for the baseline SCr, from 7 to > 365 days prior to the ED visit, enabling assessment of 92.0% of visits (Table 3, Fig. 1).

Algorithms 9 and 11 featured recovery of kidney function defined as a decrease in SCr following the index SCr value, allowing a greater number of visits to be included in the assessment. These two algorithms yielded the highest sensitivity of 97%, but at the cost of a lower specificity of 75% and 81%, respectively (Table 3, Fig. 1).

For each algorithm, the use of the mean SCr value resulted in a better sensitivity and specificity compared with the median or lowest SCr value for each time interval.

Table 2
Baseline characteristics of AKI patients compared with non-AKI patients with elevated serum creatinine.

	AKI (*N* = 586)	No AKI (*N* = 2292)	P–value
Age, years (range)	67.5 (18–98)	69.7 (18–104)	0.01
Sex, women (%)	257 (43.9)	881 (38.4)	0.02
Hypertension (%)	372 (63.5)	1283 (56.0)	0.001
Diabetes mellitus (%)	107 (18.3)	380 (16.6)	0.37
Ischemic heart disease (%)	241 (41.1)	821 (35.9)	0.02
Cerebrovascular disease (%)	89 (15.2)	312 (13.6)	0.36
Malignancy (%)	120 (20.5)	411 (17.9)	0.18
Prior history of AKI (%)	73 (12.5)	219 (9.6)	0.046
Baseline eGFR (mL/min/1.73 m^2)	69.76	48.03	< 0.0001

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.
Data presented as median (range), mean or number (%).

Table 3
Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) according to different computerized algorithms for diagnosis of AKI.

Algorithm	Sensitivity	Specificity	PPV	NPV	Visits with elevated SCr that could be evaluated
A1	0.79	0.94	0.68	0.96	726 (17.7)
A2	0.89	0.97	0.81	0.98	2919 (71.2)
A3	0.66	0.98	0.90	0.93	3049 (74.3)
A 4	0.80	0.97	0.81	0.97	2096 (51.1)
A5	0.81	0.97	0.80	0.97	2581 (62.9)
A6	0.86	0.96	0.78	0.98	3049 (74.3)
A7	**0.92**	**0.95**	**0.77**	**0.99**	**3757 (91.6)**
A8	**0.93**	**0.96**	**0.80**	**0.99**	**3772 (92.0)**
A9	0.96	0.75	0.41	0.99	3956 (96.5)
A10	0.57	0.99	0.90	0.92	2630 (64.1)
A11	0.96	0.81	0.48	0.99	3947 (96.2)

Sensitivity, Specificity, PPV and NPV calculated for each algorithm based on emergency department visits with elevated serum creatinine that could be evaluated. Bold numbers refer to the algorithms with the most favorable sensitivity and specificity.
Abbreviations: SCr, serum creatinine.

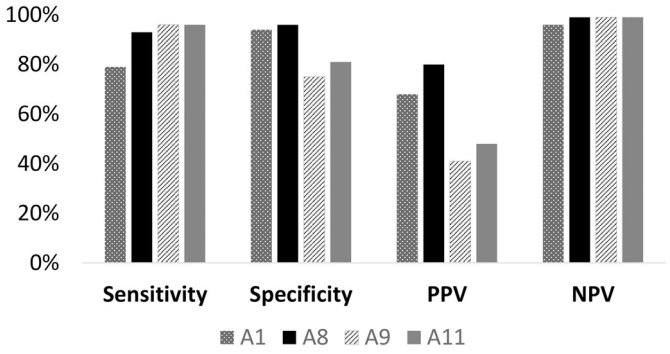

Fig. 1. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for acute kidney injury detected by computer algorithms A1, A8, A9 and A11.

4. Discussion

Computerized algorithms for detection of AKI in patients visiting the ED, perform variably compared with a nephrologist as the gold standard. However, the algorithms that perform best yield excellent sensitivity and specificity and are likely to be valuable in clinical practice. Such algorithms could be used to identify and automatically report patients in the ED who are likely to have AKI.

The difference observed between the eleven algorithms can be explained by the variable assessment period for baseline SCr in each algorithm. While adhering to the KDIGO SCr criteria yielded a highly

specific algorithm, the sensitivity was only 79%. Furthermore, only a limited number of patients with elevated SCr could be evaluated using this algorithm since a high proportion of study participants had no recent SCr value available. Thus, relying solely on the KDIGO SCr criteria would lead to missed AKI cases in the ED and underestimation of the incidence of AKI in epidemiological studies. The overall trend was that specificity increased with a longer time frame of baseline SCr. The increase in sensitivity that occurred when a reduction in SCr from the index value was added to the algorithm might be beneficial for the diagnosis of AKI, although at the expense of decreased specificity, in this case yielding unacceptably high proportion of false positive cases. A possible explanation might be that when the SCr values in the ED were assessed by the nephrologist, previous measurements were considered most significant for estimating baseline SCr. Presentation of patients to the ED with an elevated SCr and no previous measurement is a common clinical scenario which is generally considered to be AKI unless additional findings suggest otherwise. Hence, the diagnosis of AKI is usually confirmed later when additional SCr values become available, showing either worsening of the disorder or recovery of kidney function. Obviously, this approach cannot be used for identifying patients with AKI in the ED and although our study does not suggest a benefit of adding a decrease in SCr in the diagnostic evaluation of AKI, more studies that include renal recovery in the definition of AKI are needed to confirm its usefulness in epidemiological studies.

Recent guidelines recommend the use of all available clinical data (history, physical findings and results of laboratory tests and imaging studies) to aid in the selection of the best representative baseline SCr [1]. This approach can be cumbersome in clinical practice and very difficult in epidemiological studies using large databases. Therefore, many studies that have been carried out to validate the RIFLE and AKIN criteria for the diagnosis of AKI used surrogate baseline SCr derived from eGFR of 75 mL/min/1.73 m^2 according to the MDRD Study Eq. [17]. Although this appears to be an attractive strategy, the assumption involved may not be valid [18–20] and existing studies have confirmed the lack of diagnostic accuracy and misclassification of AKI when surrogate SCr based on the MDRD Eq. is used [10,17]. Thus, more emphasis should be placed on establishing baseline SCr by obtaining previous SCr measurements in studies of AKI prevalence.

In a retrospective study by Lafrance et al., the investigators sought to determine how AKI-associated in-hospital mortality risk varied with respect to the time frame used for establishing baseline kidney function [12]. Various AKI definitions were based on comparison of the peak SCr with the lowest SCr value during hospitalization and at 3, 6 or 12 months before admission. The investigators concluded that extension of the period for assessment of baseline kidney function to 12 months increased the sensitivity of diagnosis of AKI when compared with the use of SCr values obtained during hospital admission only [12]. These findings are consistent with our results as the algorithm which incorporated outpatient SCr values 12 months before the ED visit yielded a higher sensitivity for diagnosing AKI compared with values from 3 (A4) or 6 (A5) months prior to admission. Several issues in the study by Lafrance and coworkers deserve special consideration. First, the lowest SCr value in each assessment period was used to define the baseline kidney function. This approach might not be valid in cases where multiple SCr measurements exist due to normal variation of kidney function and it does not identify individuals with progressive chronic kidney disease (CKD) during the assessment period. It has previously been shown that a single estimate of baseline kidney function results in a significant misclassification of AKI [10]. Second, the longest assessment period was limited to 12 months. However, it is not uncommon that patients present to a hospital with elevated SCr and no available SCr measurement in the previous 12 months. Our study showed that using SCr measurements carried out > 365 days prior to the visit, when no more recent values are available, does not result in a high proportion of false positive cases (A8).

Siew et al. compared four methods for estimating baseline kidney function, including the most recent, average and nadir SCr values for three assessment periods (7–365 days, 7–730 days and 1–730 days before admission) with the opinion of two nephrologists in 379 patients with evidence of impaired kidney function on admission to an academic hospital [11]. The investigators concluded that the mean outpatient SCr from 7 to 365 days before admission best approximated the nephrologist's opinion. This finding is partly confirmed by our study as the algorithm which yielded the most favorable balance between sensitivity and specificity included a mean SCr value from 7 to 365 days before the ED visit (A8). Siew and colleagues observed a decline in the agreement when the assessment period for baseline kidney function was extended to two years (7–730 days) before admission. Our most favorable algorithm (A8) split the assessment period into three sub-periods and added SCr values from > 1 year before the ED visit if no other measurements were available. We believe that in addition to reflecting a common clinical situation, this strategy might also be useful in epidemiological studies on AKI as it did not affect the sensitivity or specificity. Indeed, using the more inclusive algorithms and successively adding time periods in the search for baseline SCr allowed us to evaluate over 90% of ED patients with elevated SCr.

In our best algorithm (A8), the mean SCr is used for determining baseline kidney function, whereas employing the median or the lowest SCr resulted in inferior sensitivity and specificity. We propose that using the mean SCr value to estimate baseline kidney function provides a more accurate assessment and could be incorporated in a clinical laboratory system for the purpose of early identification of AKI.

Clinical laboratories have used algorithms based on the KDIGO criteria to analyze changes in SCr to identify and report patients with AKI, both in the ED and during hospital admission [21–23]. This may have resulted in heightened attention to AKI, but studies demonstrating positive impact on clinical outcomes are scarce [23]. The national algorithm for AKI detection, launched by the NHS England in 2014, is based on 3 criteria [14]. In addition to the KDIGO SCr criteria of ≥ 26.5 μmol/L (0.3 mg/dL) rise in 48 h and ≥ 50% increase in 7 days, the 3rd criterion includes a ≥ 50% increase from a median SCr in the previous 8–365 days. Validation of this algorithm in a Scottish cohort in 2015 yielded a 92% sensitivity when ICD-10 codes were used as a reference standard [15]. Although the use of diagnostic codes for AKI is associated with certain limitations, this sensitivity is similar to what was accomplished with our most favorable algorithm (A8). Unfortunately, no specificity was reported for the NHS England AKI detection algorithm. While an AKI algorithm must be sensitive enough in order to serve its purpose, a poor specificity would result in a large number of false alerts that would require clinical attention. Another potential limitation of the NHS England AKI algorithm is the time period used for establishment of baseline SCr, as more than one-year old SCr values are ignored. In the current study, such an algorithm (A6) could not assess roughly 25% of patients with elevated SCr in the ED, whereas using more remote SCr values allowed us to evaluate > 90% of patients, an approach that we believe is superior to using a surrogate SCr value.

In light of the increasing use of AKI e-alert systems, incorporation of the results in epidemiological studies on AKI will become possible. However, it is vital that a uniform approach is adopted for accurate comparisons of studies that will be carried out in the future. From an epidemiological perspective, a high specificity is equally important as high sensitivity for a given measurement in the diagnosis of a disease. We, therefore, believe that our best algorithm (A8), which features a high sensitivity and specificity, can be used in epidemiological studies. Indeed, this algorithm might be a preferred choice for future epidemiological studies of AKI due to the lack of superior options. Algorithms that include decrements from the peak SCr value, when no previous SCr measurements are available, do not appear to be suitable for clinical or epidemiological use, as such algorithms (A9, A11) lacked specificity in our study.

It is noteworthy that the majority of the patients arriving at the ED

with an elevated SCr in the present study had CKD and a stable kidney function. We do not believe that this finding affected the performance of the AKI algorithms, which strictly relied on absolute or relative changes in SCr from baseline. We also do not think that knowledge of pre-existing CKD affected the nephrologist who used the KDIGO criteria to determine the diagnosis of AKI. Nevertheless, a bias caused by these factors cannot be excluded.

The study sample generally consisted of elderly patients and the frequency of age-related diseases was high, including hypertension, diabetes, atherosclerotic cardiovascular disease and malignancy. All these co-morbid conditions can increase the risk of AKI, and, not surprisingly, a prior history of AKI was also frequent in our study sample. Patients with a normal SCr and those without a SCr measurement were generally much younger and presumably had less co-morbidity.

A significant strength of our study is the inclusion of all individuals who presented to the ED of the University Hospital in 2010, thereby minimizing selection bias as the hospital provides emergency services for two-thirds of the nation. Moreover, we were able to obtain all previous SCr values at our institution for each individual and also had access to all pertinent clinical data for these individuals, allowing us to accurately estimate the baseline kidney function and the clinical course as needed.

The study has several limitations. First, the case review to determine the gold standard diagnosis of AKI was carried out by a single board-certified nephrologist, which may cause bias as disagreement between clinicians can potentially arise in ambiguous clinical situations. Furthermore, some of the SCr measurements dated from before standardization of the SCr assay occurred in Iceland in 2008, which might reduce the accuracy of the true estimate of baseline kidney function. However, this bias affected the algorithms and the nephrologist equally. Finally, we only examined patients with elevated SCr on arrival to the ED. Patients with AKI may present with a normal SCr if the baseline value is very low and, therefore, we may have missed occasional cases of AKI in our analysis. It should be noted that patients with normal SCr in the ED are rarely brought to the attention of nephrologists. Hence, in the design of the study we placed emphasis on those patients who might come to attention for AKI. Nevertheless, since our algorithms are based on changes in SCr, it is likely that an AKI episode in a patient with normal SCr level would be captured.

In conclusion, we have shown that a computerized algorithm based on the KDIGO criteria, with the addition of a longer time frame for evaluation of baseline SCr, yields acceptable sensitivity and specificity for the diagnosis of AKI in the great majority of patients presenting to the ED with an elevated SCr. This approach might be useful for early identification and automated electronic reporting of patients presenting to the ED with the disorder. Finally, this algorithm could be of value in epidemiological studies on AKI incidence and prevalence.

Acknowledgements

The study was supported by a grant from Landspitali University Hospital Science Fund, Reykjavik, Iceland, in the years 2012 and 2013.

Conflict of interest statement

The results presented in this paper have not been published previously in whole or in part, except in abstract format. A proportion of the data presented in this manuscript were presented in abstract form at the American Society of Nephrology Kidney Week in November of 2016 and the Biennial Congress of the Nordic Society of Nephrology in September of 2017. Declarations of interest: none. All authors contributed to the study and the writing of the manuscript.

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