PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to emergency department and at hospital admission
AUTHORS	Garg, Amit; Hwang, Y. Joseph; Shariff, Salimah; Gandhi, Sonja; Wald, Ron; Clark, Edward; Fleet, Jamie

VERSION 1 - REVIEW

REVIEWER	Ostermann, Marlies Guys and St Thomas Foundation Hospital, Department of Critical Care
REVIEW RETURNED	30-Jul-2012

THE STUDY	The authors added 2 review articles published in the Lancet (reference 3 and 4). However, an up to date review article on "Acute kidney article" was published in the Lancet a few months ago which summarised developments since the previous publication.
GENERAL COMMENTS	The authors should be congratulated for this major work. I fully agree that it is important to establish how well the ICD codes reflect reality. 1. My main concern relates to the fact how the AKIN and RIFLE criteria were applied. Firstly, both classifications suggest to use serum creatinine and urine output criteria and to determine the stage of AKI according to the values which indicate the worst stage. Secondly, the AKIN criteria suggest a 48 hour window, and the RIFLE criteria rely on a change in renal function within 7 days. Thirdly, strictly speaking the AKIN criteria demand that "hypovolaemia is excluded before AKI can be diagnosed". The authors did not adhere to these 3 points but admittedly, it can be difficult to apply these criteria retrospectively to a large databases. However, I would expect that these limitations are acknowledged. 2. I note that the baseline measurement for serum creatinine was taken at a median of 102 (41-204) days (page 7). Since chronic kidney disease is defined as "impaired kidney function for more than 3 months", it is possible that patients with chronic kidney disease were misclassified as having AKI.

REVIEWER	Adeera Levin Professor of Medicine Head Divsion of Nephrology University of British Columbia
REVIEW RETURNED	23-Aug-2012

GENERAL COMMENTS	A nice analysis and presentation. The writing is very dense and would benefit from culling so as not to lose the message for the general readers. Suggest some revisions and some clear heading which might help readers. As a question, is it possible to present the data one alternative way, which is how many of the pts with changes in serumcreatinine meeting the AKIN defintion (of >26 umol/L) were accurately classified as AKI. I appreciate that one might interpret one of your tables to be answering this question, but from a clinical point of view, if the majority of individuals captured either have creatinine changes of greater than 26 or very modest ones of <10, then this may further validate the definition as being discriminatory in clinical situations. Overall, excellent analysis and useful questions

VERSION 1 – AUTHOR RESPONSE

Reviewer: M Ostermann
Guys and St Thomas Foundation Hospital, Department of Critical Care

The authors added 2 review articles published in the Lancet (reference 3 and 4). However, an up to date review article on "Acute kidney article" was published in the Lancet a few months ago which summarised developments since the previous publication.

The authors should be congratulated for this major work. I fully agree that it is important to establish how well the ICD codes reflect reality.

Response:
We thank the reviewer for congratulating our work and acknowledging the methodology of the study. We have found the review article on AKI recently published at the Lancet to be informative and used the information in our manuscript.

Index of Change:
Page 1 Lines 7-8 under Background of the original submission was revised, a new reference (#5) was added and now reads: “Clinically, acute kidney injury (AKI) is characterized by an abrupt decline in renal function that may result in disordered fluid, acid-base and electrolyte homeostasis, retention of waste products from nitrogen metabolism, such as creatinine and urea, and/or decreased urine output.[3-5]”

1. My main concern relates to the fact how the AKIN and RIFLE criteria were applied. Firstly, both classifications suggest to use serum creatinine and urine output criteria and to determine the stage of AKI according to the values which indicate the worst stage. Secondly, the AKIN criteria suggest a 48 hour window, and the RIFLE criteria rely on a change in renal function within 7 days. Thirdly, strictly speaking the AKIN criteria demand that "hypovolaemia is excluded before AKI can be diagnosed". The authors did not adhere to these 3 points but admittedly, it can be difficult to apply these criteria retrospectively to a large databases. However, I would expect that these limitations are acknowledged.

Response:
The reviewer is correct in that we could not utilize the entire AKIN and RIFLE classification systems as the reference standard, but adapted the serum creatinine-based definitions of acute kidney injury

(AKI) from the classification systems, as mentioned in the methods. Many other large studies have also used a 'serum-creatinine only' approach when applying the AKIN and/or RIFLE criteria. We agree with the reviewer that it is important to acknowledge the limitations in greater depth in the discussion.

Index of Changes:
a) Page 12 Lines 8-9 under Discussion of the original submission was relocated to the end of the preceding paragraph: "Moreover, we did not know the degree to which patients with AKI were symptomatic from diminished kidney function or the indication that prompted presentation to the emergency department or hospital admission."

b) At Page 12 Line 9 under Discussion of the original submission, the following (including new references #37 and #38) were added and now reads: "It is important to acknowledge that for the definitions of AKI used in this study, we adapted the serum creatinine-based component of the AKIN and RIFLE classification systems. The AKIN and RIFLE classification systems recommend using both serum creatinine and urine output measurements in determining the presence and severity of AKI.[6, 7] In addition, it is recommended that the AKIN classification is applied only after an optimal state of hydration is achieved.[6] However, urine output measurement and hydration status were not available in the data sources used in the study. In truth, the accuracy of bedside urine output measurement is notoriously poor outside of intensive care settings with an indwelling catheter. Nonetheless, the change in serum creatinine is a widely used measure of kidney function in clinical settings. Moreover, the serum creatinine-based component has been solely used to identify patients with AKI using the AKIN and RIFLE classification systems in previous studies.[37, 38]"

c) Page 12 Lines 9-15 under Discussion of the original submission was revised and now reads: "The median (IQR) period between the baseline serum creatinine measurements and the hospital encounter was 102 (41-204) days for patients who presented to the emergency department and 39 (16-128) days for patients admitted to hospital. While these are reasonable baseline measurements, the AKIN and RIFLE classification systems require the change in serum creatinine to occur within 48 hours and within 7 days, respectively.[6, 7] Although it is likely that serum creatinine changes occurred just prior to the hospital encounter, we cannot say this with complete certainty given the absence of available measurements during this period."

2. I note that the baseline measurement for serum creatinine was taken at a median of 102 (41-204) days (page 7). Since chronic kidney disease is defined as "impaired kidney function for more than 3 months", it is possible that patients with chronic kidney disease were misclassified as having AKI.

Response:
The reviewer raises an excellent point that patients with chronic kidney disease (CKD) may have been misclassified as having AKI. It is exactly the reason why we performed a subgroup analysis by grouping the hospitalized cohort based on CKD status. The CKD status of the patients was ascertained by the presence or absence ICD-10 code N18x "chronic kidney disease" in the five years prior to hospital admission rather than the patient laboratory value of serum creatinine.

Moreover, we describe in Page 11 Lines 26-33 under Discussion of the original submission (Page 11 Lines 29-36 of the revised submission) that the lower specificity of the ICD-10 code N17x for AKI in patients with CKD suggests that the misclassification may have occurred. We also provide potential explanations for the misclassification; we write: "We also assessed the diagnostic performance of the ICD-10 code in subgroups of patients with and without CKD prior to the hospital encounter. For all definitions, with the exception of RIFLE Failure, the code demonstrated higher sensitivity in patients with CKD than those without CKD. However, the specificity of the code was lower in patients with

CKD than those without CKD (for all definitions of AKI). The latter finding suggests a portion of patients with stable CKD are misclassified as having AKI at their hospital encounter. For example, clinicians may not have access to patients' baseline serum creatinine measurements, or may make an AKI diagnosis without investigating the baseline measurements. In such cases, an elevated serum creatinine concentration at hospital presentation that is no different than the baseline value may still be misdiagnosed as AKI."

Reviewer: Adeera Levin
Professor of Medicine
Head Division of Nephrology
University of British Columbia

A nice analysis and presentation. The writing is very dense and would benefit from culling so as not to lose the message for the general readers. Suggest some revisions and some clear heading which might help readers.

Response:
We thank the reviewer for her encouragement and positive comments. We have now revised several headings for clarity and separated a number of paragraphs for readability. The authors had a discussion and concluded that the details presented in the methods section, are necessary for its accessibility and utilization in future research work. We have improved the clarity of the prose wherever possible.

Index of Changes:
a) Page 4 subtitle "Participants" under Methods of the original submission was revised and now reads: "Accrual of Elderly Patients in Two Settings: at Presentation to Emergency Department and at Hospital Admission"

b) Page 4 subtitle "ICD-10 Coding Algorithms for AKI" under Methods of the original submission was revised and now reads: "ICD-10 Coding Administrative Database Algorithms for AKI"

c) The paragraph on Page 7 under Results of the original submission was divided into two paragraphs at Line 5 and now reads:
"The diagnostic performance of the various coding algorithms is presented in Table 2. For both types of hospital encounters, 'all diagnosis' was the best performing ICD-10 N17x coding algorithm. At presentation to the emergency department, the sensitivity of the ICD-10 code for the RIFLE Injury definition of AKI (>= 2-fold increase in serum creatinine concentration from baseline) was 37.4% (95% confidence interval (CI): 32.1% to 43.1%).

Sensitivities were higher at hospital admission than at presentation to the emergency department for all four serum creatinine-based definitions of AKI. For example, at hospital admission, the sensitivity of the code for the RIFLE Injury definition was 61.6% (95% CI: 57.5% to 65.5%). The sensitivity of the code improved for more severe definitions of AKI, peaking at the RIFLE Injury definition. There was no substantial difference in specificity for both types of hospital encounters, with values greater than 95% in both settings. The positive predictive value of the code decreased for more severe definitions of AKI, with a nadir at the RIFLE Injury definition in both settings."

d) The paragraph spanning Page 8-9 under Results of the original submission was divided into three paragraphs at Page 8 Line 5 and Page 9 Line 1 and now reads:
"The absolute change in serum creatinine (peak value – baseline value) and relative change in serum

creatinine [(peak value – baseline value) / baseline value)] for patients with hospital encounters who were positive and negative for the ICD-10 N17x code are presented in Table 3. When considering the 'all diagnosis' algorithm, 1.2% of patients at presentation to the emergency department and 5.2% of patients at hospital admission were code positive for AKI.

The median (IQR) absolute change in serum creatinine concentration for code positive patients was 133 (62 to 288) umol/L and 98 (43 to 200) umol/L in each setting, respectively. The change for code negative patients was 2 (-8 to 14) umol/L and 6 (-4 to 20) umol/L in each setting, respectively.

When expressed in relative terms, the median (IQR) change for code positive patients was 87 (43 to 204) % and 69 (28 to 153) % in each setting, respectively. The relative change for code negative patients was 2 (-9 to 15) % and 7 (-5 to 22) % in each setting, respectively. In both settings, the difference in the mean absolute and relative change in serum creatinine between code positive and code negative patients was highly statistically significant ($p<0.001$)."

e) The second paragraph on Page 9 under Results of the original submission was divided into two paragraphs at Line 10 and now reads:
"The diagnostic performance of the 'all diagnosis' algorithm at hospital admission in patients with and without CKD is presented in Table 4. The sensitivity of the ICD-10 code for AKIN Stage 1 or greater, RIFLE Risk and RIFLE Injury definitions was higher in patients with CKD than those without CKD. For example, the sensitivity of the code for the RIFLE Injury definition was 75.6% (95% CI: 60.7% to 86.2%) in patients with CKD and 60.5% (95% CI: 56.2% to 64.5%) in patients without CKD.

The code demonstrated the highest sensitivity for the RIFLE Risk definition in patients with CKD and the RIFLE Failure definition in patients without CKD. The specificities of the code were lower in patients with CKD than those without CKD for all four definitions. For example, the specificity of the code for the RIFLE Injury definition was 82.6% (95% CI: 80.7% to 84.4%) in patients with CKD and 96.2% (95% CI: 96.0% to 96.4%) in patients without CKD."

f) The paragraph on Page 10 under Results of the original submission was divided into three paragraphs at Lines 3 and 11 and now reads:
"The absolute and relative changes in serum creatinine at hospital admission in patients with and without CKD who were code positive and code negative are presented in Table 5. When considering the 'all diagnosis' algorithm, a total of 18.9% of patients with CKD and 4.6% of patients without CKD were code positive for AKI.

The median (IQR) absolute change in serum creatinine concentration in patients with CKD who were code positive was 108 (48 to 215) umol/L and in patients without CKD who were code positive was 95 (43 to 197) umol/L. The difference in the absolute change in serum creatinine between patients with and without CKD who were AKI code positive was not significantly different ($p=0.910$). The median (IQR) absolute change in patients with CKD who were code negative was 16 (-8 to 51) umol/L and in patients without CKD who were code negative was 6 (-4 to 19) umol/L.

When expressed in relative terms, the median (IQR) change in serum creatinine in patients with CKD who were code positive was significantly lower than in patients without CKD who were code positive (53 (20 to 104) % vs. 72 (29 to 161) %; $p<0.0001$). The median (IQR) relative change in patients with CKD who were code negative was 9 (-4 to 26) % and in patients without CKD who were code negative was 6 (-5 to 22) %. For both patients with and without CKD, the difference in the mean absolute and relative changes in serum creatinine between code positive and negative patients was highly statistically significant ($p<0.001$)."

As a question, is it possible to present the data one alternative way, which is how many of the pts with

changes in serumcreatinine meeting the AKIN defintion (of >26 umol/L) were accurately classified as AKI. I appreciate that one might interpret one of your tables to be answering this question, but from a clinical point of view, if the majority of individuals captured either have creatinine changes of greater than 26 or very modest ones of <10, then this may further validate the definition as being discriminatory in clinical situations.

Overall, excellent analysis and useful questions

Response: We agree that it would be clinically informative to assess how well the serum creatinine-based classification systems discriminate patients with or without AKI. The definitions for the diagnostic performance characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) are presented in the Supplementary Materials Table 1 to assist readers.

Index of Changes:
a) At Page 11 Line 10 under Discussion of the original submission, the following was added and now reads: “Of the patients who satisfied the RIFLE Injury definition of AKI from their increase in serum creatinine, 61.6 (95% CI: 57.5-65.5) % of them were code positive AKI when the ICD-10 code was expressed as ‘all diagnosis’.”

b) At Page 11 Line 11 under Discussion of the original submission, the following was added and now reads: “Of the patients who did not satisfied the RIFLE Injury definition of AKI, 95.6 (95% CI: 95.4-95.8) % of them were code negative for AKI.”

VERSION 2 – REVIEW

REVIEWER	Ostermann, Marlies Guys and St Thomas Foundation Hospital, Department of Critical Care
REVIEW RETURNED	22-Oct-2012

GENERAL COMMENTS	My previous comments have been satisfactorily addressed. I have no further suggestions.