Risk prediction for acute kidney injury in acute medical admissions in the UK

Blackburn, Anna; Gunda, Smita; Lopez, Berenice; Edwards, James; Spittle, Nick; Preston, Rob

Published in:
QJM

DOI:
10.1093/qjmed/hcy277

Publication date:
2019

Document Version
Peer reviewed version

Risk Prediction for Acute Kidney Injury in Acute Medical Admissions in the UK

Running title: the RISK study

The Risk Investigators*

** Individual co-authors are listed in the supplementary materials*

Contact details:

Lui G Forni, Department of Clinical & Experimental Medicine, Faculty of Health Sciences, University of Surrey & Intensive Care Unit, Royal Surrey County Hospital NHS Foundation Trust; Egerton Road, Guildford UK

Word count: 2963 (abstract 329)

Key words: Acute Kidney Injury, AKI, clinical prediction score, risk score, acute medicine

Abstract:

Background

Acute Kidney Injury (AKI) is associated with adverse outcomes; identifying patients who are at risk of developing AKI in hospital may lead to targeted prevention. This approach is advocated in national guidelines but is not well studied in acutely unwell medical patients. We therefore aimed to undertake a UK-wide study in acute medical units (AMUs) with the following aims: to define the proportion of acutely unwell medical patients who develop hospital-acquired AKI (hAKI); to determine risk factors associated with the development of hAKI; and to assess the feasibility of using these risk factors to develop an AKI risk prediction score.

Methods

In September 2016, a prospective multicentre cohort study across 72 UK AMUs was undertaken. Data were collected from all patients who presented over a 24-hour period. Chronic dialysis, community-acquired AKI (cAKI) and those with fewer than two creatinine measurements were subsequently excluded. The primary outcome was the development of h-AKI.

Results

2,446 individuals were admitted to the AMUs of the 72 participating centres. 384 patients (16%) sustained AKI of whom 287 (75%) were cAKI and 97 (25%) were hAKI. After exclusions, 1,235 participants remained in whom chronic kidney disease (OR 3.08, 95% CI 1.96-4.83), diuretic prescription (OR 2.33, 95% CI 1.5-3.65), a lower haemoglobin concentration and an elevated serum bilirubin were independently associated with development of hAKI. Multivariable model discrimination was moderate (c-statistic 0.75), and this did not support the development of a robust clinical risk prediction score. Mortality was higher in those with hAKI (adjusted OR 5.22; 95% CI 2.23-12.20).

Conclusion

AKI in AMUs is common and associated with worse outcomes, with the majority of cases community acquired. The smaller proportion of hAKI cases, only moderate discrimination of prognostic risk factor modelling and the resource implications of widespread application of an AKI clinical risk score across all AMU admissions suggests that this approach is not currently justified. More targeted risk assessment or automated methods of calculating individual risk may be more appropriate alternatives.

Introduction

The importance of acute kidney injury (AKI) in hospitalised patients is demonstrated by its high incidence, strong associations with both short and long-term morbidity and mortality, and accompanying health economic burden (1-4)(5). It follows that identification of those at risk, if combined with effective strategies for prevention, could be highly beneficial. Acutely unwell medical patients represent a particularly important population, accounting for the largest percentage of the AKI caseload (6). AKI in this group can be divided into those who have already sustained AKI at hospital admission (community-acquired AKI, cAKI) and those who sustain AKI during their hospital stay (hospital-acquired AKI, hAKI); efforts to reduce AKI risk at time of hospital admission will have direct relevance only to hAKI (6). There are many well-described factors that increase the risk of AKI including age, presence of co-morbidities, sepsis, previous AKI and certain prescribing patterns, but these have not been extensively studied in the specific setting of acutely unwell medical patients (7, 8). Moreover, international AKI guidelines, including those from the National Institute for Health and Care Excellence (NICE, CG169), state that patients with acute illness and who have one or more of these factors should be regarded as being at higher risk (9). Practically, however, this does not translate into effective risk assessment on an individual patient basis. The large number of risk factors, many of which are very common, means that a very high percentage of medical patients admitted to hospital have at least one of these. 80% of general medical patients over the age of 60 have been reported to have at least one AKI risk factor in addition to age alone, consequently this approach does not allow reliable discrimination between those at low and higher risk (10).

A more evolved strategy may be the development of clinical prediction models for AKI (11, 12). To date, this has predominantly been described in relatively homogenous surgical populations or those scheduled to receive iodinated contrast, where timing of potential renal injury is relatively clear (13-16). Crucially, at least in the setting of percutaneous coronary intervention, interventions in response to AKI risk have been shown to reduce the incidence of contrast-induced AKI (17). Conversely, there have been fewer attempts to apply this “prophylactic” approach to general medical cohorts, and where this has been attempted results have been conflicting (9, 18). Furthermore,

risk scores have not generally been validated outside of the centres in which they were developed, raising concerns about their applicability for widespread adoption.

We therefore aimed to undertake a UK-wide prospective multicentre observational study in acute medical units (AMUs) with the following aims: to define the proportion of acutely unwell medical patients who develop hAKI; to determine risk factors associated with the development of hAKI; and to assess the feasibility of using these risk factors to develop an AKI risk prediction model for medical patients admitted acutely.

Methods

Study design, participants and setting

A prospective multi-centre cohort study was conducted in 72 UK acute medical units (AMUs) across England, Wales, Scotland and Northern Ireland in September 2016. A full list of centres is included in supplementary material and is available via the study website (https://www.kidneyresearchuk.org/research/the-risk-study). The study was set up and co-ordinated by members of the national AKI-CSG (Clinical Study Group, www.kidneyresearchuk.org/research/acute-kidney-injury-clinical-study-group), who also acted as a steering committee for the study. Each centre collected data from all patients aged 18 years or older admitted to their AMU over a single 24-hour period. Subsequently, patients with cAKI (defined as AKI within the first 24 hours of admission) and patients receiving dialysis for end-stage kidney disease were excluded. Patients were also excluded if they had fewer than two serum creatinine measurements during the hospital admission. Patients were followed up until hospital discharge or day seven of admission, whichever was sooner. The study was approved by the Yorkshire and Humber NHS Research Ethics committee who waived the requirement for individual patient consent. The study did not receive any funding and all investigators voluntarily gave their time to complete data collection.

Outcomes and data collection

Data were collected at the time of admission for a range of parameters that were generated from routine clinical care including: demographics; primary reason for admission; co-morbidities; medications; physiological observations; urinalysis results; laboratory results; and blood gas analysis. The full list of data points collected is included in the supplementary material (See Supplementary File 1). All serum creatinine results between admission and up to seven days post admission were recorded. Where results were not available they were recorded as 'unknown'. The primary outcome was the development of hAKI, defined as a change in serum creatinine meeting the KDIGO criteria and occurring >24 hours after hospital admission (19). Urine output data were not used to define AKI because hourly urine output measurement was frequently unavailable or unlikely to be reliable in the MAU setting. Baseline creatinine was defined as the serum creatinine concentration on admission, after exclusion of cAKI. Secondary outcomes in patients who sustained hAKI included

mortality, need for renal replacement therapy, and requirement for escalation to higher level of care. Data were entered into a standardised paper case report form (CRF) and subsequently entered into a secure on-line CRF.

Statistical methods

Data were analysed using the statistical package R (version 3.4.1). A p-value of less than 0.05 was regarded as significant. Variables were included for analysis if data were available for ≥80% of the study cohort. Continuous predictors were analysed as quartiles to adjust for non-linear associations and allow for missing data, with the latter included as 'unknown'. Univariable analysis was conducted using the Chi-squared test to identify differences between the cohort that developed hAKI and those individuals that did not. Variables with a p-value of <0.2 were included in the multivariable analysis. The multivariable analysis was conducted using binary logistic regression and a backwards stepwise procedure to select variables for the final model. The calibration of the model was assessed by the Hosmer-Lemeshow goodness-of-fit test. Discrimination was assessed using the area under the receiver operating characteristic curve (AUROC).

Results

Cohort selection and baseline characteristics

2,446 individuals were admitted to the AMUs of the 72 participating centres. 1,843 (75.3%) were admitted via the Emergency Department and the most common reasons for admission were chest pain (10.7%); respiratory infection (9.0%); and mobility-related problems (8.7%). A participant flow diagram is shown in Figure 1. 287 (12%) patients had cAKI, 41 (2%) were receiving dialysis for end-stage kidney disease, 865 (35%) were discharged without a repeat serum creatinine and 18 (1%) did not have serum creatinine measured at all. This left 1,235 participants who were included in the final analysis. A full description of baseline characteristics of this group is shown (Table 1).

Development of hAKI

97 of the 1,235 (7.9%) individuals in the study cohort developed hAKI. If the denominator of patients at risk is changed to include the 865 patients with a single creatinine measure (to indicate workload from the total population who may potentially undergo risk assessment at time of AMU admission), then the proportion of patients with hAKI fell to 4.6%. The majority of patients with hAKI were classified as AKI stage 1 (85 cases, 87% of those with hAKI, 7% of study population), with only 12 cases classified as stage 2 or 3 (13% of those with hAKI, 0.9% of study population).

On univariable analysis, the development of any stage of hAKI was associated with a number of variables, as shown in Table 2. These included: increased age; a diagnosis of hypertension, cardiovascular disease, CKD, atrial fibrillation or heart failure; the prescription of diuretics or beta-blockers; a lower body temperature; a low haemoglobin concentration; and a high bilirubin level. Notably, individuals with CKD were almost four times as likely to develop hAKI (OR 3.94, 95% CI 2.58-6.03) and those prescribed diuretics were three times as likely (OR 3.07, 95% CI 2.01-4.67). Variables that were not associated with hAKI included admission blood pressure, renin-angiotensin system (RAS) inhibitor prescription, non-steroidal anti-inflammatory drug (NSAID) prescription, diabetes mellitus and serum markers of inflammation.

The results of the multivariable analysis are shown in Table 3, with factors that

remained independently associated with the development of hAKI being CKD stages 3-5, the prescription of diuretics, a lower haemoglobin concentration and an elevated serum bilirubin. We also show two other models for comparison: one that included 'conventional' risk factors for AKI based on NICE guidelines (including CKD and diuretic prescription) and the other being a previously published and validated Acute Kidney Injury Prediction Score (20, 21). The c-statistic was calculated to examine the discrimination of each of the models and was 0.75 (95% CI 0.70-0.80) for the RISK model, which although discriminatory was not high enough to proceed to the development of a robust clinical risk prediction score. The c-statistic for the other models was 0.73 (95% CI 0.67-0.78) for established risk factors and 0.72 (95% CI 0.67-0.78) for the APS. The ROC curve for the RISK model is shown in Figure 2A. Validation analysis using the Hosmer-Lemeshow test suggested good calibration of the model (χ^2 5.48, P=0.14). A summary of the observed and predicted frequency of hAKI with each quintile of risk is shown (Figure 2B).

Outcomes associated with hAKI

Only one of the 97 individuals who developed hAKI required renal replacement therapy. However, hAKI was associated with more adverse outcomes compared to those that did not develop AKI. 5/97 (5.1%) of patients who developed hAKI were transferred to HDU/ITU, compared to 19/1138 (1.7%) of the patients that did not develop hAKI (p=0.05). In addition, 9/97 (9.3%) of the hAKI group died during their admission to hospital, compared to 23/1138 (2.0%) of those without hAKI (p< 0.001). After adjustment for age, sex and co-morbidities, mortality in individuals with hAKI remained significantly higher in comparison to those without (OR 5.22; 95% CI 2.23-12.20). As an additional comparator, in the cAKI group 13/261 (5.0%) of individuals died during hospital admission.

Discussion

We report a large, national cohort study of AKI in UK acute medical units, confirming that AKI is common in this group and associated with adverse outcomes, but that hospital acquired AKI (hAKI) makes up a relatively small proportion of the cases. We identify the most important clinical risk factors for hAKI (including pre-existing CKD and diuretic prescription) but our results do not allow the development of a robust risk prediction score based upon these clinical variables.

AKI is defined through increases in serum creatinine and/or oliguria; it is therefore a syndrome with significant heterogeneity and with many potential causes. The incidence of AKI is high and is increasing, with reports suggesting that up to one in five hospitalised adults worldwide are affected (1, 2). Our results are consistent with published rates of AKI, in that 16% of total AMU admissions sustained AKI. That almost three quarters of these patients were cAKI (in which AKI was present on or within the first 24 hours of admission) highlights that prompt recognition and treatment of cAKI is a priority for AMUs, particularly as evidence is emerging to suggest that a systematic focus on basic elements of AKI management may improve outcomes (22-24). Conceptually, identifying those at risk of AKI and instituting preventative strategies should theoretically translate into reductions in AKI-associated harm. This message has been reinforced by observational reports such as the National Confidential Enquiry into Patient Outcome and Death, which adjudicated 30.8% of post-admission AKI cases as being preventable (25, 26). In an AMU setting, risk assessment is relevant only to those who sustain AKI later on during their hospital stay but our data suggest that hAKI occurs in a relatively small proportion of patients (4.6% of AMU admissions). In part, this reflects current AMU practice in which many patients are discharged after a brief hospital stay and without a repeat serum creatinine result, which occurred in over a third of our cohort. Furthermore, of the 97 patients who did develop hAKI, only 12 had AKI stage 2 or 3 (0.9% of the study cohort), and only one patient required renal replacement therapy. These findings are consistent with previously published studies (25). In those individuals with cAKI efforts should be focussed on prevention of worsening AKI and promoting renal recovery.

Alongside establishing the number of patients who could potentially benefit from risk assessment, the performance of methods to assess AKI risk is also critical. Combining the risk factors that we identified into a multivariable model provided at best only a moderate ability to discriminate between those who did and did not subsequently develop hAKI. A model using 'recognised' risk factors for AKI generated an AUC value that was only slightly lower (providing CKD and diuretic prescription were included because of their strong effect on model performance), and results from a previously described single centre clinical risk prediction score were similar. Therefore, these results do not support the development of a routine clinical prediction score for use in general AMU populations, as the blanket application of such a tool with only moderate performance in the setting of a low event rate is likely to generate a significant workload in return for limited benefit. However, this does not mean that the risk of AKI should be ignored. Outcomes are significantly worse when hAKI does occur, and there are examples of effective AKI prevention in other settings; these include a quality improvement study in six US hospitals that reduced the incidence of contrast induced AKI following percutaneous coronary intervention (17) and a pharmacist-led intervention in paediatric patients receiving high risk medications (27). However, before a similar approach can be introduced into AMU settings, further work is required to determine how best to 'operationalise' risk assessment. Potential strategies may include more focussed AKI risk assessment in specific groups rather than all-comers. Alternatively, if risk assessment was performed at 24 hours rather than admission, it may be possible to have more focussed approach by excluding the 35% of low-risk patients who had no repeat creatinine and a short length of stay. More sophisticated computational methods of real-time rolling risk assessment that do not require manual data entry, or the addition of new AKI biomarkers to improve performance of a clinical risk score may also be ways of improving risk assessment (28). The latter approach has shown to be successful in a paediatric ICU setting (29), and a recent pilot study in a UK AMU setting has demonstrated that the addition of a biomarker to the APS clinical prediction tool has potential utility to identify low risk groups, with a negative predictor value for hAKI that approached 97% (Hodgson et al in press).

Commented [NS1]: No longer in press! Can add reference

Several of the risk factors that we observed to be associated with the development of hAKI were expected (such as increasing age, co-morbidities such as CKD and heart failure); of these, pre-existing CKD and diuretic prescription at time of admission had

the strongest associations and may identify a group of particular interest. Some factors that are recognised as potential risk factors for AKI were not strongly associated with hAKI in this setting, for example RAS inhibitors, admission blood pressure or diabetes mellitus. In addition, laboratory tests that may not traditionally be considered AKI risk factors (low haemoglobin, high bilirubin) were independently associated with hAKI in our population. These findings emphasise that the development of methods to assess risk of AKI should be based on evidence derived from the populations in which they are intended to be used. This is particularly true in view of the heterogeneity in aetiology of AKI across patient groups. Our national approach incorporating 72 centres coupled to data collection encompassing a wide range of patient characteristics, physiological data, prescribing information and laboratory results, provides results that are likely to be applicable to AMUs in the UK and possibly in other similar healthcare settings. Our comprehensive approach to data collection also suggests there is limited room from improving risk prediction in this setting using clinical variables alone. In the future, application of risk algorithms embedded within electronic patient records may facilitate identification of high risk cases.

Our study does have some weaknesses. AKI was defined using only serum creatinine and patients who developed AKI solely defined by urine output criteria would have been missed. However, our data also show that applying urine output criteria in this population where most patients do not have a urethral catheter is not practical (only 11% of patients had hourly urine output recorded). In addition, using the first creatinine of hospital admission as a baseline value may potentially have resulted in under-recognition of hAKI (for example, if creatinine had already begun to rise but not reached KDIGO definition of AKI at time of admission) although the effects of this are likely to be small. The data collection period was short, and it is possible that results may have been different at a different time of year (e.g. higher incidence of AKI in winter). Also patients admitted directly to higher levels of care such as ICU or HDU were not captured which may have led to an underestimation of the incidence of AKI. Finally, because of logistical considerations we did not collect data on longer term outcomes after hospital discharge (e.g. renal recovery, hospital readmission rates) that would have been informative.

Conclusions

AKI remains a significant clinical problem in acutely unwell medical patients. The majority of cases are community acquired, so the prompt recognition and treatment of these patients in AMUs is a clear priority. The smaller proportion of hAKI cases and only moderate discrimination of prognostic risk factor modelling suggests that the increased workload that would be required to apply a manual AKI clinical risk score across all AMU admissions using currently available techniques is not currently justified. More targeted risk assessment or automated methods of calculating individual risk may be more appropriate alternatives, but would require evaluation in future studies.

Table 1. Cohort characteristics

	All individuals (n=1,235)
Age, years (median, IQR)	73 (56–83)
Female sex (n, %)	632 (51)
Length of stay in days (median, IQR)	5 (3-7)
Admission via ED (n, %)	932 (75)
Reason for admission (n, %):	
Respiratory tract infection	149 (11)
Fall or mobility problem	108 (9)
Chest pain	99 (8)
Abdominal pain	71 (6)
Asthma or chronic obstructive lung disease	66 (5)
Dizzyness and/or collapse	65 (5)
Delirium	61 (5)
Soft tissue infection and/or ulcer	51 (4)
Diarrhoea and/or vomiting	49 (4)
Urinary tract infection	48 (4)
Gastrointestinal bleeding	39 (3)
Deliberate self-harm and drug overdose	39 (3)
Heart failure	36 (3)
Thromboembolic disease	20 (2)
Reduced consciousness and/or seizure	19 (2)
Stroke or transient ischaemic attack	13 (1)
Other reason	302 (24)

Co-morbidity (n,%):	
Hypertension	436 (35)
Cardiovascular disease	360 (29)
Diabetes mellitus (type I or II)	278 (23)
Chronic kidney disease	266 (22)
Atrial fibrillation	203 (16)
Chronic obstructive lung disease	199 (16)
Heart failure	156 (13)
Active malignancy	149 (12)
Dementia	113 (9)
Liver disease	85 (7)
Medication (n, %):	
Diuretic	314 (25)
Beta-blocker	298 (24)
Renin angiotensin system inhibitor	285 (23)
Other antihypertensive	223 (18)
Corticosteroid	196 (16)
Oral hypoglycaemic agent	159 (13)
Non-steroidal anti-inflammatory	94 (8)
Insulin	76 (6)
Other chemotherapy/immunosuppression	51 (4)
Observations (median, IQR):	
Systolic blood pressure, mmHg	129 (114-146)
Diastolic blood pressure, mmHg	72 (64-82)
Pulse rate, per minute	72 (73-98)
Respiratory rate, per minute	18 (16-20)
Temperature, degrees Celsius	36.6 (36.3-37.1)
Supplemental oxygen requirement (n, %)	339 (29)
AVPU score, not ‘Alert’ (n, &)	59 (5)

Blood tests (median, IQR):	
Haemoglobin, g/L	126 (113-139)
White blood cells, $x10^9$/L	9.5 (7.0-12.9)
Platelets, $x10^9$/L	245 (188-317)
Sodium, mmol/L	137 (134, 140)
Potassium, mmol/L	4.2 (3.9, 4.6)
Urea, mmol/L	6.1 (4.4, 8.6)
Creatinine, umol/L	79 (63, 102)
Bilirubin, umol/L	10 (7, 16)
Albumin, g/L	37 (32, 41)
ALT, U/L	19 (13, 31)
CRP, mg/L	23 (5, 80)

Abbreviations: n, number of individuals; %, percentage of individuals; IQR, inter-quartile range; ED, emergency department; AVPU, (scale) Alert Voice Pain Unconscious; ALT, alanine aminotransferase; CRP, C-reactive peptide

Table 2. Comparison of HAKI cohort with controls

	No AKI (n = 1138)	**hAKI (n = 97)**	**P-value**
Age quartiles, years:			0.03
≤ 56	309 (27)	12 (12)	
57-73	278 (24)	31 (32)	
74-83	286 (25)	28 (29)	
≥ 84	263 (23)	26 (27)	
Unknown	2 (0)	0 (0)	
Female sex	585 (51)	47 (48)	0.65
Co-morbidity:			
Hypertension	391 (34)	46 (46)	0.02
Cardiovascular disease	322 (28)	38 (39)	0.03
Diabetes mellitus (type I or II)	252 (22)	26 (27)	0.35
Chronic kidney disease	219 (19)	47 (48)	<0.001
Atrial fibrillation	176 (15)	27 (28)	0.003
Chronic obstructive lung disease	179 (16)	20 (21)	0.27
Heart failure	128 (11)	28 (29)	<0.001
Active malignancy	136 (12)	13 (13)	0.80
Dementia	106 (9)	7 (7)	0.61
Liver disease	76 (7)	9 (9)	0.45
Medication:			
Diuretic	267 (23)	47 (48)	<0.001
Beta-blocker	262 (23)	36 (37)	<0.01
Renin angiotensin system inhibitor	258 (23)	27 (28)	0.30
Other antihypertensive	205 (18)	18 (19)	1.00
Corticosteroid	179 (16)	17 (18)	0.75
Oral hypoglycaemic agent	150 (13)	9 (9)	0.35

Commented [JP2]:

Non-steroidal anti-inflammatory	85 (7)	9 (9)	0.66
Insulin	67 (6)	9 (9)	0.27
Other chemotherapy/immunosuppression	46 (4)	5 (5)	0.79
Observations:			
Systolic blood pressure quartiles, mmHg			0.46
≤ 114	290 (25)	28 (29)	
115 - 129	280 (25)	17 (18)	
130 - 146	284 (25)	24 (25)	
≥ 147	277 (24)	28 (29)	
Unknown	7 (1)	0 (0)	
Diastolic blood pressure quartiles, mmHg			0.28
≤ 64	280 (25)	30 (31)	
65 - 72	285 (25)	21 (22)	
73 - 82	291 (26)	18 (19)	
≥ 83	265 (23)	28 (29)	
Unknown	8 (1)	0 (0)	
Pulse rate quartiles, per minute			0.39
≤ 73	300 (26)	22 (23)	
74 - 85	306 (27)	21 (22)	
86 - 98	258 (23)	24 (25)	
≥ 99	268 (24)	30 (31)	
Unknown	6 (1)	0 (0)	
Respiratory rate quartiles, per minute			0.43
≤ 16	357 (31)	24 (25)	
17 - 18	348 (31)	27 (28)	
19 - 20	214 (19)	22 (23)	
≥ 21	205 (18)	23 (24)	

Unknown	14 (1)	1 (1)	
Body temperature quartiles, degrees celcius			0.03
≤ 36.3	293 (26)	39 (40)	
36.4 - 36.6	266 (23)	17 (18)	
36.7 - 37.1	292 (26)	22 (23)	
≥ 37.2	273 (24)	19 (20)	
Unknown	14 (1)	0 (0)	
Supplemental oxygen requirement	809 (28)	30 (31)	0.52
AVPU score, not 'Alert'	55 (5)	4 (4)	0.95
Blood tests			
Haemoglobin quartiles, g/L			<0.01
≤ 113	278 (24)	39 (40)	
114 - 126	273 (24)	27 (28)	
127 - 139	283 (25)	15 (15)	
≥ 140	291 (26)	14 (14)	
Unknown	14 (1)	2 (2)	
White blood cell quartiles, $x10^9$/L			0.40
≤7.0	289 (25)	19 (20)	
7.1 - 9.5	282 (25)	28 (29)	
9.6 - 12.9	276 (24)	19 (20)	
≥ 13.0	274 (24)	29 (30)	
Unknown	17 (1)	2 (2)	
Platelet quartiles, $x10^9$/L			0.59
≤ 188	282 (25)	22 (23)	
189 - 245	280 (25)	26 (27)	
246 - 317	286 (25)	22 (23)	
≥ 318	276 (24)	24 (25)	
Unknown	14 (1)	3 (3)	
Serum sodium quartiles, mmol/L			0.36
≤ 134	286 (25)	29 (30)	

135 - 137	274 (24)	29 (30)	
138 - 140	329 (29)	22 (23)	
≥ 141	244 (21)	17 (18)	
Unknown	5 (0)	0 (0)	
Potassium quartiles, mmol/L			0.18
≤ 3.9	324 (28)	26 (27)	
4.0 - 4.2	258 (23)	29 (20)	
4.3 - 4.6	268 (24)	17 (18)	
≥ 4.7	201 (18)	26 (27)	
Unknown	87 (8)	9 (9)	
Bilirubin quartiles, umol/L			<0.01
≤ 7	285 (25)	20 (21)	
8 - 10	230 (20)	14 (14)	
11 - 16	243 (21)	15 (15)	
≥ 17	229 (20)	34 (35)	
Unknown	151 (13)	14 (14)	
Albumin quartiles, g/L			0.29
≤ 32	247 (22)	23 (24)	
33 - 37	280 (25)	28 (29)	
38 - 41	231 (20)	12 (12)	
≥ 42	204 (18)	15 (15)	
Unknown	176 (15)	19 (20)	
ALT quartiles, U/L			0.31
≤ 13	270 (24)	21 (22)	
14 - 19	217 (19)	22 (23)	
20 - 31	216 (19)	11 (11)	
≥ 32	230 (20)	21 (22)	
Unknown	205 (18)	22 (23)	
CRP quartiles, mg/L			0.22
≤ 5	257 (23)	14 (14)	

6 - 22	206 (18)	18 (19)	
23 - 80	233 (20)	28 (29)	
≥ 81	241 (21)	20 (21)	
Unknown	201 (18)	17 (18)	

Abbreviations: AVPU, (scale) Alert Voice Pain Unconscious; ALT, alanine aminotransferase; CRP, C-reactive peptide

Table 3. Comparison of multivariate models

	Classical risk factors		**APS**		**RISK Study model**	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age, years						
< 60	REF	REF	REF	REF	-	-
60-79	1.41 (0.74-2.66)	0.29	1.53 (0.81-2.87)	0.19	-	-
≥ 80	1.17 (0.60-2.28)	0.65	1.30 (0.67-2.52)	0.44	-	-
Co-morbidity						
Chronic kidney disease	3.44 (2.11-5.60)	<0.001	3.42 (2.12-5.51)	<0.001	3.08 (1.96-4.83)	<0.001
Diabetes mellitus (type I or II)	0.80 (0.47-1.35)	0.40	0.82 (0.49-1.37)	0.45	-	-
Cardiovascular disease[a]	0.97 (0.60-1.55)	0.88	-	-	-	-
Heart failure	1.50 (0.85-2.65)	1.16	2.15 (1.29-3.58)	<0.01	-	-
Liver disease	1.36 (0.49-3.81)	0.55	1.82 (0.83-3.96)	0.13	-	-
Medication						
Diuretic(s)	2.14 (1.30-3.50)	<0.01	-	-	2.33 (1.50-3.64)	<0.001
Renin angiotensin system inhibitor	1.02 (0.62-1.69)	0.94	-	-	-	-
Non-steroidal anti-inflammatory	1.66 (0.78-3.55)	0.19	-	-	-	-
Observations						
Respiratory rate ≥ 20 per min	-	-	1.55 (1.00-2.40)	0.05	-	-
AVPU score, not 'Alert'	-	-	0.76 (0.26-2.23)	0.62	-	-
Blood tests						
Haemoglobin, g/L						
≥ 140	-	-	-	-	REF	REF
127 - 139	-	-	-	-	1.03 (0.48-2.21)	0.95
114 - 126	-	-	-	-	1.75 (0.87-3.50)	0.11
≤ 113	-	-	-	-	2.22 (1.14-4.34)	0.02
Unknown	-	-	-	-	3.26 (0.64-16.56)	0.15
Bilirubin, umol/L						
≤ 7	-	-	-	-	REF	REF

8 - 10	-	-	-	-	0.93 (0.45-1.92)	0.84
11-16	-	-	-	-	0.96 (0.47-1.97)	0.91
≥ 17	-	-	-	-	2.33 (1.26-4.28)	<0.01
Unknown	-	-	-	-	1.50 (0.72-3.14)	0.28
AUROC (95% CI)	**0.73 (0.67-0.78)**		**0.72 (0.67, 0.78)**		**0.75 (0.70-0.80)**	

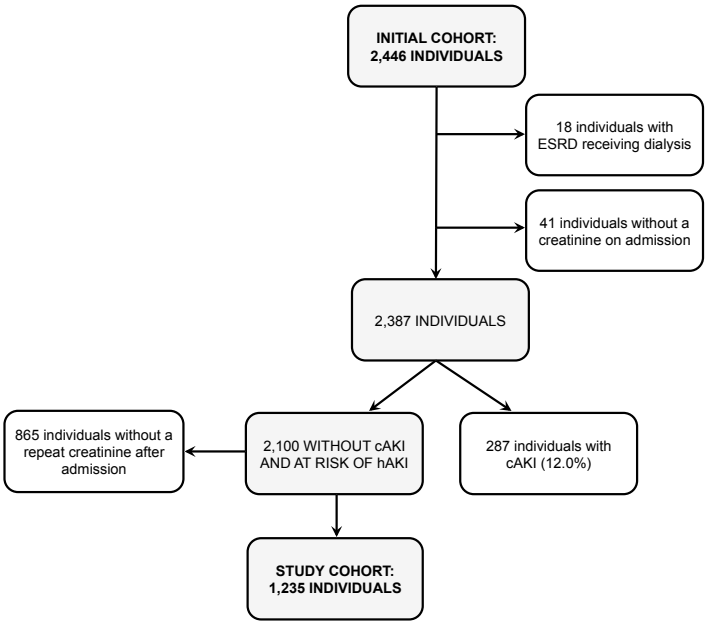

Figure 1. Flow diagram illustrating cohort-selection process. Abbreviations: cAKI, community-acquired AKI; hAKI, hospital-acquired AKI; ESRD, end-stage renal disease

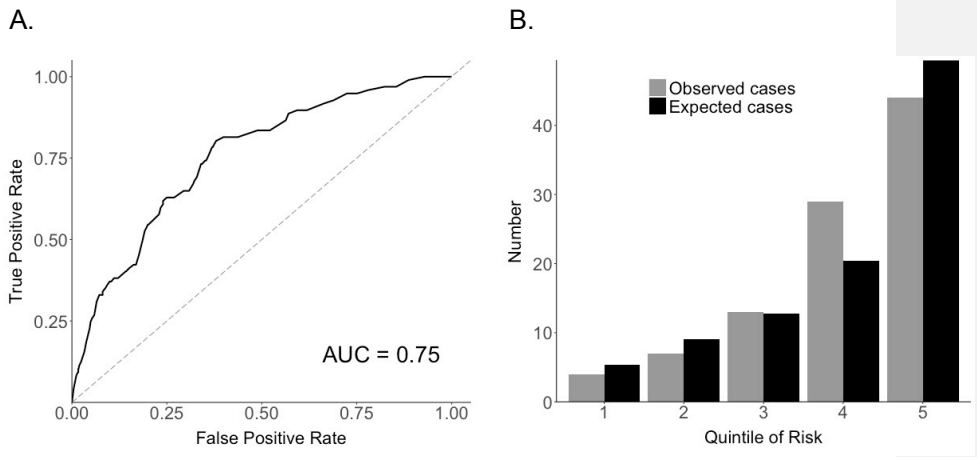

Figure 2. (A). ROC curve for RISK model; (B). Hosmer-Lemeshow calibration plot demonstrating the observed and predicted frequency of hAKI with each quintile of risk.

References:

1. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1-138.
2. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482-93.
3. Bellomo R, Kellum J, Ronco C. Acute renal failure: time for consensus. Intensive care medicine. 2001;27(11):1685-8.
4. Bagshaw SM, Gibney RT. Conventional markers of kidney function. Critical care medicine. 2008;36(4 Suppl):S152-8.
5. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2014;29(7):1362-8.
6. Selby NM, Crowley L, Fluck RJ, McIntyre CW, Monaghan J, Lawson N, et al. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. Clinical journal of the American Society of Nephrology : CJASN. 2012;7(4):533-40.
7. Bedford M, Stevens P, Coulton S, Billings J, Farr M, Wheeler T, et al. Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission: a cohort and nested study. Southampton UK: Queen's Printer and Controller of HMSO.; 2016 Feb.
8. Drawz PE, Miller RT, Sehgal AR. Predicting hospital-acquired acute kidney injury--a case-controlled study. Ren Fail. 2008;30(9):848-55.
9. National Institute for Health and Care Excellence. Acute Kidney Injury: Prevention, Detection and Management Up to the Point of Renal Replacement Therapy. (Clinical guideline CG169). London: National Clinical Guideline Centre.; 2013 Aug.
10. Gareth Roberts DP, Rowan McCarthy, Hemanth Bolusani, Paul Mizen, Mohamed Hassan, Rachel Hooper, Kimberly Saddler, Mo Hu, Sonal Lodhi, Ella Toynton, John Geen, Vikas Lodhi, Catherine Grose,, Phillips aA. Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? Clinical Kidney Journal. 2015;8(6):673–80.
11. Rabar S, Lau R, O'Flynn N, Li L, Barry P. Risk assessment of fragility fractures: summary of NICE guidance. Bmj. 2012;345:e3698.
12. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49-73.
13. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. Ann Thorac Surg. 2012;93(1):337-47.
14. Silver SA, Shah PM, Chertow GM, Harel S, Wald R, Harel Z. Risk prediction models for contrast induced nephropathy: systematic review. Bmj. 2015;351:h4395.
15. Caragata R, Wyssusek KH, Kruger P. Acute kidney injury following liver transplantation: a systematic review of published predictive models. Anaesth Intensive Care. 2016;44(2):251-61.
16. Wilson T, Quan S, Cheema K, Zarnke K, Quinn R, de Koning L, et al. Risk prediction models for acute kidney injury following major noncardiac surgery: systematic review. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2016;31(2):231-40.
17. Brown JR, Solomon RJ, Sarnak MJ, McCullough PA, Splaine ME, Davies L, et al. Reducing Contrast-Induced Acute Kidney Injury Using a Regional Multicenter Quality Improvement Intervention. Circulation: Cardiovascular Quality and Outcomes. 2014.
18. Mehta RL, Cerdá J, Burdmann EA, Tonelli M, García-García G, Jha V, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. The Lancet.
19. KDIGO clinical practice guideline for acute kidney injury. Kidney Int, Suppl. 2012;17:1-138.

20. Forni LG, Dawes T, Sinclair H, Cheek E, Bewick V, Dennis M, et al. Identifying the patient at risk of acute kidney injury: a predictive scoring system for the development of acute kidney injury in acute medical patients. Nephron Clinical practice. 2013;123(3-4):143-50.
21. Hodgson LE, Dimitrov BD, Roderick PJ, Venn R, Forni LG. Predicting AKI in emergency admissions: an external validation study of the acute kidney injury prediction score (APS). BMJ Open. 2017;7(3):e013511.
22. Kolhe NV, Reilly T, Leung J, Fluck RJ, Swinscoe KE, Selby NM, et al. A simple care bundle for use in acute kidney injury: a propensity score-matched cohort study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2016;31(11):1846-54.
23. Al-Jaghbeer M, Dealmeida D, Bilderback A, Ambrosino R, Kellum JA. Clinical Decision Support for In-Hospital AKI. Journal of the American Society of Nephrology. 2018;29(2):654-60.
24. Chandrasekar T, Sharma A, Tennent L, Wong C, Chamberlain P, Abraham KA. A whole system approach to improving mortality associated with acute kidney injury. QJM: An International Journal of Medicine. 2017;110(10):657-66.
25. Finlay S, Bray B, Lewington AJ, Hunter-Rowe CT, Banerjee A, Atkinson JM, et al. Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. Clinical medicine. 2013;13(3):233-8.
26. National Confidential Enquiry into Patient Outcome and Death. Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure) http://www.ncepod.org.uk/2009report1/Downloads/AKI_report.pdf. NCEPOD; 2009.
27. Goldstein SL, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, et al. Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury. Pediatrics. 2013;132(3):e756.
28. Koyner JL, Adhikari R, Edelson DP, Churpek MM. Development of a Multicenter Ward-Based AKI Prediction Model. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(11):1935-43.
29. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of Biomarkers with the Renal Angina Index for Prediction of Severe AKI in Critically Ill Children. Clinical Journal of the American Society of Nephrology. 2014.