J Crit Care 87 (2025) 155016

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Predicting a strongly positive fluid balance in critically ill patients with acute kidney injury: A multicentre, international study

Kyle C. White [a,b,c,d,*], Rinaldo Bellomo [f,g,h,e], Kevin B. Laupland [i,c], Michelle L. Gatton [w], Marlies Ostermann [j], Philipa McIlroy [k], Stephen Luke [l,m], Peter Garrett [n,o], Alexis Tabah [p,c,d], Stephen Whebell [q], Prashanti Marella [r,d], James McCullough [s,o], Kiran Shekar [t,d], Antony G. Attokaran [u,d], Aashish Kumar [v], Jason Meyer [a], Barnaby Sanderson [j], Ary Serpa-Neto [e,f], on behalf of the Queensland Critical Care Research Network (QCCRN)

[a] Intensive Care Unit, Princess Alexandra Hospital, Woolloongabba, QLD, Australia
[b] Intensive Care Unit, Queen Elizabeth II Jubilee Hospital, Coopers Plains, QLD, Australia
[c] School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia
[d] Mayne Academy of Critical Care, Faculty of Medicine, University of Queensland, St Lucia, QLD, Australia
[e] Department of Intensive Care, Austin Hospital, Heidelberg, VIC, Australia
[f] Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia
[g] Department of Critical Care, University of Melbourne, Melbourne, VIC, Australia
[h] Department of Intensive Care, Royal Melbourne Hospital, Melbourne, VIC, Australia
[i] Intensive Care Services, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
[j] Department of Critical Care, King's College London, Guy's & St Thomas' Hospital, London, United Kingdom
[k] Intensive Care Unit, Cairns Hospital, Cairns, QLD, Australia
[l] Intensive Care Services, Mackay Base Hospital, Mackay, QLD, Australia
[m] College of Medicine and Dentistry, James Cook University, Townsville, QLD, Australia
[n] Intensive Care Unit, Sunshine Coast University Hospital, Birtinya, QLD, Australia
[o] School of Medicine and Dentistry, Griffith University, Mount Gravatt, QLD, Australia
[p] Intensive Care Unit, Redcliffe Hospital, Redcliffe, QLD, Australia
[q] Intensive Care Unit, Townsville Hospital, Townsville, QLD, Australia
[r] Intensive Care Unit, Caboolture Hospital, Caboolture, QLD, Australia
[s] Intensive Care Unit, Gold Coast University Hospital, Southport, QLD, Australia
[t] Adult Intensive Care Services, The Prince Charles Hospital, Chermside, QLD, Australia
[u] Intensive Care Unit, Rockhampton Hospital, The Range, QLD, Australia
[v] Intensive Care Unit, Logan Hospital, Logan, QLD, Australia
[w] School of Public Health and Social Work, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia

ARTICLE INFO

Keywords:
Critical illness
Acute kidney injury
Oliguria
Creatinine
Water-electrolyte imbalance
Fluid balance
Diuretics

ABSTRACT

Background: In critically ill patients with acute kidney injury (AKI), a fluid balance (FB) > 2 L at 72 h after AKI diagnosis is associated with adverse outcomes. Identification of patients at high-risk for such fluid accumulation may help prevent it.

Methods: We used Australian electronic medical record (EMR)-based clinical data to develop the "AKI-FB risk score", validated it in a British cohort and used it to predict a positive FB >2 L at 72 h after AKI diagnosis.

Results: We developed the AKI-FB score in 32,030 patients with a median age of 63 years and a median APACHE 2 score of 16. We validated it in 4465 patients, with significant differences in admission diagnoses and interventions. The key score variables were admission after trauma, sepsis or septic shock, and, on the day of AKI diagnosis, highest creatinine, daily cumulative FB, mechanical ventilation, noradrenaline use, noradrenaline equivalent dose >0.07 μg/kg/min, lactate ≥2 mmol/L, transfusion, and nutritional support. A score threshold of 32 had a sensitivity of 75 % and a specificity of 72 % for predicting a > 2 L positive FB with an AUC-ROC of 0.805; 95 % CI 0.799 to 0.810. External validation demonstrated an AUC of 0.761 (95 % CI 0.746 to 0.775).

* Corresponding author at: Intensive Care Unit, Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, 4102 Brisbane, Queensland, Australia.
E-mail address: kyle.white@health.qld.gov.au (K.C. White).

https://doi.org/10.1016/j.jcrc.2025.155016
Received 1 September 2024; Accepted 6 January 2025
Available online 23 January 2025
0883-9441/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Conclusion: We developed and validated the "AKI-FB risk score" to predict patients who developed a positive FB >2 L within 72 h of AKI diagnosis. This prediction score was robust and facilitated the identification of high-risk AKI patients who could be the tarted for preventive measures and be included in future clinical trials of FB management.

1. Introduction

Acute kidney injury (AKI) is common in critically ill patients [1,2] and is associated with significant morbidity and mortality [2–4]. Managing fluid balance (FB) is a cornerstone of its treatment [5–7]. However, there is uncertainty about current practice, how best to conduct such FB management, and how to prevent fluid accumulation.

Avoiding a strongly positive FB appears important. For example, in the absence of hypovolaemia, further administration of fluid to patients with AKI may lead to harm [8,9]. Furthermore, a positive FB may prolong AKI [10], delay renal recovery, [11] and increase the risk of mortality [12,13]. Moreover, in a population of critically ill patients with a mean FB of 2 L 72 h after AKI diagnosis, a study demonstrated an independently increased risk of mortality for every mL of positive FB after the diagnosis of AKI [14]. Consistent with these notions, fluid therapy has been identified as a research priority in critically ill patients with AKI [15].

Despite such interest, a recent scoping review of fluid management of critically ill adult patients with AKI found little evidence to guide therapy [15]. Most studies focused on enhanced fluid removal with diuretics and renal replacement therapy (RRT), with few examining the role of decreasing fluid intake [15]. Furthermore, recent epidemiological research has demonstrated significant variability in FB 72 h after the diagnosis of AKI, ranging from strongly positive to very negative. [14,16]. Finally, in populations with sepsis-associated AKI, those diagnosed with AKI only because of oliguria had high rates of rapid renal recovery and survival, suggesting the need to consider such patients separately [17].

Given the above considerations, it appears important to identify patients who are likely to accumulate a strongly positive FB. Accordingly, in critically ill patients with AKI, we aimed to test the hypothesis that a risk score could be developed and validated to carry good discriminative performance for the subsequent accumulation of a strongly positive FB, defined as >2 L by 72 h.

2. Materials and methods

2.1. Study design

We performed a large, retrospective cohort study of granular, routinely collected, electronic medical record (EMR)-based clinical data.

2.2. Study sites

The study included sites from two countries. The derivation cohort came from 12 closed-model ICUs in Queensland, Australia, which included five tertiary, three outer metropolitan, and four regional ICUs. The validation cohort came from one tertiary ICU in London, United Kingdom. The study evaluated all adult patients admitted between January 1, 2015, and December 31, 2021.

2.3. Data sources

Data was collected from Australia-based ICUs using the eCritical MetaVision™ (iMDsoft, Boston, MA, USA) clinical information systems [18–21] and the Australia and New Zealand Intensive Care Society (ANZICS) CORE Adult Patient Database (APD) [22–25]. For the UK cohort, ICU data was extracted from the ICIP (Intellivue Clinical Information Portfolio) data management system. The data included daily laboratory reports, medications, microbiology, haemodynamics, FB, patient demographics, diagnoses, severity of illness, and outcomes. Primary and secondary diagnoses from the International Classification of Diseases 10 Australia Modification (ICD-10-AM) codes, as well as mortality data, were collected from the Queensland Health Admitted Patient Data Collection (QHAPDC) [26–28] and Australian Births, Deaths. and Marriage Registry [29,30], respectively for the Australian cohort and from the ICIP for the UK cohort. Admission diagnoses were grouped into categories to optimise data accuracy and interpretability (Supplementary Methods, Table S1). The Charlson-defined co-morbidities and index were calculated from the ICD-10 codes (Supplementary Methods, Table S2) [31,32]. The conversion of vasopressor dosage to norepinephrine equivalent and calculation of vasoactive inotrope score was carried out per protocol (Supplementary Methods, Table S3-S4) [33].

2.4. Identification of acute kidney injury

AKI was determined based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria, utilising daily serum creatinine and hourly urine output data [34]. A rolling assessment was conducted throughout the ICU admission to determine hourly urine output per kilogram of body weight. In cases where hourly urine output measurements were missing, imputation of hourly urine output was implemented as described in the Online Supplement, Table S5.

In our data, no pre-ICU serum creatinine values were available, so we needed to estimate the baseline creatinine using the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation. We used standard approaches to estimate the glomerular filtration rate (eGFR) of 75 mL/min/1.73m^2 for patients without chronic kidney disease (CKD) and an eGFR of 40 mL/min/1.73m^2 for patients who had a known CKD history [35–37]. We then compared daily serum creatinine values to the estimated baseline creatinine and identified patients with AKI.

2.5. Participant identification

Analogous to potential prospective clinical trials, patients were included in the analysis if they were aged 18 or higher and developed an AKI within 72 h of ICU admission. Patients were excluded if they required RRT at the time of AKI diagnosis. Furthermore, patients were excluded if they had end-stage renal disease requiring dialysis, were pregnant, were admitted with palliative intent, received ECMO during their ICU admission, were transferred from another ICU, or had a diagnosis of diabetic ketoacidosis or hyperosmolar hyperglycaemic state. Detailed definitions of inclusion and exclusion criteria are presented in Supplementary Table S6. Data on pregnancy status, admission with palliative intent, or ECMO usage, was not collected for the the UK data used for external validation.

2.6. Fluid balance data

Fluid input was categorised by adding all crystalloid fluid (including 5 % dextrose and fluids for medication administration), colloid fluid (4 % and 20 % albumin), nutrition (enteral and parenteral nutrition), blood products (except albumin), and other inputs (oral intake and, at some sites, IV medication flushes). Fluid output was separated into urine output, drain output (all drains including intercostal catheters and surgical drains), gastrointestinal (GI) output (nasogastric aspirates, bowel losses), and other outputs (miscellaneous fluid loss). If and when RRT

was started, the contribution of the net ultrafiltration rate was included.

2.7. Outcomes

The primary outcome was the area under the curve receiver operator curve (AUC-ROC) for a strongly positive FB.

A strongly positive FB was defined as an FB greater than 2 L 72 h after diagnosis of AKI. The threshold of 2 L was chosen because previous research had demonstrated a mean cumulative FB of 1984 mL (95 % CI 1880 mL – 2085 mL) 72 h after AKI diagnosis in a large cohort of critically ill patients [14]. Furthermore, after adjusting for confounders, an FB greater than 2 L 72 h after AKI diagnosis was independently associated with an increased risk of mortality.

Exploratory outcomes included calculation of the AUC-ROC for severely positive FB values, defined as an FB $>$ 3 L and $>$ 4 L within 72 h after the diagnosis of AKI.

Secondary outcomes were ICU and hospital mortality, renal recovery at ICU discharge, and major adverse kidney events at 30 days. Secondary outcome definitions are provided in Supplementary Table S7.

2.8. Statistical analysis

Continuous variables are reported as median (quartile 25th – quartile 75th) and compared between cohorts and between FB groups using the Wilcoxon rank-sum test. Categorical variables are reported as numbers and percentages and compared using the Fisher exact test. Patients were divided into two groups: FB at 72 h $>$ 2 L vs. $\leq$ 2 L. A variety of logistic regression techniques were used to develop the proposed score according to published recommendations [38,39]. All analyses were performed in R v.4.0.2.

2.8.1. Identification of candidate variables

Variables related to the patient and diagnosis and variables measured on the day of the AKI diagnosis were considered for assessment. All variables were selected a priori based on clinical knowledge and previous evidence (Table 1). Bivariate comparisons of all variables between groups were performed. Continuous variables were explored for linearity by considering both quartiles and deciles and then were categorised using pre-defined and clinically relevant cut-offs or by the median. Missing data was imputed using multiple imputations by chained equations, considering all potential variables and the outcome as predictors.

In the imputed dataset, all selected variables were entered in a Least Absolute Shrinkage and Selection Operator (LASSO) regression model to identify significant predictors for the outcome. This technique applies L1 regularisation to the logistic regression model, penalising the absolute size of regression coefficients and encouraging sparsity. Initially, 10-fold cross-validation was performed to select the optimal regularisation parameter (lambda). Then, the model was refitted using the selected lambda to obtain the final LASSO model. Coefficients were extracted from this model, and non-zero coefficient variables, excluding the intercept, were identified as significant predictors. Finally, all identified variables were entered in a multivariable logistic regression model, and only variables with a $p < 0.05$ were retained to calculate the score. These variables were then subjected to a correlation matrix analysis of co-linearity. Variance inflation factors were also assessed.

2.8.2. Construction of the score

β parameters (regression coefficients) were re-estimated using logistic regression with bootstrapping technique, sampling the whole dataset using 500 resamples with replacement. A predictive score, the AKI-FB risk score, was calculated by multiplying the obtained β coefficient by ten and rounding off the value, and these values were summed to produce an overall risk score for each patient. A simplified version of the score was created to facilitate bedside use, selecting only the most relevant variables (based on the strength of association) and ease of

Table 1
Variables Considered for the Predictive Model.

Variable	Overall (n = 32,030)	Strongly Positive FB # (n = 7924)	No Strongly Positive FB # (n = 24,106)	p value
Female sex – no. (%)	12,146 (37.9)	3022 (38.1)	9124 (37.8)	0.650
Type of admission – no. (%)				
Emergency admission	20,910 (65.3)	6139 (77.5)	14,771 (61.3)	< 0.001
Elective surgery	11,585 (36.2)	1891 (23.9)	9694 (40.2)	< 0.001
Post cardiac arrest	1619 (5.1)	588 (7.4)	1031 (4.3)	< 0.001
Post-trauma	2548 (8.0)	921 (11.6)	1627 (6.7)	< 0.001
Sepsis or septic shock* – no. (%)				< 0.001
None	24,104 (75.3)	5087 (64.2)	19,017 (78.9)	
Sepsis	4937 (15.4)	1433 (18.1)	3504 (14.5)	
Septic shock	2989 (9.3)	1404 (17.7)	1585 (6.6)	
Co-morbidities – no. (%)				
Metastatic cancer	921 (2.9)	212 (2.7)	709 (2.9)	0.230
Diabetes	1172 (3.7)	300 (3.8)	872 (3.6)	0.490
Liver cirrhosis	732 (2.3)	243 (3.1)	489 (2.0)	< 0.001
Haematological cancer	543 (1.7)	156 (2.0)	387 (1.6)	0.031
Immunosuppression	2549 (8.0)	674 (8.5)	1875 (7.8)	0.040
Cardiovascular disease	1119 (3.5)	213 (2.7)	906 (3.8)	< 0.001
Respiratory disease	1353 (4.2)	269 (3.4)	1084 (4.5)	< 0.001
Total SOFA*	6 (4–8)	7 (5–9)	5 (4–7)	< 0.001
SOFA >6 – no. (%)	12,014 (37.5)	4553 (57.5)	7461 (31.0)	< 0.001
Renal assessment*				
Highest creatinine, μmol/L	101 (71–157)	121 (79–178)	95 (70–148)	< 0.001
Highest creatinine >101 μmol/L	14,496 (49.4)	4489 (60.1)	10,007 (45.7)	< 0.001
Highest urea, mmol/L	7.2 (5.0–11.1)	8.2 (5.6–12.4)	6.9 (4.9–10.6)	< 0.001
Highest urea >7.2 mmol/L	14,594 (50.3)	3091 (41.7)	11,503 (53.3)	< 0.001
Renal replacement therapy – no. (%)	550 (1.7)	199 (2.5)	351 (1.5)	< 0.001
AKI stage – no. (%)				< 0.001
1	21,920 (68.4)	4633 (58.5)	17,287 (71.7)	
2	6866 (21.4)	2423 (30.6)	4443 (18.4)	
3	3244 (10.1)	868 (11.0)	2376 (9.9)	
Fluid management*				
Use of diuretic – no. (%)	5893 (18.4)	818 (10.3)	5075 (21.1)	< 0.001
Daily accumulated fluid balance, mL~	689 (0–1712)	2122 (1142–3163)	406 (−184–1115)	< 0.001
Fluid balance >690 mL – no. (%)	16,015 (50.0)	6702 (84.6)	9313 (38.6)	< 0.001
Fluid balance tertiles – no. (%)				< 0.001
< −100 mL	6969 (21.8)	279 (3.5)	6690 (27.8)	
-100 to 100 mL	2395 (7.5)	205 (2.6)	2190 (9.1)	

(continued on next page)

Table 1 (*continued*)

Variable	Overall (*n* = 32,030)	Strongly Positive FB [#] (*n* = 7924)	No Strongly Positive FB [#] (*n* = 24,106)	*p* value
≥ 100 mL	22,666 (70.8)	7440 (93.9)	15,226 (63.2)	
Daily accumulated urine output, mL	897 (474–1470)	800 (369–1265)	930 (500–1547)	< 0.001
Urine output <500 mL – no. (%)	8462 (26.4)	2491 (31.4)	5971 (24.8)	< 0.001
Organ support*[*]				
Ventilation – no. (%)	19,057 (59.5)	6084 (76.8)	12,973 (53.8)	< 0.001
Highest noradrenaline dose, μg/kg/min	0.07 (0.02–0.15)	0.11 (0.05–0.21)	0.05 (0.00–0.11)	< 0.001
Noradrenaline use – no. (%)[&]				< 0.001
None	18,318 (57.2)	2673 (33.7)	15,645 (64.9)	
≤ 0.07, μg/kg/min	6877 (21.5)	1760 (22.2)	5117 (21.2)	
> 0.07, μg/kg/min	6835 (21.3)	3491 (44.1)	3344 (13.9)	
Laboratory tests[*]				
Highest pH	7.37 (7.31–7.43)	7.33 (7.26–7.40)	7.38 (7.32–7.44)	< 0.001
pH < 7.35	12,551 (39.2)	4361 (55.0)	8190 (34.0)	< 0.001
Highest lactate, mmol/L	2.1 (1.4–3.4)	2.7 (1.7–4.9)	2.0 (1.3–3.1)	< 0.001
Lactate ≥2 mmol/L – no. (%)	16,865 (54.7)	5264 (67.0)	11,601 (50.5)	< 0.001
Lowest PaO_2 / FiO_2	263 (190–340)	238 (165–317)	271 (200–348)	< 0.001
PaO_2 / FiO_2 ≤ 263 – no. (%)[^]	12,836 (50.3)	3916 (58.7)	8920 (47.3)	< 0.001
Other variables[*]				
Transfusion of blood products – no. (%)	4012 (12.5)	1399 (17.7)	2613 (10.8)	< 0.001
Nutrition support – no. (%)	7508 (23.4)	3628 (45.8)	3880 (16.1)	< 0.001

Data are median (quartile 25th – quartile 75th) or N (%).
Abbreviations: SOFA = sequential organ failure assessment; AKI = acute kidney injury.
[*] On the day of acute kidney injury diagnosis.
[#] Strongly positive fluid balance defined as fluid balance greater than 2000 mL 72 h after diagnosis of AKI.
[&] Categories represent no noradrenaline use and above and below the median noradrenaline dose.
[^] Value represents value below the median PaO_2 / FiO_2 ratio.
[%] Daily fluid balance on the day of AKI diagnosis before the diagnosis of AKI.

collection and use at the bedside.

2.8.3. Internal validation

Logistic regression models were used to reassess the AKI-FB risk score performance in the original dataset without imputation and only in patients with all variables required to determine the score available. Model discrimination and calibration were assessed using the area under the receiver operating characteristics (AUC-ROC) curve, Brier score, and calibration belts. In addition, leave-one-out cross-validation, 10-fold cross-validation, repeated 10-fold cross-validation, and bootstrapping with 1000 resampling were used to check internal consistency and validation.

2.8.4. Cut-off assessment

The sensitivity and specificity of a cut-off were reported using the closest top-left method, where the optimal threshold is the point nearest to the top-left part of the plot with perfect sensitivity or specificity. In addition, five groups based on the AKI-FB risk score were created, combining the minimum description length principle and considering the simplicity of generating the groups. Using previously published descriptive terms, the AUC was classified as having no discrimination value or poor, acceptable, excellent, and outstanding discrimination for AUC values of 0.5, 0.5–0.7, 0.7–0.8, 0.8–0.9, and > 0.9, respectively [40,41].

2.8.5. Comparison with other scores

The AKI-FB risk score was compared to Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, Sequential Organ Failure Assessment (SOFA) on the day of AKI, and Australian and New Zealand Risk of Death (ANZROD) using AUC-ROC.

2.8.6. External validation

The external validation was performed completely independently after the AKI-FB risk score was built from the derivation cohort. The score was externally validated using data from Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom (validation cohort).

2.9. Statement of ethics

In Queensland, the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) approved the study, with an individual waiver of consent granted. In the UK, the study had institutional approval. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

3. Results

3.1. Participants

We assessed 89,184 ICU admissions for eligibility. After applying inclusion and exclusion criteria, we identified 32,030 admissions for analysis. A complete list of patients meeting the exclusion criteria is presented in Online Supplement Table S8. The external validation cohort comprised 14,081 ICU admissions, with 3754 meeting eligibility criteria and included in the analysis.

The patient characteristics for the derivation and validation cohorts are presented in Online Supplement Table S9. The derivation cohort's median age was 63 years (IQR 50–72), and a third were female (12,146; 38 %). The median Charlson co-morbidity index was 3 (IQR 1–5), and the most common admission diagnosis was cardiovascular (10,164; 32 %), followed by gastrointestinal (4509; 14 %) and respiratory (3712; 12 %). Most patients were admitted from the operating theatre (16,653; 52 %) or the emergency department (9483; 30 %). The median APACHE 2 score was 16 (IQR 12–21). On the day of ICU admission, more than half of the patients were mechanically ventilated (18,400; 57 %), and almost half required vasopressor therapy (15,754; 49 %).

The validation cohort's median age was 62 years (IQR 50–73), and the median Charlson co-morbidity index was 2 (IQR 1–4). In contrast to the derivation cohort, the United Kingdom (UK) cohort had higher rates of localised cancer (25 % vs 11 %; $p < 0.001$), more chronic pulmonary disease (23 % vs 11 %; $p < 0.001$), and less congestive heart failure (4.9 % vs 12 %).

When compared to the derivation cohort, patients in the validation cohort were more likely to be admitted with sepsis and less likely to be admitted with cardiovascular diagnoses. Furthermore, the UK cohort had similar rates of mechanical ventilation but fewer patients receiving vasopressors. Finally, UK patients were given diuretics more often and had higher admission serum creatinine values.

3.2. Predictors of outcome

Table 1 displays the variables that were considered for inclusion in the prediction score, along with a comparison of patients with vs. without positive FB > 2 L at 72 h. All variables selected by LASSO regression (Online Supplement Fig. S1) were entered into the preliminary multivariable model (Online Supplement Table S10).

Table S11 in the Online Supplement shows the preliminary model. This model included the following variables that were significantly associated with outcome: admission post-trauma or post-elective surgery, previous chronic respiratory disease, diagnosis sepsis or septic shock, maximum SOFA score before AKI diagnosis greater than 6, and the following variable on the day of AKI diagnosis: the highest creatinine, use of any diuretic, a daily accumulated FB, use of mechanical ventilation, and vasopressor requirement, as well as a noradrenaline equivalent (NEE) dose greater than or equal to 0.07 μg/kg/min, maximum lactate greater than 2 mmol/L, PaO_2 / FiO_2 ratio less than 264, transfusion of any blood products and any nutritional support There was no multicollinearity between the variables in the preliminary multivariable model (Table S11 and Fig. S2 in Online Supplement).

3.3. AKI-FB risk score

To enhance the bedside applicability, we developed a parsimonious model. This model retained nine variables from the preliminary multivariable model. This simplified, final version excluded five variables and was created to avoid the bedside challenges of SOFA calculation, the misinterpretation of chronic respiratory disease status, or any miscalculation of the P/F ratio. As presented in Table 2, we used this parsimonious model to develop the final AKI-FB risk score. The final model included admission post-trauma, diagnosis of sepsis or septic shock, and on the day of AKI diagnosis, highest creatinine, daily cumulative FB categorised as less than −100 mL, greater than 100 mL, or between -100 and 100 mL, use of mechanical ventilation, noradrenaline use, and a NEE dose greater than 0.07 μg/kg/min, lactate greater than or equal to 2 mmol/L, transfusion of any blood products, and the administration of nutritional support.

Table 2
Positive Fluid Balance Prediction Score.

Variable	Score
Type of admission	
Post-trauma	5
Sepsis or septic shock*	
None	0
Sepsis	4
Septic shock	2
Renal assessment*	
Highest creatinine >100 μmol/L	6
Fluid management*	
Daily accumulated fluid balance#	
< −100 mL	0
-100 to 100 mL	7
≥ 100 mL	19
Organ support*	
Use of ventilation	3
Noradrenaline use	
None	0
≤ 0.07, μg/kg/min	1
> 0.07, μg/kg/min	8
Lactate ≥2 mmol/L	3
Other variables*	
Transfusion of blood products	2
Nutrition support	11
Total Score	**0 to 61**

Abbreviations: AKI is acute kidney injury.
* On the day of acute kidney injury diagnosis.
# Daily fluid balance on the day of AKI diagnosis before the diagnosis of AKI.

The percentage of patients with FB > 2 L at 72 h according to the AKI-FB risk score is shown in Fig. 1. We created five groups created based on the AKI-FB risk score (≤ 10, 11–20, 21–30, 31–40, and > 40). In these five groups, 2 %, 8 %, 17 %, 39 %, and 62 % of the corresponding patients had an FB > 2 L at 72 h, respectively (Fig. 1). The best cut-off value for discrimination was a score of 32, with a sensitivity of 75 % (95 % CI 74–76 %) and a specificity of 72 % (95 % CI 73–74 %) (Table 3). In addition, an online calculator was developed and made available at https://aryserpa.shinyapps.io/Risk_Score_Calculator. Moreover, clinical examples are provided in Online Supplement Figs. S3 – S5.

3.4. Validation and sensitivity analysis

The internal validation of the AKI-FB risk score demonstrated excellent discrimination (AUC-ROC, 0.805; 95 % CI 0.799 to 0.810; Brier score = 0.148) (Table 3 and Fig. 2). The model's predictive performance remained excellent in all internal validation assessments, demonstrating AUC-ROC between 0.810 and 0.818 (Online Supplement Table S12). The AKI-FB risk score was then validated in patients with all variables available in the external UK cohort. Such external validation demonstrated acceptable discrimination (AUC 0.761; 95 % CI 0.746 to 0.775; Brier score = 0.197) (Table 3 and Fig. 2).

Furthermore, a sensitivity analysis was performed to assess the performance of the AKI-FB risk score depending on the method by which the AKI was diagnosed. There was greater discrimination for AKI diagnosed by urine output alone (AUC 0.806; 95 % CI 0.799–0.813) than AKI diagnosed by creatinine alone (AUC 0.780; 95 % CI 0.767–0.791) and AKI diagnosed by both urine output and creatinine (AUC 0.783; 95 % CI 0.768–0.799) ($p < 0.001$).

Lastly, we assessed the performance of the AKI-FB risk score to predict patients with a severely positive FB at 72 h (Fig. 3). The AKI-FB showed excellent discrimination for predicting an FB greater than 3 L (AUC 0.803; 95 % CI 0.796 to 0.810) or greater than 4 L (AUC 0.804; 95 % CI 0.797 to 0.811) in the internal validation. Moreover, the discrimination remained excellent in the external validation for both greater than 3 L (0.811; 95 % CI 0.794 to 0.829) and 4 L (0.812; 95 % CI 0.794 to 0.829).

4. Discussion

4.1. Key findings

We studied over 30,000 critically ill patients with AKI and developed the "AKI-FB risk score" for the prediction of a strongly positive FB 72 h after diagnosis of AKI. The "AKI-FB risk score" had excellent predictive ability and was superior to general critical care prediction scores in the derivation cohort. Furthermore, when validated in a large cohort from another country, the AKI-FB risk score demonstrated acceptable predictive performance. Moreover, the AKI-FB risk score also demonstrated excellent discrimination for predicting a severely positive FB. Finally, a score of 32 or higher had high sensitivity and specificity for identifying patients early, who subsequently went on to develop a positive FB greater than 2 L at 72 h.

4.2. Relationship to literature

The AKI-FB risk score is the first prediction score developed to

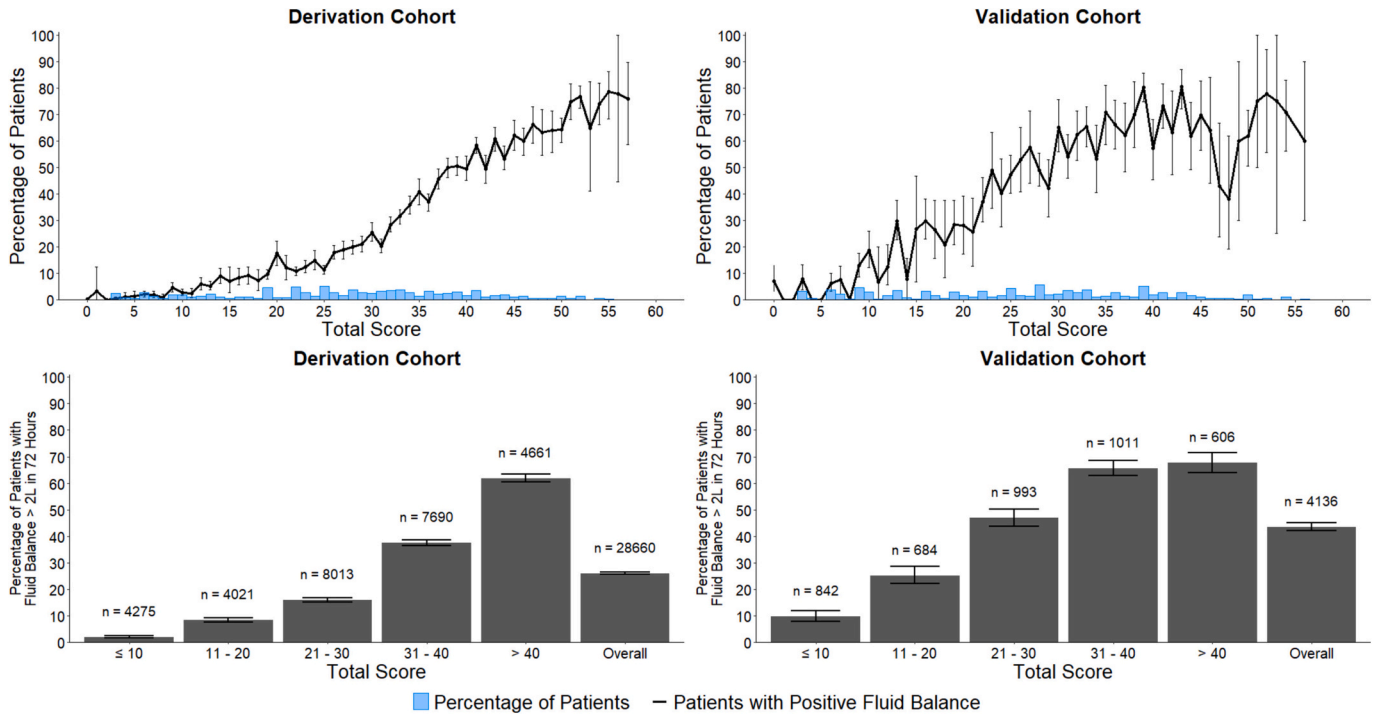


Fig. 1. Percentage of Patients with a fluid balance >2000 mL 72 h after diagnosis of AKI according to Total Score.

Table 3
Predictive Model Performance in the Derivation and Validation Cohort.

	Derivation		Validation	
	Estimates (95 % CI)	*p*-value	Estimates (95 % CI)	*p*-value
Odds ratio	1.11 (1.10 to 1.12)	< 0.001	1.08 (1.07 to 1.09)	< 0.001
Discrimination				
AUC-ROC	0.805 (0.799 to 0.810)	–	0.761 (0.746 to 0.775)	–
Calibration				
Brier score*	0.148	–	0.197	–
Best cut-off**	32	–	26	–
Sensitivity, %	74.9 (74.0 to 75.9)	–	75.1 (73.2 to 77.0)	–
Specificity, %	72.3 (71.7 to 72.9)	–	66.0 (64.1 to 68.0)	–

Abbreviations: AUC = area under and the curve; ROC = Receiver Operating Characteristic curve.

* The Brier score ranges from 0 to 1. A lower Brier score indicates better predictive accuracy and that the predicted probabilities are closer to the actual outcomes. It was calculated using the predicted probabilities of the model including the score as the independent variable.

** Best cut-off identified with the closest top-left method (the optimal threshold is the point closest to the top-left part of the plot with perfect sensitivity or specificity).

identify patients with AKI who are likely to develop a strongly positive FB, defined as an FB greater than 2 L 72 h. A threshold of 2 L was used because previous research demonstrated a mean cumulative FB of nearly 2 L at 72 h after AKI diagnosis in a large cohort of critically ill patients [15]. Furthermore, a mean FB greater than 2 L was associated with an increased risk of mortality, highlighting its potential clinical significance. Previously literature has identified patient characteristics, or clinical variables, that are associated with a positive FB. However, they were not coalesced into a clinically applicable prediction score [14,42].

4.3. Implications

The main implication of the derivation and validation of the AKI-FB risk score is that patients who are likely to develop a strongly positive FB after the diagnosis of an AKI can now be identified with acceptable to excellent discrimination. The application of the AKI-FB risk score may then occur in several ways. First, the score can be applied to risk stratification in AKI trials. Second, it can be used to set inclusion criteria for clinical trials investigating FB management in critically ill patients with AKI, aiming to enrol patients where there is a greater feasibility of producing a difference in FB. Third, the AKI-FB risk score could be adopted in clinical practice as an alert where clinicians would be able to intervene early to prevent the accumulation of fluid, if deemed clinically appropriate and safe.

4.4. Strengths and limitations

Our study has several strengths. First, we utilised detailed, routinely collected EMR data, which were entered by non-research staff, thus minimising sampling bias. In addition, the granularity of the data allowed for the timing of diagnosis of AKI to be determined down to the first hour of occurrence. This is in contrast to the use of calendar day-based diagnosis, as has been standard so far in critical care research. The derivation of the AKI-FB risk score was obtained in a large cohort from 12 ICUs, which represent the majority of the population serviced in the state of Queensland, Australia. This approach enhanced the generalizability of the score to other patients with AKI in resource-intensive health services. Furthermore, the validation of the AKI-FB risk score, in a completely external cohort, located in another country provides strength and rigour to the validation process.

We acknowledge several limitations. First, pre-admission creatinine values were not available, and we had to estimate baseline renal function. This may have resulted in the misclassification of AKI; however, we corrected for known CKD and utilised a published and widely used method [36,43]. Second, we did not make any adjustments for insensible fluid loss. Thus, the reported FB may overestimate the actual fluid balance. However, modifying FB for insensible losses is not a standard

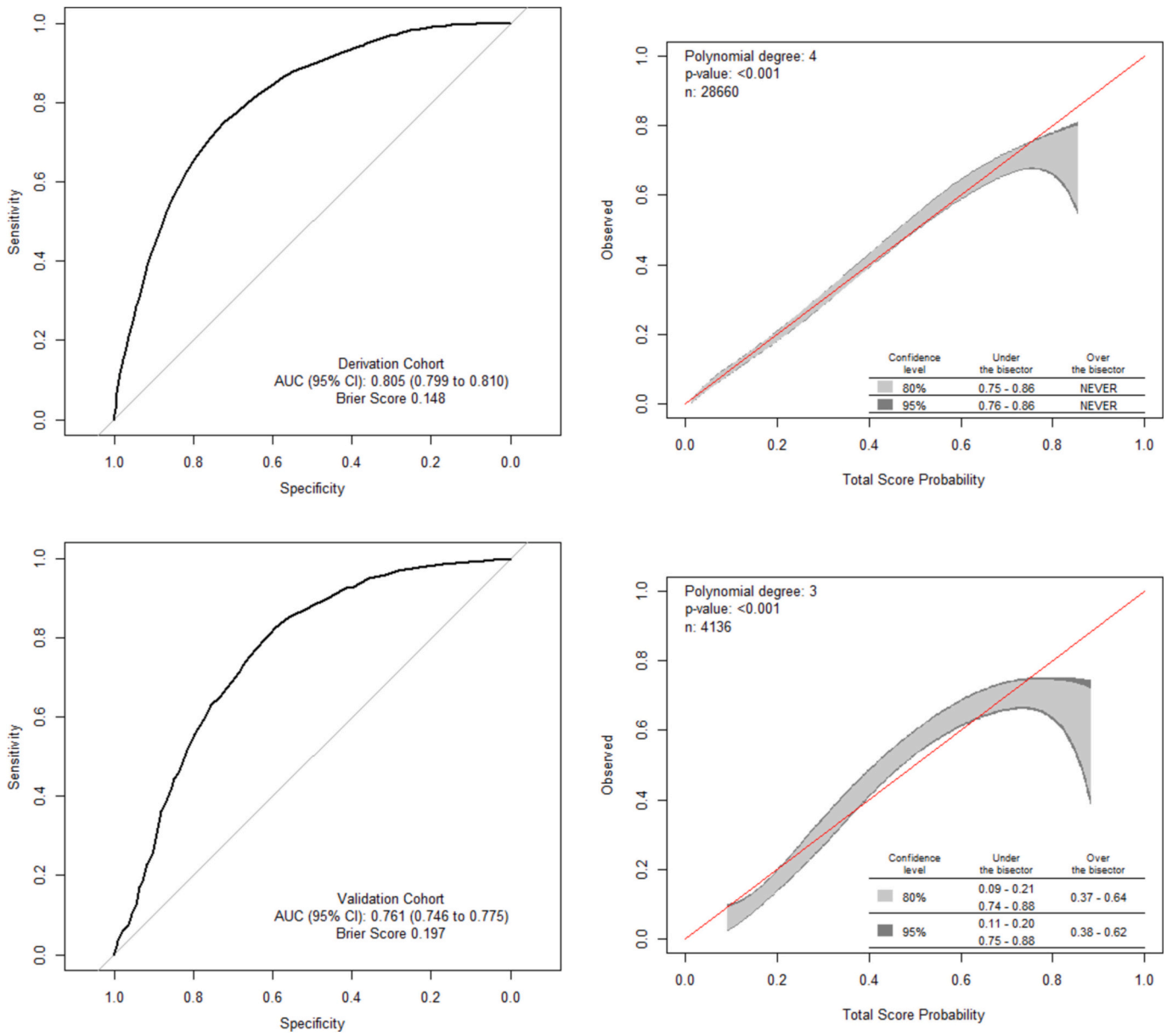


Fig. 2. Validation of AKI-FB risk score.

procedure in clinical practice and is fraught with inaccuracy. Third, we report data on FB, not fluid accumulation, and acknowledge that a positive FB does not necessarily equate with fluid accumulation, as the preadmission fluid status is typically unknown. On the other hand, FB has been used as a surrogate parameter and, in observational studies, has consistently been associated with adverse outcomes in critically ill patients [13,44,45]. Fourth, we did not normalise FB per patient weight and utilised absolute values, an approach that is pragmatic but may misrepresent the relative quantity of positive FB. Finally, the study population was confined to a single non-Australian ICU and did not encompass resource-limited settings. Global variability in FB management and the availability of lactate measurement may restrict the external validity of the findings.

5. Conclusion

We have developed a comprehensive risk prediction score, the "AKI-FB risk score", which can predict the probability of a > 2 L, 3 L or 4 L positive FB within 72 h of the AKI diagnosis with excellent discrimination. The AKI-FB risk score has now undergone external validation, comprises nine readily identifiable clinical variables, can be implemented via an online calculator and can be readily applied to the conduct of future trials. It can also be used to generate alerts and to guide clinicians. Implementing this prediction score should facilitate the identification of patients at risk of a strongly positive FB and allow investigators or clinicians to test whether interventions can be deployed to decrease fluid accumulation and improve clinical outcomes.

Funding sources

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Take Home Message.

The AKI-FB risk score was developed to predict a strongly positive fluid balance, defined as greater than two liters, within 72 h of an acute kidney injury diagnosis. The score, which was developed using electronic medical record-based clinical data from a Queensland cohort and validated in a United Kingdom cohort, demonstrated robust predictive

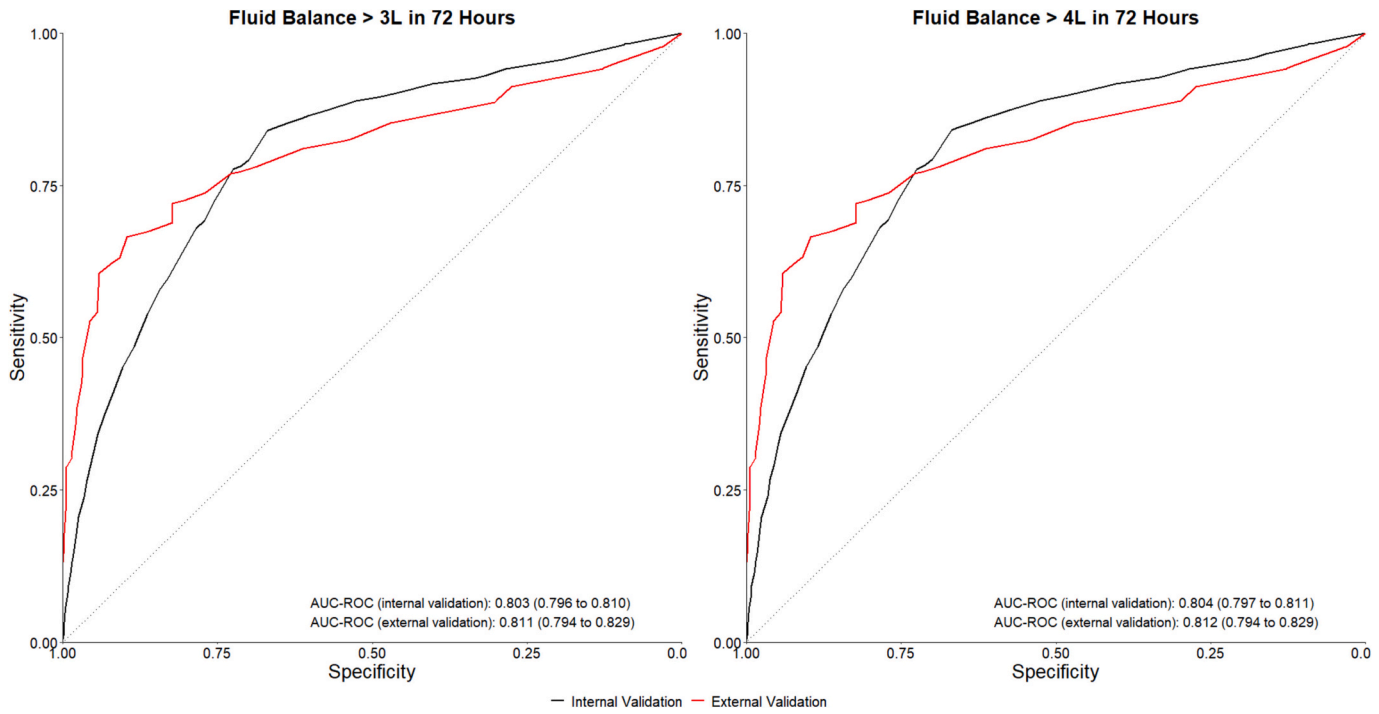


Fig. 3. Validation of AKI-FB risk score to predict a positive fluid balance >3 l or > 4 l at 72 h after the diagnosis of acute kidney injury

performance.

CRediT authorship contribution statement

Kyle C. White: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Rinaldo Bellomo:** Writing – review & editing, Writing – original draft, Conceptualization. **Kevin B. Laupland:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Michelle L. Gatton:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization. **Marlies Ostermann:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Philipa McIlroy:** Writing – review & editing, Data curation. **Stephen Luke:** Writing – review & editing, Data curation. **Peter Garrett:** Writing – review & editing, Data curation. **Alexis Tabah:** Writing – review & editing, Data curation. **Stephen Whebell:** Writing – review & editing, Data curation. **Prashanti Marella:** Writing – review & editing, Data curation. **James McCullough:** Writing – review & editing, Data curation. **Kiran Shekar:** Writing – review & editing, Data curation. **Antony G. Attokaran:** Writing – review & editing, Data curation. **Aashish Kumar:** Writing – review & editing, Data curation. **Jason Meyer:** Writing – review & editing, Project administration, Formal analysis, Data curation. **Barnaby Sanderson:** Writing – review & editing, Data curation. **Ary Serpa-Neto:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Prashanti Marella:** Writing – review & editing, Data curation. **Phillipa McIlroy:** Writing – review & editing, Data curation. **James McCullough:** Writing – review & editing, Data curation. **Aashish Kumar:** Writing – review & editing, Data curation. **Stephen Luke:** Writing – review & editing, Data curation. **Kyle White:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Jason Meyer:** Writing – review & editing, Project administration, Formal analysis, Data curation. **Alexis Tabah:** Writing – review & editing, Data curation. **Antony G. Attokaran:** Writing – review & editing, Data curation. **Kevin B. Laupland:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Kiran Shekar:** Writing – review & editing, Data curation. **Stephen Whebell:** Writing – review & editing, Data curation. **Michelle Gatton:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank the ANZICS CORE management committee and the clinicians, data collectors, and researchers at the following contributing sites: Caboolture Hospital, Cairns Hospital, Gold Coast University Hospital, Logan Hospital, Mackay Base Hospital, Princess Alexandra Hospital, Redcliffe Hospital, Rockhampton Hospital, Royal Brisbane and Women's Hospital, Sunshine Coast University Hospital, The Prince Charles Hospital, and The Townsville Hospital.

The authors acknowledge the Statistical Analysis and Linkage Unit of the Statistical Services Branch (SSB), Queensland Health for linking the data sets used in this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2025.155016.

Data availability statement

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for research under Sect. 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

References

[1] Koeze J, Keus F, Dieperink W, Horst I van der, Zijlstra JG, Meurs M van. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. BMC Nephrol 2017;18(1):70.
[2] Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intens Care Med 2015;41(8):1411–23.
[3] Rossaint J, Zarbock A. Acute kidney injury: definition, diagnosis and epidemiology. Min Urol E Nefrol Ital J Urol Nephrol 2015;68(1):49–57.
[4] Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic Dialysis and death among survivors of acute kidney injury requiring dialysis. Jama 2009;302 (11):1179–85.
[5] Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol 2010;6(2):107–15.
[6] Goldstein SL. Fluid management in acute kidney injury. J Intensive Care Med 2014; 29:183–9.
[7] Perner A, Prowle J, Joannidis M, Young P, Hjortrup P, Pettila V. Fluid management in acute kidney injury. Intensive Care Med 2017;43(6):807–15.
[8] Raimundo MR, Crichton S, Syed Y, Martin J, Ostermann M. Fluid accumulation increases the risk of AKI progression and death in critically ill patients with early AKI. Crit Care 2014;18:S134–5.
[9] Zhang J, Crichton S, Dixon A, Seylanova N, Peng ZY, Ostermann M. Cumulative fluid accumulation is associated with the development of acute kidney injury and non-recovery of renal function: a retrospective analysis. Crit Care 2019;23(1):392.
[10] Grams ME, Estrella M, Coresh J, Brower RG, Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol 2011;6(5):966–73.
[11] Zhang J, Seylanova N, Crichton S, Dixon A, Ostermann M. Cumulative fluid balance is a risk factor for AKI development and progression. Br J Diab 2019;19: 81–2.
[12] Teixeira C, Garzotto F, Piccinni P, Brienza N, Iannuzzi M, Gramaticopolo S, et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care 2013;17(1):R14.
[13] Wang N, Jiang L, Zhu B, Wen Y, Xi XM. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care Lond Engl 2015;19(1):371.
[14] White KC, Serpa-Neto A, Hurford R, Clement P, Laupland KB, Ostermann M, et al. How a positive fluid balance develops in acute kidney injury: a binational, observational study. J Crit Care 2024 Aug;82:154809.
[15] Pickkers P, Ostermann M, Joannidis M, Zarbock A, Hoste E, Bellomo R, et al. The intensive care medicine agenda on acute kidney injury. Intens Care Med 2017;43 (9):1198–209.
[16] White KC, Laupland KB, Ostermann M, Serpa-Neto A, Gatton ML, Hurford R, et al. Current fluid management practice in critically ill adults on continuous renal replacement therapy: a binational, observational study. Blood Purif 2024;53(8): 624–33.
[17] White KC, Serpa-Neto A, Hurford R, Clement P, Laupland KB, See E, et al. Sepsis-associated acute kidney injury in the intensive care unit: incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes. A multicenter, observational study. Intensive Care Med 2023:1–11.
[18] White K, Tabah A, Ramanan M, Shekar K, Edwards F, Laupland KB. 90-day case-fatality in critically ill patients with chronic liver disease influenced by presence of portal hypertension, results from a multicentre retrospective cohort study. J Crit Care 2023;1(38):5–10.
[19] Marella P, Ramanan M, Shekar K, Tabah A, Laupland KB. Determinants of 90-day case fatality among older patients admitted to intensive care units: a retrospective cohort study. Aust Crit Care 2024 Jan;37(1):18–24.
[20] Laupland KB, Ramanan M, Shekar K, Edwards F, Clement P, Tabah A. Long-term outcome of prolonged critical illness: a multicentered study in North Brisbane, Australia. PLoS ONE 2021;16(4):e0249840.
[21] Sieben NA, Dash S. A retrospective evaluation of multiple definitions for ventilator associated pneumonia (VAP) diagnosis in an Australian regional intensive care unit. Infect Dis Heal 2022;27(4):191–7.
[22] Bagshaw SM, George C, Bellomo R, Committe ADM. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transpl 2008;23(5):1569–74.
[23] Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. Jama 2017;317(3):290–300.
[24] Corrigan C, Duke G, Millar J, Paul E, Butt W, Gordon M, et al. Admissions of children and adolescents with deliberate self-harm to intensive care during the SARS-CoV-2 outbreak in Australia. JAMA Netw Open 2022;5(5):e2211692.
[25] Kirsi-Maija K, Michael B, David P, Jamie CD, Rinaldo B. Systemic inflammatory response syndrome criteria in defining severe Sepsis. New Engl J Med 2015;372 (17):1629–38.
[26] Vallmuur K, Cameron CM, Watson A, Warren J. Comparing the accuracy of ICD-based severity estimates to trauma registry-based injury severity estimates for predicting mortality outcomes. Injury 2021;52(7):1732–9.
[27] Watson A, Watson B, Vallmuur K. Estimating under-reporting of road crash injuries to police using multiple linked data collections. Accid Anal Prev 2015;83:18–25.
[28] Nghiem S, Afoakwah C, Byrnes J, Scuffham P. Lifetime costs of hospitalised cardiovascular disease in Australia: an incidence-based estimate. Hear Lung Circ 2021;30(8):1207–12.
[29] Win KTH, Thomas B, Emeto TI, Fairley L, Thavarajah H, Vangaveti VN, et al. A comparison of clinical characteristics and outcomes between indigenous and non-indigenous patients presenting to Townsville hospital emergency department with chest pain. Hear Lung Circ 2022;31(2):183–93.
[30] O'Beirne J, Skoien R, Leggett BA, Hartel GF, Gordon LG, Powell EE, et al. Diabetes mellitus and the progression of non-alcoholic fatty liver disease to decompensated cirrhosis: a retrospective cohort study. Méd J Aust 2023 Oct 16;219(8):358–65.
[31] Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57(12):1288–94.
[32] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Méd Care 2005;43(11):1130–9.
[33] Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. New Engl J Med 2017;377(5):419–30.
[34] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.
[35] Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. New Engl J Med 2021;385(19):1737–49.
[36] Cooper DJ, Plewes K, Grigg MJ, Patel A, Rajahram GS, William T, et al. An evaluation of commonly used surrogate baseline creatinine values to classify AKI during acute infection. Kidney Int Rep 2021;6(3):645–56.
[37] Larsen T, See EJ, Holmes NE, Bellomo R. Estimating baseline creatinine to detect acute kidney injury in patients with chronic kidney disease. Nephrology 2023;28 (8):434–45.
[38] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Br Méd J 2015;350(4):g7594.
[39] Labarère J, Renaud B, Bertrand R, Fine MJ. How to derive and validate clinical prediction models for use in intensive care medicine. Intens Care Med 2014;40(4): 513–27.
[40] Homer D, Lemeshow S, Sturdivant R. Applied Logistic Regression. New York, NY: John Wiley and Sons; 2023. p. 160–4.
[41] Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5(9):1315–6.
[42] White KC, Nasser A, Gatton ML, Laupland KB. Current management of fluid balance in critically ill patients with acute kidney injury: a scoping review. Crit Care Resusc 2023 Jul 27;25(3):126–35.
[43] Bouchard J. Estimating baseline serum creatinine for assessing acute kidney injury: not a one size fits all approach. Kidney Int Rep 2021;6(3):562–4.
[44] Ostermann M, van Straaten HMO, Forni LG. Fluid overload and acute kidney injury: cause or consequence? Crit Care Lond Engl 2015;19(1):443.
[45] Kuo G, Chen SW, Lee CC, Chen JJ, Fan PC, Wang SY, et al. Latent trajectories of fluid balance are associated with outcomes in cardiac and aortic surgery. Ann Thorac Surg 2020;109:1343–9.