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A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients

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Abstract

Background. The Acute Dialysis Quality Initiative Working Group recently developed the RIFLE criteria, a consensus definition for acute kidney injury (AKI). We sought to evaluate the RIFLE criteria on the day of ICU admission in a large heterogenous population of critically ill patients.

Methods. Retrospective interrogation of prospectively collected data from the Australian New Zealand Intensive Care Society Adult Patient Database. We evaluated 120 123 patients admitted for ≥24 h from 1 January 2000 to 31 December 2005 from 57 ICUs across Australia.

Results. The median (IQR) age was 64.3 (50.8–75.4) years, 59.5% were male, 28.6% had co-morbid disease, 50.3% were medical admissions and the initial mean (±SD) APACHEII score was 16.9 (±7.7). According to the RIFLE criteria, on the day of admission, AKI occurred in 36.1%, with a maximum RIFLE category of Risk in 16.3%, Injury in 13.6%, and Failure 6.3%. AKI, defined by any RIFLE category, was associated with an increase in hospital mortality (OR 3.29, 95% CI 3.19–3.41, $P < 0.0001$). The crude hospital mortality stratified by RIFLE category was 17.9% for Risk, 27.7% for Injury and 33.2% for Failure. By multivariable analysis, each RIFLE category was independently associated with hospital mortality (OR: Risk 1.58, Injury 2.54 and Failure 3.22).

Conclusion. In a large heterogenous cohort of critically ill patients, the RIFLE criteria classified >36% with AKI on the day of admission. For successive increases in severity of RIFLE category, there were increases in hospital mortality. The RIFLE criteria represent a simple tool for the detection and classification of AKI and for correlation with clinical outcomes.

Keywords: acute kidney injury; acute renal failure; mortality; multi-centre; RIFLE criteria

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Introduction

Acute kidney injury (AKI) is a common clinical problem encountered in critically ill patients and characteristically portends an increase in morbidity and mortality [1].

Epidemiologic studies have previously described the incidence and clinical outcomes associated with AKI [2–9]; however, inferences from these investigations are often limited due to variation in definitions used to classify AKI. This lack of agreement has been unfortunate and likely held up scientific progress in critical care nephrology [10,11].

The Acute Dialysis Quality Initiative (ADQI) Working Group, comprised of experts in the fields of nephrology and critical care, recently published the RIFLE classification, a new consensus and evidence-based definition for AKI [12]. The RIFLE classification defines three grades of severity of AKI (Risk, Injury and Failure) based on changes to serum creatinine and urine output and two clinical outcomes (Loss and End-stage).

The RIFLE classification has been evaluated in a number of clinical studies of critically ill patients with AKI to assess its validity, clinical relevance and predictive ability for mortality [13–26]. Yet, these investigations are limited by having assessed either a small cohort [13,15,19–21,23] a selected subpopulation of critically ill patients [15,16,18–23,26], by omitting urine output criteria ([14,24,25]) or by being performed at a single institution [13, 15–21,23,25]. These shortcomings are important for a definition that needs robustness in heterogenous patients from multiple centres.

Accordingly, we interrogated the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) to obtain information on AKI as defined by the RIFLE criteria in a large cohort of critically ill patients from 57 Australian hospitals over a 5-year period. The ANZICS APD is a high quality clinical database containing data from >600 000 individual adult admissions to 135 intensive care units (ICUs) from 1987 to the present [27]. Our primary objectives were to evaluate: (1) the occurrence of AKI within 24 h of ICU admission, (2) the RIFLE criteria

in a large multi-centre heterogenous population of critically ill patients and (3) the robustness of the RIFLE criteria and their relationship with hospital mortality.

Subjects and methods

This was a retrospective analysis of prospectively collected data. We interrogated the ANZICS APD for all adult (age ≥18 years) ICU admissions for a duration ≥24 h from 1 January 2000 to 31 December 2005. In the event of multiple admissions, only the initial ICU admission was considered to avoid bias. Those patients re-admitted within 72 h after initial discharge were considered as part of the initial index admission. Patients with pre-existing end-stage kidney disease on chronic dialysis ($n = 4026$, 3.4%) or with prior kidney transplant ($n = 69$, 0.06%) were excluded. We selected only those ICUs that had continuously contributed data to the APD during this 5-year period. This comprised of 57 ICUs (19 tertiary referral, 15 metropolitan, 12 regional/rural and 11 private hospitals).

Identification of cases

AKI severity was classified according to the RIFLE criteria [12]. The RIFLE criteria (acronym indicating Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function and End-stage kidney disease) classify AKI into three categories of severity (Risk, Injury and Failure) and two categories of clinical outcome (Loss and End-stage kidney disease). For the purposes of this study, the outcome RIFLE categories Loss and End-stage kidney disease have not been evaluated. Urine output was described in 92.4% of patients ($n = 111\,091$); however, only the cumulative 24-h output was available and no patient weights were described. Thus for the purposes of this study, we used a minor modification of the RIFLE urine output criteria, assuming an average patient weight of 70 kg, into <35 mL/h (Risk), <21 mL/h (Injury) or <4 mL/h (Failure). Baseline serum creatinine values were estimated by the Modification of Diet in Renal Disease (MDRD) equation as recommended by the ADQI Working Group (assuming a lower limit of normal baseline GFR of 75 mL/min) and similar to previous studies [12,16,24–26]. For analysis, patients were assigned to their worst RIFLE category according to either serum creatinine or urine output criteria.

Data collection

Standard demographic, clinical and physiologic data were retrieved. Demographic information included age, sex, and dates and source of admission. Clinical data encompassed primary diagnosis, surgical status, presence of co-morbidities, and need for mechanical ventilation. Physiologic data included Glasgow Coma Scale (GCS), vital signs, PaO2/FiO2 ratio, serum pH and serum potassium. Data on kidney function included serum creatinine, urea and urine output [27]. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III and Simplified Acute Physiology Score (SAPS) II systems [28,29].

Pre-existing co-morbidities were defined by use of the chronic health evaluation for APACHE II, APACHE III and SAPS II systems as outlined in the ANZICS APD data dictionary [27].

Several primary admission diagnostic categories were created [27]. Sepsis/septic shock encompassed admissions for primarily sepsis-related diagnoses and included sepsis associated with pneumonia, gastrointestinal disease, urinary tract infections, central nervous system infections, soft tissue infections and the unique ANZICS APD additions of sepsis with shock of undetermined source. A cardiac diagnosis encompassed non-surgical admissions with cardiogenic shock, cardiac arrest, congestive heart failure and acute myocardial infarction. A respiratory diagnosis encompassed primary respiratory arrests, aspiration syndrome, non-cardiogenic pulmonary oedema, exacerbations of chronic obstructive pulmonary disease or asthma and pulmonary embolism. A primary hepatic diagnosis included admission with hepatic failure or liver transplant. A diagnosis of gastrointestinal haemorrhage included bleeding due to peptic ulcers, diverticulosis and varices. All other non-surgical gastrointestinal diagnoses were categorized as other. A metabolic/poisoning diagnosis incorporated non-operative causes of metabolic coma, diabetic ketoacidosis, drug overdoses or other endocrinopathies. A primary neurologic diagnosis incorporated stroke, intracerebral haemorrhage, subarachnoid haemorrhage, epidural haematoma or other neurologic cause for coma.

Statistical analysis

Analysis was performed using Stata version 8.2 (Stata Corp, College Station, TX, USA). In the event of missing data values, data were not replaced. Normally or near normally distributed variables are reported as means with standard deviations (SD) and compared by Student's *t*-test, analysis-of-variance or simple linear regression. Non-normally distributed continuous data are reported as medians with interquartile ranges (IQR) and compared by Mann–Whitney *U*-test or Kruskal–Wallis test. Categorical data were reported as proportions and compared using Fisher's Exact Test. Multivariable logistic regression analysis was used to assess the association of each RIFLE category with hospital mortality. *A priori* selected variables included age, sex, co-morbidity, surgical/medical, primary diagnosis, need for mechanical ventilation, non-renal APACHE II score, hospital site and the RIFLE classification. The non-renal APACHE II score was chosen to control for multicollinearity between the RIFLE classification and general scoring systems that include points for AKI based on serum creatinine. In addition, the discrimination of the RIFLE criteria for hospital mortality was compared with that of the general severity of illness scoring systems. In each of these additional multivariable models, the complete severity of illness scoring system was substituted for the RIFLE classification. Model fit was assessed by the goodness-of-fit test and discrimination was assessed by the area under the receiver operator characteristic (AuROC) curve. Data are presented as odds ratios (OR) with 95% confidence

Table 1. Patient demographics and primary diagnosis at ICU admission for the entire cohort

Characteristics	Total ($n = 120\,123$)
Age (years)	65.3 (50.8–75.4)
Male sex (%)	59.5
Co-morbid disease (%)	28.6
Cardiovascular	15.6
Respiratory	8.4
Immunocompromised	4.9
Metastatic cancer	2.9
Hepatic	2.3
Hematologic malignancy	1.7
Non-elective admission (%)	61
Surgical admission (%)	49.7
Cardiovascular (%)	46.1
Trauma (%)	7.7
Primary diagnosis (%)	
Sepsis/septic shock	27.8
Respiratory	11.7
Neurologic	9.3
Cardiac	9.3
Gastrointestinal (other)	8.8
Hepatic	5.9
Metabolic/poisoning	5.3
Gastrointestinal bleeding	2.3

Table 2. Incidence of AKI stratified by RIFLE criteria

RIFLE category (%)	SCr criteria only	UO criteria only	Both[a]
None	83 620 (69.6)	106 500 (88.7)	76 728 (63.9)
Risk	17 184 (14.3)	5869 (4.9)	19 547 (16.2)
Injury	13 253 (11.0)	5724 (4.8)	16 344 (13.6)
Failure	6066 (5.1)	2010 (1.7)	7504 (6.3)
Any RIFLE category	36 503 (30.4)	13 603 (11.4)	43 395 (36.1)

Abbreviations: RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease; SCr = serum creatinine.
[a]Classification into RIFLE category based on fulfilling worst criteria for either serum creatinine or urine output.

intervals (CI). A *P*-value of <0.05 was considered statistically significant for all comparisons.

Results

During the 5-year study period, 124 088 patients were admitted to the 57 ICUs, and 120 123 (96.8%) had complete data for evaluation (Table 1).

Acute kidney injury stratified by the RIFLE criteria

Acute kidney injury occurred in 36.1% within 24 h of ICU admission, with a maximum RIFLE category Risk in 16.2%, Injury in 13.6% and Failure 6.3%. The incidence of AKI defined by RIFLE categories and stratified by serum creatinine and urine output criteria are shown in Figure 1 and Table 2.

The odds of AKI (any RIFLE category) were higher in older patients (age ≥65 years) (OR 2.74, 95% CI 2.67–2.81, $P < 0.0001$), females (OR 1.22, 95% CI 1.20–1.26, $P < 0.0001$) and those with co-morbid disease (OR 1.3, 95% CI 1.26–1.33, $P < 0.0001$). These patients were also more likely to be medical rather than surgical (OR 2.04, 95% CI 1.99–2.09, $P < 0.0001$) and have a primary cardiac (OR 2.43, 95% CI 2.34–2.53, $P < 0.0001$), septic (OR 1.42, 95% CI 1.38–1.46, $P < 0.0001$) or hepatic (OR 1.38, 95% CI 1.31–1.45, $P < 0.0001$) diagnosis.

A more advanced RIFLE category was associated with greater severity of illness measured by APACHE II ($P < 0.001$), APACHE III ($P < 0.001$) and SAPS II ($P < 0.001$) scores, respectively (Table 2). A higher RIFLE category was associated with lower mean arterial pressures ($P < 0.001$), higher heart rates ($P < 0.001$) and lower PaO2/FiO2 ratios ($P < 0.001$). Similarly, worsening RIFLE category was associated with lower serum pH values ($P < 0.001$) and higher serum potassium concentrations ($P < 0.001$). Absolute serum creatinine ($P < 0.001$) and urea ($P < 0.001$) values increased, while urine output ($P < 0.001$) decreased with worsening RIFLE category (Table 3).

Hospital mortality, length of stay and discharge location

AKI was associated with a significant increase in hospital mortality (24.2% versus 8.9%, OR 3.29, 95% CI 3.19–3.41, $P < 0.0001$). Crude hospital mortality stratified by RIFLE categories showed an increasing linear trend with rates of 17.7% for Risk, 27.7% for Injury, 33.2% for Failure. Table 4 and Figure 1 describe the crude mortality for each RIFLE category stratified by serum creatinine criteria alone, urine output criteria alone and both.

In multivariable analysis, each RIFLE category, defined by either serum creatinine or urine output criteria, was independently associated with hospital mortality (Table 5). A similar finding of an increased odds of death with more severe RIFLE category was also found when the analysis was restricted to RIFLE categories defined by only serum creatinine criteria (OR for Risk 2.02, Injury 3.87, Failure 4.35; $P < 0.001$ for each) or only urine output criteria (OR for Risk 2.94, Injury 3.66, Failure 5.02; $P < 0.001$ for each).

The full model, incorporating the combined serum creatinine and urine output RIFLE criteria and non-renal APACHE II score, showed good and comparable discrimination for hospital mortality when compared to similar multivariable models that used only the general severity of illness scores and excluded the RIFLE classification (Table 5).

AKI was also associated with longer durations of stay for survivors in both the ICU and hospital (Table 4). In addition, those with AKI were less likely to be discharged home and more likely to be transferred to another acute care hospital or long-term rehabilitation centre.

Discussion

We conducted a 5-year analysis of >120 000 ICU admissions to 57 ICUs in Australia, using a large clinical database, to evaluate the occurrence of AKI defined by the RIFLE classification and assess its robustness for hospital mortality. We found that AKI defined by the RIFLE criteria occurred in an estimated 36.1% of patients within 24 h of ICU admission. We also found that these patients were more

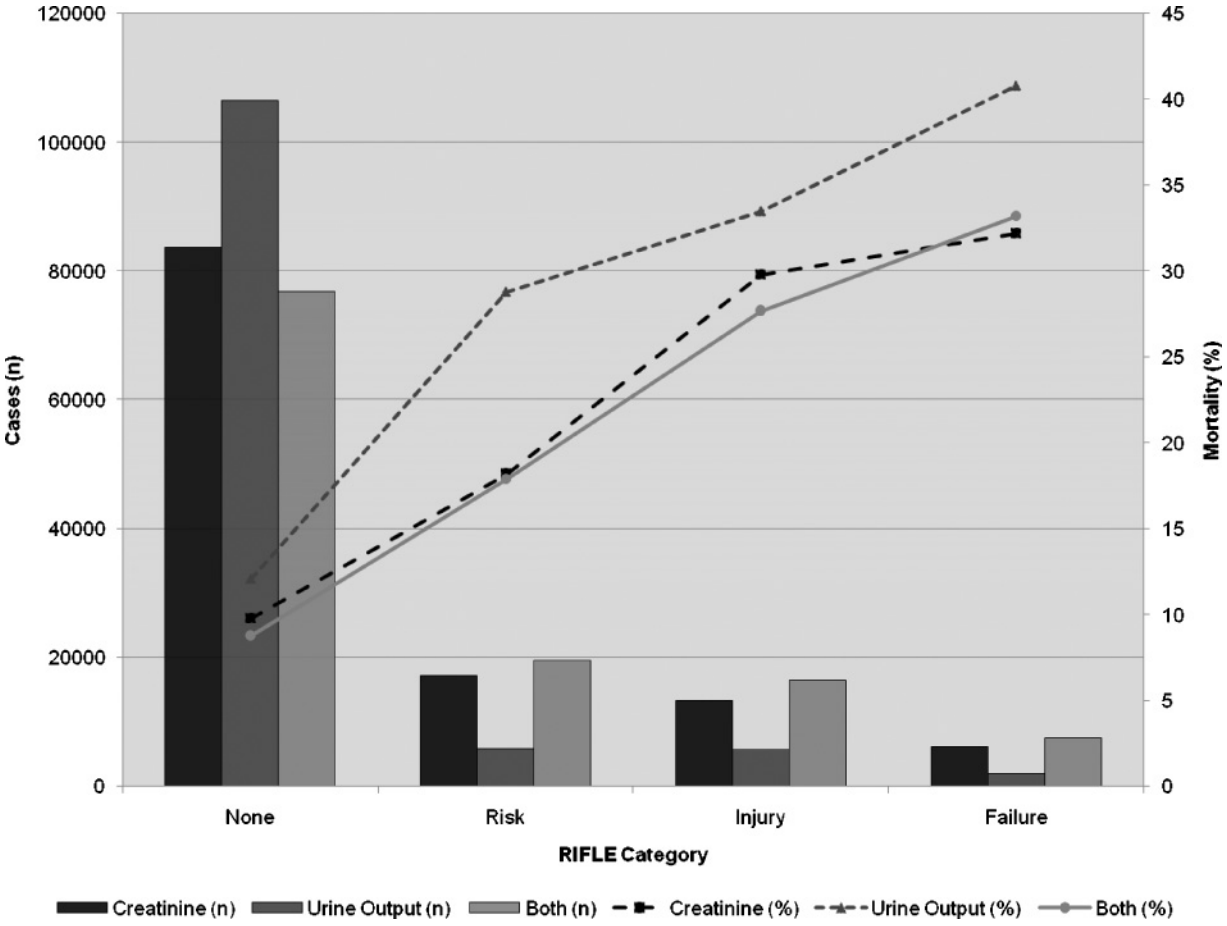

Fig. 1. Summary of the occurrence of AKI and hospital mortality by RIFLE category for creatinine only, urine output only and for both creatinine and urine output from the ANZICS APD 2000–2005.

likely to be older, female and have co-morbid illnesses. Likewise, we found that AKI was more common in admissions for medical indications and with primary diagnoses of cardiac, septic or hepatic disease. Importantly, we found increasing severity of illness, more aberrant changes in acute physiology and more abnormal laboratory values with each worsening RIFLE category. We also found that worsening RIFLE category correlated with an increasing linear trend in hospital mortality. This association persisted in multivariate analysis after adjustment for several co-variates including age, sex, co-morbid illness, medical admission type, admission diagnosis, need for mechanical ventilation, non-renal severity of illness and hospital site. Moreover, we found a similar trend for increased mortality with worsening RIFLE category when evaluating the serum creatinine criteria and the urine output criteria independently. This finding would suggest that the RIFLE categories, when defined by both serum creatinine and urine output criteria, have prognostic and predictive value. Overall, we found that the RIFLE classification was robust and correlated well with hospital mortality. Finally, we showed that worsening RIFLE category correlated with longer durations of stay in ICU and hospital for survivors and was associated with a higher likelihood hospital discharge to a rehabilitation facility or another acute care hospital rather than home.

A determination of the incidence and burden related to AKI in critically ill patients has been the focus of considerable research effort [1–9,30–35]. Unfortunately, the incidence and outcomes of AKI across many studies have been inconsistent and limited in scope. This was largely a product of the variations for how AKI was defined and/or classified and the study population being assessed. This lack of widespread generalizability in the literature has been identified as a barrier that has likely impeded advancements in the field of critical care nephrology [10,11].

More recently, however, the ADQI Working Group, comprised of a panel of international experts in the fields of nephrology and critical care medicine, developed the evidence-based RIFLE definition/classification system for AKI [12]. This system has several advantages compared to AKI defined by simple biochemical endpoints alone or need for renal replacement therapy (RRT).

First, the RIFLE criteria appear sensitive to early changes in kidney function and can classify grades of severity of AKI. By the RIFLE criteria, AKI has been detected in an estimated 18% of all hospitalized patients and in up to 67% of a large population of critically ill patients [17,25]. These estimates would suggest that the incidence of detectable AKI is much higher than previously appreciated

Table 3. Patient characteristics and laboratory values at ICU admission

Characteristic	None ($n = 76\,728$)	Risk ($n = 19\,547$)	Injury ($n = 16\,344$)	Failure ($n = 7504$)	*P*
Illness severity scores					
APACHE II [mean (SD)]	14.7 (6.6)	18.1 (6.9)	21.8 (8.0)	25.6 (8.2)	<0.001
APACHE III [mean (SD)]	45.9 (22.1)	61.5 (24.3)	76.0 (28.4)	87.1 (30.4)	<0.001
SAPS II [mean (SD)]	27.8 (13.0)	36.2 (14.4)	43.7 (16.3)	50.0 (17.2)	<0.001
Mean arterial pressure (mmHg) [mean (SD)]	84.8 (27.1)	81.9 (28.1)	78.6 (27.9)	78.4 (29.3)	<0.001
Heart rate (beats/min) [mean (SD)]	91.9 (31)	95.8 (33.1)	100.3 (34)	101.7 (34.9)	<0.001
PaO2/FiO2 ratio [mean (SD)]	281 (152)	255 (144)	246 (159)	244 (145)	<0.001
PaCO2 (mmHg) [mean (SD)]	42.7 (12.6)	43.4 (14.2)	43.1 (14.6)	40.7 (14.7)	<0.001
Temperature (°C) [mean (SD)]	36.7 (1.5)	36.7 (1.6)	36.7 (1.7)	36.6 (1.7)	<0.001
Glasgow Coma Scale [median (IQR)]	15 (14–15)	15 (14—15)	15 (12–15)	15 (11–15)	<0.001
Mechanical ventilation (%)	52.3	51.5	53.3	47.5	<0.001
pH [mean (SD)]	7.35 (0.1)	7.32 (0.1)	7.29 (0.1)	7.25 (0.1)	<0.001
Potassium (mmol/L) [mean (SD)]	4.2 (0.7)	4.4 (0.8)	4.5 (1.0)	4.8 (1.2)	<0.001
Creatinine (mg/dL) [median (IQR)]	0.85 (0.68–1.02)	1.36 (1.15–1.58)	2.04 (1.58–2.5)	4.24 (3.36–6.09)	<0.001
Urea (mg/dL) [median (IQR)]	15.1 (11.2–20.1)	24.4 (18.5–32.2)	36.1 (25.2–50.1)	61.6 (43.1–86.6)	<0.001
Urine output (L/24 h) [median (IQR)]	2.00 (1.38–2.85)	1.84 (1.22–2.61)	1.58 (0.95–2.44)	1.34 (0.62–1.53)	<0.001

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score.
SI conversion rates: serum creatinine 1 mg/dL = 88.4 μmol/L; serum urea 1 mg/dL = 0.357 mmol/L.

Table 4. Clinical outcomes stratified by RIFLE category

Clinical outcome	None ($n = 76\,728$)	Risk ($n = 19\,547$)	Injury ($n = 16\,344$)	Failure ($n = 7504$)	*P*
Crude mortality (%)					
Creatinine criteria only	9.8	18.2	29.8	32.2	<0.001
Urine output criteria only	12.1	28.8	33.5	40.8	<0.001
Both	8.9	17.9	27.7	33.2	<0.001
ICU Length of stay (days)					
Dead [median (IQR)]	4.1 (2.1–8.6)	4.0 (2.1–8.2)	3.7 (1.9–8.0)	3.4 (1.9–7.9)	<0.001
Alive [median (IQR)]	2.1 (1.6–3.9)	2.7 (1.7–5.0)	3.3 (1.9–6.6)	3.9 (2.1–7.7)	<0.001
Hospital length of stay (days)					
Dead [median (IQR)]	10.4 (4.6–23)	9.9 (4–3.22)	8.6 (3.4–20.3)	9.0 (3.4–20.3)	<0.001
Alive [median (IQR)]	10.6 (6.9–19.1)	13 (7.9–23.7)	15.7 (9.0–29)	17.9 (9.9–32.8)	<0.001
Discharge location of survivors (%)					
Home	85.3	80.8	77	75.3	<0.001
Transfer to other hospital	9.9	12.2	14.5	17	<0.001
Rehabilitation/long-term care	4.8	7.0	8.5	7.7	<0.001

[1,34,36,37]. Our study, the first multi-centre assessment of RIFLE incorporating both GFR and urine output criteria in a large heterogenous cohort of critically ill patients showed AKI was present in 36.1%. In addition, our study is the first to demonstrate that the addition of the urine output criteria to the RIFLE categories has predictive and prognostic value. While we recognize we made a modification to the urine output criteria for the purposes of this study, our findings would indicate that future investigations should incorporate, rather than simply omit, the urine output data into the RIFLE classification [14,24,25]. We also showed that each RIFLE category discriminated distinct subgroups of patients with differences in demographics, acute physiology and severity of illness. While our study may under-estimate the true burden of AKI due to assessment within 24 h of ICU admission only, our study of >43 300 episodes of AKI likely represents a more widely generalizable evaluation of the RIFLE criteria.

Second, the RIFLE criteria allow for monitoring of progression of AKI. In a large cohort of critically ill patients, Hoste *et al*. were first to show that 56% of those with AKI classified by RIFLE progressed to a greater severity category and that such a progression had important prognostic implications [17]. The RIFLE definition also incorporates provisions for detection of AKI in patients with pre-existing chronic kidney disease (CKD). The accurate account of this subgroup was previously problematic. However, the higher than expected occurrence of AKI using RIFLE may in part be attributable to an uncovering of AKI in those with CKD by the RIFLE definition/classification that were not previously identified [38].

Finally, the RIFLE criteria appear robust for discriminating clinical relevant outcomes, such as mortality and length of hospitalization. Our study showed a significant increase in hospital mortality and longer durations of stay in ICU and hospital associated with increasing severity of RIFLE category. Moreover, in multivariate analysis that controlled for severity of illness, we found that each RIFLE category was independently associated with hospital mortality and that the OR increased as RIFLE category worsened. These findings extend those of prior investigations that described step-like increases in hospital mortality associated with

Table 5. Predictive ability for hospital mortality by separate multivariable logistic regression models for RIFLE definition/classification system and general severity of illness scores

Model[a]	Odds ratio (95% CI)	*P*	AuROC curve
(A) RIFLE category[b]			
Risk	2.24 (2.1–2.3)	<0.001	0.66
Injury	3.95 (3.8–4.1)	<0.001	
Failure	5.13 (4.9–5.4)	<0.001	
(B) RIFLE category[b]			
Risk	1.58 (1.5–1.7)	<0.001	0.81
Injury	2.54 (2.4–2.7)	<0.001	
Failure	3.22 (3.0–3.4)	<0.001	
(C) RIFLE category[b]			
Risk	1.40 (1.3–1.5)	<0.001	0.85
Injury	1.96 (1.9–2.1)	<0.001	
Failure	2.17 (2.0–2.3)	<0.001	
APACHE II score (per point)	1.13 (1.13–1.14)	<0.001	0.85
APACHE III score (per point)	1.04 (1.04–1.04)	<0.001	0.86
SAPS II score (per point)	1.07 (1.07–1.07)	<0.001	0.85

(A) The baseline model that includes only the RIFLE criteria as independent variables for hospital mortality (Goodness-of-fit $P = 1.0$.); (B) the full model incorporating both RIFLE criteria and all co-variates as independent variables, without adjustment for severity of illness, for hospital mortality (Goodness-of-fit $P = 1.0$.) and (C) the full models incorporating all co-variates and either the RIFLE criteria with non-renal APACHE II score or no RIFLE criteria and the complete general severity of illness scores.

Abbreviations: RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease; APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score; AuROC = area under the receiver operator characteristic; CI = confidence interval. Goodness-of-fit for RIFLE category model, APACHE II model, APACHE III model and SAPS II model were $P = 1.0$, $P = 1.0$, $P = 1.0$ and $P = 1.0$, respectively.

[a]Each model included age, sex, co-morbidity, surgical status, mechanical ventilation, admission diagnosis and hospital site.

[b]Reference variable: no acute kidney injury.

worsening RIFLE category [17,24,25]. While we found similar discrimination for hospital mortality when compared with general severity of illness scores, it should be emphasized that the RIFLE criteria only focus on the kidney aspects of an acute illness episode. Therefore, we believe that when the RIFLE criteria are crudely evaluated, their performance will always be inferior to that of general severity of illness scoring systems [11]. However, we have shown that the RIFLE criteria exhibit a modest and clinically relevant association with hospital mortality. This is an important feature and provides additional evidence of its robustness as a definition/classification system.

The RIFLE criteria have also been assessed in two small observational cohort studies where patients were classified into a RIFLE category at the time RRT was initiated [15,22]. In a single centre study of 207 ICU patients with AKI treated with CRRT, Bell *et al*. found the RIFLE criteria a simple and effective tool to classify the severity of AKI. Moreover, these authors showed that the RIFLE category—Failure was associated with higher 30-day and long-term mortality [15]. Alternatively, in the study by Maccariello *et al*. of 214 ICU patients receiving RRT, the RIFLE criteria performed poorly for prediction of hospital mortality and provided no significant prognostic value [22]. However, this study was small and patients were started on RRT when allocated a RIFLE category. Thus, most if not all, of these patients likely had severe AKI despite failure to fulfil the biochemical and clinical criteria for the RIFLE category—Failure. Accordingly, this may have contributed to systematic bias and misclassification of outcomes by RIFLE category. Likewise, this finding may also reflect variations in clinical practice and differences in timing of initiation of RRT [39]. One plausible solution to this issue would be for future studies to document the date of fulfilment of each RIFLE category relative to initiation of RRT (ideally in the context of a randomized trial evaluating early versus delayed RRT).

More recently, the Acute Kidney Injury Network (AKIN) Working Group, an international collaboration of nephrologists and intensivists, have proposed refinements to the RIFLE criteria [40]. In particular, the AKIN group sought to increase the sensitivity of the RIFLE criteria by recommending that a smaller change in serum creatinine [$\geq$0.3 mg/dL (26.2 μmol/L)] be used as a threshold to define the presence of AKI and identify patients with RIFLE category Risk and that a time constraint of 24–48 h be used to ensure the process was acute and occurring within a clinically relevant timeframe. In addition, any patients receiving RRT were to now be classified as RIFLE category Failure. However, classifying any patients receiving RRT to RIFLE category—Failure may lead to potential bias. RRT is not an outcome *per se*, but rather a supportive and therapeutic tool. As such, there is inherent risk in suggesting RRT as an outcome, in particular considering the wide variation in its indications and timing of implementation. Overall, it is currently unknown whether discernible advantages exist with one approach to definition and classification versus the other. This issue requires further investigation.

Finally, Ostermann *et al*. recently reported on the incidence of RIFLE criteria in a cohort of near 42 000 ICU patients from 19 hospitals in the UK and Germany [24]. Remarkably, the incidence of AKI was essentially identical to that seen in our study at close to 36%. Their study, however, dealt with a historical population admitted to ICU between 1989 and 1999, whereas in our cohort, patients

were admitted between 2000 and 2005. In addition, this study did not incorporate any urine output data for patient classification by RIFLE categories. In keeping with such historical features, patient mortality was also markedly greater in the injury and failure categories compared to our patients.

There are limitations to our study that warrant discussion. First, we are only able to estimate the occurrence of AKI at or within the first 24 h of ICU admission due to the method of data capture of the ANZICS APD. Thus, we cannot comment on the occurrence and outcomes for patients with ICU-acquired AKI which may be associated with a worse outcome [41]. We recognize this may result in an underestimate of the true burden of AKI. Second, we calculated an estimate of baseline function by use of the MDRD equation as recommended by the ADQI Working Group [12]. Third, due to the nature of the data collection from the ANZICS APD, we had to use a modification of the RIFLE criteria for urine output. The rationale for these modifications was to approximate increasing severity of oliguria over a 24-h period. We believe the urine output criteria are an important contribution to the RIFLE classification; however, we recognize this as a limitation to our study that may also contribute to a misclassification of some patients and result in an overestimate of the occurrence of AKI. Fourth, we were unable to describe changes over time to kidney function or transition between RIFLE criteria. Fifth, we were unable to describe the association of initial RIFLE category to other clinical outcomes such as the proportion of patients receiving RRT, long-term survival or renal recovery. Finally, the diagnosis of AKI by the RIFLE criteria in our study depends on the detection of changes in conventional surrogate markers of kidney function (serum creatinine and urine output). While these are familiar to clinicians, regrettably, these are not ideal surrogate markers. Both have limitations and neither reflect real-time dynamic changes in kidney function nor reflect genuine kidney injury. Moreover, serum creatinine requires times to accumulate before being detected as abnormal, thus potentially contributing to a delay in the diagnosis of AKI. Future refinement of the RIFLE criteria and additional investigations should ideally incorporate newly characterized biomarkers of kidney function and/or acute injury such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and interleukin-18 [42–46].

In summary, we conducted the large multi-centre study of the RIFLE criteria for AKI in critically ill patients. In this heterogenous cohort of >120 000 critically ill patients, we found that the RIFLE criteria classified 36.1% with AKI on ICU admission. We found that each increase in severity of RIFLE category was associated with an increase in mortality. We conclude that the RIFLE definition represents a simple, easy to use and robust tool for the detection and classification of AKI on ICU admission and for correlation with relevant clinical outcomes.

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Conflict of interest statement. None declared.

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