sparser data collection in larger numbers of patients within the primary clinical context; ability to explain population trends and magnitude of pharmacokinetics parameter variability; and potential to construct more detailed models evaluating mixed effects of covariates (7, 17). However, these study designs must not stray too far from more classic pharmacokinetic methods (e.g., structured sampling times and standardized dosages identified a priori) to avoid losing important information in the translation from mathematical model outputs to practical implications. The impact of nascent genetic and pharmacogenomic fields on pharmacokinetic-pharmacodynamic interactions must also be considered (18). In the meantime, large PPK studies, like the current study, are necessary to increase our understanding of the pharmacokinetic-pharmacodynamic behavior of drugs commonly administered to critically ill patients in applicable real-world settings, and to guide dose individualization using original population-specific information gathered amid the mixed effects of critical illness.

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Creatinine Tells a Longer Story Than Just "How Are My Kidneys?"*

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In this issue of *Critical Care Medicine*, Udy et al (1) present an important study exploring an association between low admission creatinine values and mortality in the ICU. Given the ubiquity and frequency of creatinine measurements in the current era, there has been a growing interest into whether these measurements can provide other useful information aside from their common role in estimating renal function—specifically, do they provide insight into nutritional status or lean body mass?

In the past 10 to 15 years, there has been an explosion of renal biomarker research in an effort to diagnose acute kidney injury (AKI) at an earlier stage (2). Despite these advances, serum creatinine and blood urea nitrogen concentration measurements remain the most widely used tools to estimate renal function in the hospitalized patients and changes in creatinine concentration continue to serve as the basis for defining AKI (3, 4). Creatinine-based AKI definitions have demonstrated consistent power at predicting mortality outcomes in the acutely ill (5, 6), and even small changes in serum creatinine during hospitalization are associated with worse mortality outcomes as Thakar et al (7) published in this journal in 2009.

*See also p. 73.

Key Words: acute kidney injury; creatinine; malnutrition; mortality

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Critical care physicians clearly recognize that the presence of AKI is a marker of severity of illness and negatively impacts outcomes significantly. However, historically, we often breathe a sigh of relief when a patient is admitted with a seemingly normal creatinine and good urine output. In this light, it is important for intensive care practitioners to recall that creatinine is an imperfect marker of renal function. Serum creatinine concentration is not only determined by renal clearance (glomerular filtration and secretion in the distal nephron), but the endogenous creatinine production rate is impacted by patient factors such as muscle mass, protein intake, volume status, and muscle injury (8). Chronic illness, age, malnutrition, and pathologic conditions such as protein-losing disorders (enteropathies, nephrotic syndrome, etc) also impact muscle mass and creatinine production (8).

Therefore, low serum creatinine levels could be either a marker of either 1) good renal function or, more ominously, 2) concerning patient factors such as marked malnutrition or chronic illness. There are prior smaller retrospective studies in ICU patients demonstrating an association between between low admission creatinine levels and increased ICU mortality (9). In this issue of *Critical Care Medicine*, Udy et al (1) report a massive retrospective study of approximately 1,045,000 ICU admissions across 172 ICUs by analyzing data from the prospective, bi-national Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation, adult patient database .

To eliminate the concern that volume resuscitation on ICU admission may lower creatinine concentrations, Udy et al (1) stratified patients based on the peak (highest) recorded creatinine concentration during the first 24 hours of ICU admission rather than the lowest creatinine value. Using a reference creatinine value of 70–79 µmol/L (0.79–0.89 mg/dL), they found that there is a progressive increased risk of ICU mortality at peak admission creatinine values below 60 µmol/L (0.68 mg/dL) such that values less than 30 µmol/L (0.34 mg/dL) were associated with an adjusted odds ratio of 2.03 for ICU mortality. Furthermore, this report confirmed the widely accepted fact that higher serum admission creatinine values (presumably from AKI prior to ICU admission or chronic kidney disease) are also associated with increasing ICU mortality. Interestingly, the magnitude of the effect of increasing creatinine may be less than that seen with low admission creatinine values.

These data by Udy et al (1) have a plausible basis in physiology and are supported by previous clinical studies. Underweight and low body mass index are known risk factors for death in ICU patients (10, 11). Furthermore, malnutrition's association with higher mortality extends to non-ICU patients with chronic illness. For example, there is a well-known "obesity paradox" in the chronic hemodialysis population whereby obesity seems protective against death and low body mass index (i.e., malnutrition) is associated with a consistent increase risk of death (12–15). It can be reasonably postulated that low serum creatinine on ICU admission reflects low muscle mass, low lean body mass, or malnutrition and be a sign of chronic illness.

However, it is important to note that low admission creatinine may have other explanations. Perhaps most important for intensive care providers is the specter of the "augmented renal clearance," which is a phenomenon whereby patients experience marked increase in functional creatinine clearance and glomerular filtration rate in acute illness leading to lower creatinine measurements (16) and difficulty in attaining and maintaining therapeutic antimicrobial concentrations with uncertain effects on ICU mortality (17). Finally, the study by Udy et al (1) is not without some further limitations. For example, in using the peak (rather than the lowest) creatinine in 24 hours, the authors do not report the proportion of the patients whose creatinine values were increasing (or extent to which they were increasing) during the first 24 hours. A patient with a rising creatinine within 24 hours despite volume resuscitation already has established AKI and would be expected to have a worse prognosis.

Although these results by Udy et al (1) are not entirely novel (9), they are nonetheless important and merit consideration by intensive care providers—possibly 1) prompting earlier implementation of adequate nutrition support in those with low admission creatinine values; and 2) developing further hypothesis and research objectives. At a minimum, the massive size and breadth of the dataset allow for more generalization of these findings than previous studies.

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Lung Protective Ventilator Strategies: Beyond Scaling Tidal Volumes to Ideal Lung Size*

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Over the past three decades, our understanding of alveolar injury induced by tidal and end-inspiratory overstretching forces from mechanical ventilators has grown dramatically. The simple concept of excessive tidal volumes (referenced to ideal lung size) and excessive end inspiratory airway pressures (plateau pressures or P_{plat} >30 cm H_2O) being the major determinants of overstretch injury has been enhanced by at least two important developments. First has been an awareness that transpulmonary pressure (TPP = alveolar pressure minus pleural pressure) is a more appropriate reflection of alveolar stretch (1). Thus, a P_{plat} that seems excessive may, in fact, be acceptable if global pleural pressures are high (a consequently low TPP). Second has been the appreciation that global effects may not be reflective of regional effects. Specifically, in heterogeneous lung injury, the distribution of delivered tidal volume (V_T) may result in poor/absent volume delivery to diseased units and produce overstretching in healthier units (2). Simply scaling delivered tidal volume to an ideal lung size (i.e. , reflected by ideal body weight [IBW]) does not take this into account. Thus, a "normal" tidal volume (e.g., 6 mL/kg IBW) may be excessive in heterogeneous lung injury where the lung units with the best mechanics receive the bulk of the tidal breath resulting in regional overstretch injury.

These concepts are changing our way of managing patients on mechanical ventilators. No longer is the P_{plat} necessarily the upper threshold for injury—instead, the TPP at end inspiration is being considered the appropriate parameter to reflect potential overstretch injury. Ideally, esophageal pressure measurements (P_{es} is an approximation of P_{pl}) should be used to calculate an end inspiratory TPP (P_{plat}–P_{es}) (1). Unfortunately, esophageal manometry is technically challenging and is rarely used clinically. Nevertheless, clinicians are increasingly aware of the concept of TPP and often empirically adjust their upper P_{plat} limits accordingly in patients with known processes that elevate P_{pl} (e.g., anasarca, obesity, and abdominal compartment syndrome). The approach to V_T settings is also changing. Simply scaling the tidal volume on an ideal lung size (i.e., V_T/kg IBW) has increasingly been challenged as inappropriate. Specifically, many investigators, primarily using visual techniques such as CT scans, have described the "baby lung" concept of functional lung volume in diffuse lung injury (3, 4). They have argued that measurements of actual functional lung volume, which take into account the heterogeneous loss of lung tissue in lung injury, would be a more appropriate scaling factor for V_T than for ideal lung volume

In this issue of *Critical Care Medicine*, Beitler et al (5) address these concepts through a re-analysis of data obtained in a study of positive end-expiratory pressure interactions with respiratory system mechanics (6). Forty two of the subjects in this study had simultaneous measurements of volume, airway pressure, and esophageal pressures during a recruitment maneuver (RM) at a pressure of 40 cm H_2O for 30 seconds. These RMs produced an average maximal TPP of 21 cm H_2O and were thus a rational upper physiologic limit. The volume delivered during the RM (V_{RM}) was used as an index of lung volume potentially available for ventilation (functional or recruitable lung volume). All of these subjects were ventilated with tidal volumes targeted to an ideal lung size with an average of 7.6 mL/kg IBW.

Two endpoints in this study were mechanical indicators of excessive end-inspiratory global stress (TPP at end inspiration) and tidal stress (TPP change over the tidal breath). Although there is some controversy about the interpretation of TPP changes over a tidal breath (7), the end-inspiratory TPP is certainly a reasonable reflection of end inspiratory global stress and stretch. Not surprisingly, low values for V_{RM} reflected poor respiratory system compliance (C_{rs}) and high end inspiratory lung stress. Furthermore, low values for V_{RM} were also associated with increased mortality. Importantly, low values for V_{RM} when coupled with tidal volumes scaled to IBW produced high values for V_T/V_{RM}, which were found to be more predictive of end inspiratory lung stress than either V_T/kg IBW or V_T/C_{rs}.

*See also p. 91.

Key Words: recruitment maneuvers; tidal volumes; transpulmonary pressure; ventilator induced lung injury

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The Association Between Low Admission Peak Plasma Creatinine Concentration and In-Hospital Mortality in Patients Admitted to Intensive Care in Australia and New Zealand*

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Objective: To evaluate the independent association between low peak admission plasma creatinine concentrations and in-hospital mortality in patients requiring critical care in Australia and New Zealand.

Design: Multicenter, binational, retrospective cohort study.

Setting: Data were extracted from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation adult patient database.

Patients: All available records for the period 2000 to 2013 were utilized. The following exclusion criteria were applied: all readmission episodes (within the same hospital stay), missing in-hospital mortality, admission post kidney transplantation, chronic renal replacement therapy (hemodialysis or peritoneal dialysis), and missing peak plasma creatinine concentration. Demographic, anthropometric, admission, illness severity, laboratory, and outcome data were then extracted. Patients were categorized on the basis of their peak (maximum) plasma creatinine concentration recorded in the first 24 hours of ICU admission. Illness severity–adjusted associations with in-hospital mortality relative to a reference category of 70–79 μmol/L were then determined using multivariate logistic regression.

Interventions: Nil.

Measurements and Main Results: Data pertaining to 1,250,449 admissions were available for the study period. Following exclusions, 1,045,718 patients were included. Regression analysis identified that peak plasma creatinine concentrations less than 60 μmol/L measured in the first 24 hours after ICU admission imply a steadily increasing adjusted in-hospital mortality risk. In cases where this value is markedly low (< 30 μmol/L), the adjusted odds of dying in-hospital is over two-fold higher than the reference category and exceeds the risk implied with elevated (≥ 180 μmol/L) values. This finding was also independent of anthropometric data.

Conclusions: In a large heterogenous cohort of critically ill patients, low admission peak plasma creatinine concentrations are independently associated with increased risk-adjusted in-hospital mortality. Further research should now focus on the potential mechanisms underpinning this finding, such as a low skeletal muscle mass and/or fluid overload. (*Crit Care Med* 2016; 44:73–82)

Key Words: creatinine; critical illness; mortality

Creatinine is an amino acid derivative (molecular mass 113 D), routinely measured in plasma. Approximately 3% is released into the circulation per day from muscle metabolism of creatine and phosphocreatine (1). Creatinine is then freely filtered across the glomerulus and secreted by

*See also p. 242.

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proximal tubular cells, such that plasma values are routinely used as an index of renal function. In cases where plasma creatinine concentrations are acutely elevated, clinicians regularly attribute this to a decline in the glomerular filtration rate, although increased muscle mass, and recent dietary protein intake may confound this assessment. Despite these caveats, large epidemiological studies have confirmed the negative impact on clinical outcomes of relatively small rises in plasma creatinine concentrations (2–5).

The implications of a low or low-normal plasma creatinine concentration are less certain. As a marker of decreased muscle mass and somatic protein storage, low plasma creatinine concentrations are associated with aging, chronic illness, and poor nutritional status (6). In this context, a recent large observational study in critically ill patients has identified a low (< 24.9 kg/m^2) admission body mass index (BMI) as being an independent risk factor for higher ICU and in-hospital mortality (7). However, BMI suffers from numerous practical limitations in the ICU (such as accurately weighing patients) and does not readily discriminate between lean, fat, and water body mass.

Low plasma creatinine concentrations may therefore provide a useful marker of functional skeletal muscle mass and thus potentially inform clinical outcomes in the critically ill. Cartin-Ceba et al (8) explored this concept in their retrospective cohort study, whereby a baseline creatinine concentration less than or equal to 0.8 mg/dL (77.8 μmol/L) was associated with increased in-hospital mortality, independent of BMI. Although this analysis utilized data from over 11,000 patients, the setting was geographically limited to two tertiary referral centers (8), reducing the generalizability of these results. Additional analyses employing larger, diverse datasets are therefore warranted to confirm and extend these observations (9).

The primary aim of this retrospective cohort study was therefore to evaluate the independent association between in-hospital mortality and low peak plasma creatinine concentrations in the first 24 hours after ICU admission, in patients requiring critical care in Australia and New Zealand.

MATERIALS AND METHODS

We conducted a retrospective cohort study utilizing data from the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation, adult patient database (APD) (10). The ANZICS-APD is a well-established binational voluntary database, containing data on over 1.5 million admissions to 175 ICUs in Australia and New Zealand. Approval to undertake the study was granted by The Alfred Hospital (Melbourne, Victoria, Australia) Human Research Ethics Committee (Project No. 243/14), with waiver of individual patient informed consent.

Data Extraction

Data were obtained for the period 2000 to 2013, utilizing all available records. The following exclusion criteria were applied: all readmission episodes (within the same hospital stay), missing in-hospital mortality, admission post kidney transplantation, chronic renal replacement therapy (hemodialysis or peritoneal dialysis), and missing peak plasma creatinine concentration. The following variables were then extracted where recorded: age, gender, height, weight, comorbidities, admission source and category, physiologic and laboratory measures in the first 24 hours, and vital status at hospital discharge. Height and weight were included in the APD minimum mandatory dataset from 2010 but were variably collected prior to this. Illness severity was determined using the Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores (11), Simplified Acute Physiology Score II (12), and the Australian and New Zealand Risk of Death (ANZROD) prediction model (13).

Patients were categorized on the basis of their peak plasma creatinine concentration into the following groups (in μmol/L): less than 30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, 100–119, 120–139, 140–179, and at least 180. Peak plasma creatinine was defined as the highest value recorded in the first 24 hours after ICU admission. BMI was calculated as weight (kg)/[height (m)]^2, where anthropometric data were available. Four BMI categories where then generated (in kg/m^2): underweight (< 18.5), normal (18.5–24.99), overweight (25.00–29.99), and obese (≥ 30.00). Total urine output for the first 24 hours was categorized as follows (in L): less than 0.50, 0.50–0.99, 1.00–1.99, 2.00–3.99, and at least 4.00. Using the lowest value recorded in the first 24 hours, four categories of plasma albumin concentration were also generated (in g/L): up to 19, 20–24, 25–44, and at least 45. Diagnostic subgroups, including nonoperative, postoperative, elective, trauma, and infection-related admissions, were identified using standard APACHE diagnostic codes (11) or from those used in recent publications (14).

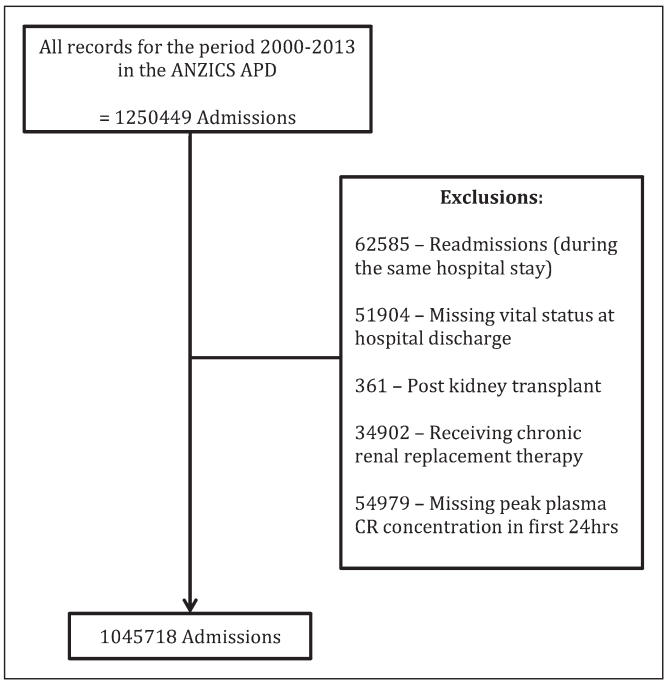

Figure 1. Study selection process. All available records were extracted from the Australian and New Zealand Intensive Care Society (ANZICS) adult patient database (APD) for the period 2000 to 2013. Following exclusions, 1,045,718 admissions were included in analysis. CR = creatinine.

TABLE 1. Demographic, Admission, Illness Severity, and Outcome Data for the Study Cohort

Variable	
Age, yr, mean (SD)	61.3 (18.1)
Male gender, *n* (%)	614,759 (58.8)
Weight, kg, mean (SD), *n* = 118,158	82.2 (23.2)
Height, m, mean (SD), *n* = 98,667	1.68 (0.19)
ICU admission type, *n* (%)	
Nonoperative	465,771 (44.5)
Postoperative	572,320 (54.7)
Elective surgical	470,594 (45.0)
Trauma	56,450 (5.4)
Infection related	148,164 (14.2)
Hospital admission source, *n* (%)	
Home	766,003 (73.3)
Other hospital	169,288 (16.2)
Chronic care facility	12,549 (1.2)
ICU admission source, *n* (%)	
Operating theater	560,934 (53.6)
Emergency department	265,694 (25.4)
Hospital ward	135,612 (13.0)
Other ICU	81,922 (7.8)
Illness severity scores	
APACHE II, mean (SD)/median (IQR)	15.2 (7.5)/14 (10–19)
APACHE III, mean (SD)/median (IQR)	50.3 (27.0)/45 (32–63)
Simplified Acute Physiology Score II, mean (SD)/median (IQR)	29.8 (15.7)/27 (19–37)
APACHE III risk of death, %, mean (SD)/median (IQR)	13.7 (21.1)/4.2 (1.3–15.1)
Peak plasma creatinine concentration, μmol/L, mean (SD)	108.7 (99.7)
Plasma albumin concentration, g/L, mean (SD), *n* = 960,254	29.0 (7.2)
≤ 19, *n* (%)	91,166 (8.7)
20–24, *n* (%)	158,685 (15.2)
25–44, *n* (%)	697,245 (66.7)
≥ 45, *n* (%)	13,158 (1.3)
Missing, *n* (%)	85,464 (8.2)
BMI, kg/m^2, mean (SD), *n* = 96,630	28.6 (7.4)
Underweight (BMI < 18.50), *n* (%)	2,799 (0.3)
Normal (BMI 18.50–24.99), *n* (%)	29,068 (2.8)
Overweight (BMI 25.00–29.99), *n* (%)	32,693 (3.1)
Obese (BMI ≥ 30.00), *n* (%)	32,070 (3.1)
Missing, *n* (%)	949,088 (90.8)
Total urine output over 24 hr, L, mean (SD), *n* = 939,920	2.0 (1.3)
< 0.5, *n* (%)	48,920 (4.7)
0.5–0.99, *n* (%)	109,509 (10.5)
1.0–1.99, *n* (%)	382,908 (36.6)
2.0–3.99, *n* (%)	335,536 (32.1)
≥ 4.0, *n* (%)	63,047 (6.0)
Missing, *n* (%)	105,798 (10.1)
ICU length of stay, d, mean (SD)/median (IQR)	3.4 (5.9)/1.8 (0.9–3.5)
Hospital length of stay, d, mean (SD)/median (IQR)	15.5 (23.1)/9.2 (5.3–17.0)
ICU mortality, *n* (%)	74,383 (7.1)
In-hospital mortality, *n* (%)	114,237 (10.9)

APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, IQR = interquartile range.

Statistical Analysis

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as counts and percentages. To explore the relationship with mortality, logistic regression models were used with peak plasma creatinine values divided into 12 categories and referenced against a concentration of 70–79 μmol/L (8). A multivariable model was constructed adjusting for an a priori-defined list of covariates, including illness severity, site of admission, age, gender, and year of admission, with results reported as odds ratios (95% CI). To facilitate a measure of illness severity that was independent of peak plasma creatinine concentration and age, patient risk of death was calculated with both age and creatinine components removed in accordance with ANZROD methodology (13). Analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC). To improve the robustness of the findings, a two-sided *p* value of 0.01 was considered to be statistically significant.

RESULTS

Demographic, Admission, and Illness Severity Data

Data pertaining to 1,250,449 admissions were available for the study period (2000–2013), drawn from 172 ICUs across Australia and New Zealand. Following exclusions (**Fig. 1**), 1,045,718 admissions were included in analysis. Demographic, admission, illness severity, biochemical, and outcome data for this cohort are presented in **Table 1**. As illustrated, BMI could only be calculated for 9% ($n = 96,630$), where height and weight were both recorded. Overall in-hospital mortality was low (10.9%), with over half of the cohort (54.7%) being admitted postoperatively. Patients with lower peak plasma creatinine concentrations (< 70 μmol/L) were younger, had lower BMIs, and were less commonly male patients. These data, including admission subgroups and illness severity characteristics relative to peak plasma creatinine category, are provided in **Appendix A** (Supplemental Digital Content 1, http://links.lww.com/CCM/B458).

In-Hospital Mortality

Crude and illness severity–adjusted associations between peak plasma creatinine concentration in the first 24 hours of ICU admission and in-hospital mortality, relative to the risk of a value between 70 and 79 μmol/L, are presented in **Figure 2** and **Table 2**. Covariates in the adjusted analysis include year of ICU admission, age, gender, institution, and ANZROD predicted mortality (with age and plasma creatinine components removed). This analysis was repeated in the subset of patients where height and weight were recorded ($n = 96,630$). These anthropometric measures were included as covariates, with illness severity–adjusted associations presented in **Table 3** and Figure 2. The association between peak plasma creatinine and in-hospital mortality in both models was highly significant ($p < 0.01$).

As illustrated, when compared with a peak plasma creatinine concentration of 70–79 μmol/L, lower values (< 60 μmol/L) measured within the first 24 hours of ICU admission are associated with steadily increasing adjusted in-hospital mortality. Indeed, in cases where this value is markedly low (< 30 μmol/L), the adjusted odds of dying in-hospital is over two-fold higher than the reference category (Fig. 2). No statistical interaction was evident between peak plasma creatinine category and year of ICU admission, suggesting that the relationships between plasma creatinine and mortality were stable across the entire period of data collection. Data for postoperative, nonoperative, elective, trauma, and infection-related admissions are presented in **Figure 3**. Relatively consistent findings are demonstrated across varying admission subtypes.

Interactions With Urine Output, Plasma Albumin Concentration, and BMI

To further explore any potential causative mechanisms, the association between low (< 70 μmol/L) peak plasma creatinine concentrations and in-hospital mortality was examined in a series of predefined patient subgroups. These were based on categories of total 24-hour urine output, plasma albumin concentration, and BMI, as previously outlined. Illness severity–adjusted associations

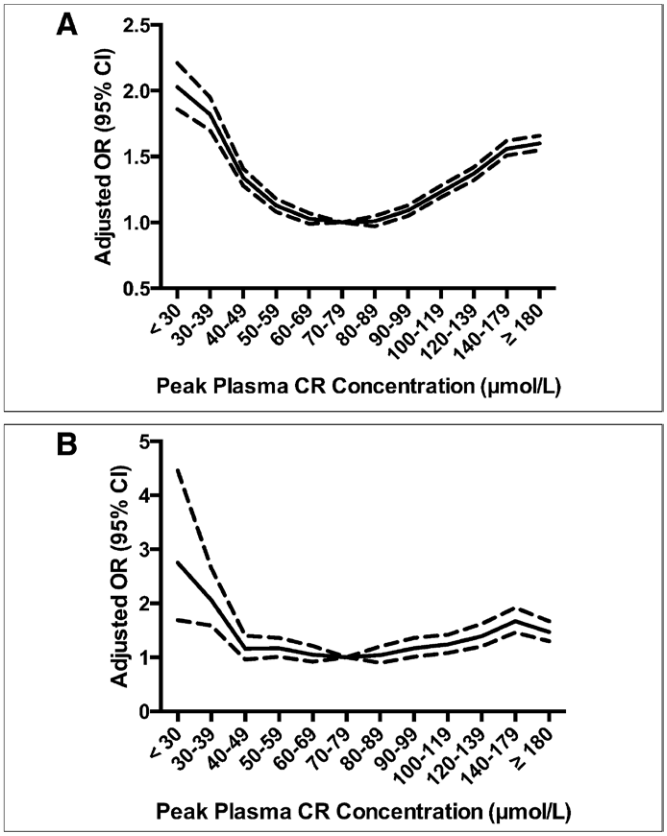

Figure 2. Association between in-hospital mortality and peak admission plasma creatinine (CR) concentration. Adjusted odds ratio (OR [*solid line*] (95% CI [*dashed lines*]) for in-hospital mortality is plotted on the *y*-axis, against peak admission plasma creatinine concentration on the *x*-axis. **A**, All patients ($n = 1,047,518$) adjusted for year of ICU admission, age, gender, institution, and Australian and New Zealand Risk of Death (ANZROD) predicted mortality (with age and plasma CR components removed). **B**, Those with height and weight data ($n = 96,630$), adjusted for year of ICU admission, age, gender, institution, height, weight, and ANZROD predicted mortality (with age and plasma CR components removed).

between peak plasma creatinine concentration and in-hospital mortality (utilizing the same covariates used in prior modeling), relative to the risk of a value between 70 and 79 μmol/L, are presented in **Figure 4** and **Table 4**. As illustrated, other than for very low values (< 30 μmol/L), the relationship between in-hospital mortality risk and plasma creatinine concentrations appeared consistent across all BMI categories. In contrast, higher plasma albumin concentrations displayed an escalating in-hospital mortality risk in patients with low plasma creatinine concentrations (< 50 μmol/L), while a higher 24-hour urine output appears to confer a declining risk.

DISCUSSION

This retrospective cohort study, utilizing data from over 1 million admissions to multiple ICUs in Australia and New Zealand, has demonstrated a significant, clinically meaningful, independent association between low peak plasma creatinine concentrations and increased in-hospital mortality. Specifically, peak plasma creatinine concentrations less than 60 μmol/L measured in the first 24 hours after ICU

TABLE 2. Crude and Illness Severity Adjusted Odds Ratio (95% CI) for In-Hospital Mortality According to Admission Peak Plasma Creatinine

Peak Plasma Creatinine (μmol/L)	Number in Category	In-Hospital Mortality Number (%)	OR for In-Hospital Mortality (95% CI)	Adjusted OR for In-Hospital Mortality (95% CI)
< 30	6,530	1,269 (19.4)	4.11 (3.85–4.39)	2.03 (1.86–2.21)
30–39	15,060	1,562 (10.4)	1.97 (1.86–2.09)	1.82 (1.70–1.95)
40–49	49,579	3,382 (6.8)	1.25 (1.20–1.30)	1.34 (1.28–1.41)
50–59	100,204	5,651 (5.6)	1.02 (0.98–1.05)	1.13 (1.08–1.18)
60–69	137,893	7,283 (5.3)	0.95 (0.92–0.98)	1.03 (0.99–1.07)
70–79	147,034	8,148 (5.5)	1.00 (Reference)	1.00 (Reference)
80–89	132,219	8,162 (6.2)	1.12 (1.09–1.16)	1.01 (0.97–1.05)
90–99	99,253	7,464 (7.5)	1.39 (1.34–1.43)	1.09 (1.05–1.13)
100–119	122,300	13,124 (10.7)	2.05 (1.99–2.11)	1.23 (1.19–1.28)
120–139	66,032	10,334 (15.6)	3.16 (3.07–3.26)	1.37 (1.32–1.42)
140–179	67,104	14,969 (22.3)	4.89 (4.76–5.04)	1.56 (1.51–1.62)
≥ 180	102,510	32,889 (32.1)	8.05 (7.85–8.26)	1.60 (1.55–1.66)
Covariates in Adjusted Analysis				
		Adjusted OR for In-Hospital Mortality (95% CI)		*p*
Peak plasma creatinine concentration		See above		< 0.01
Year of ICU admission				< 0.01
2000		1.89 (1.80–1.99)		
2001		1.80 (1.72–1.89)		
2002		1.83 (1.74–1.91)		
2003		1.73 (1.65–1.81)		
2004		1.61 (1.54–1.68)		
2005		1.58 (1.51–1.64)		
2006		1.53 (1.47–1.60)		
2007		1.37 (1.32–1.43)		
2008		1.28 (1.23–1.34)		
2009		1.24 (1.19–1.29)		
2010		1.16 (1.11–1.20)		
2011		1.11 (1.07–1.16)		
2012		1.03 (0.99–1.07)		
Age		1.066 (1.065–1.068)		< 0.01
Male gender		0.99 (0.98–1.01)		0.36
Institution		–		< 0.01
Australian and New Zealand Risk of Death predicted mortality		1.070 (1.069–1.070)		< 0.01

OR = odds ratio.

In-hospital mortality risk is reported relative to a peak admission plasma creatinine of 70–79 μmol/L. Year of ICU admission (referenced against 2013), age (as per Acute Physiology and Chronic Health Evaluation III scoring system), gender, institution (entered as site identification number), and Australian and New Zealand Risk of Death predicted mortality (with age and plasma creatinine components removed) were also included as covariates in adjusted analysis. The dash indicates that no OR was calculated.

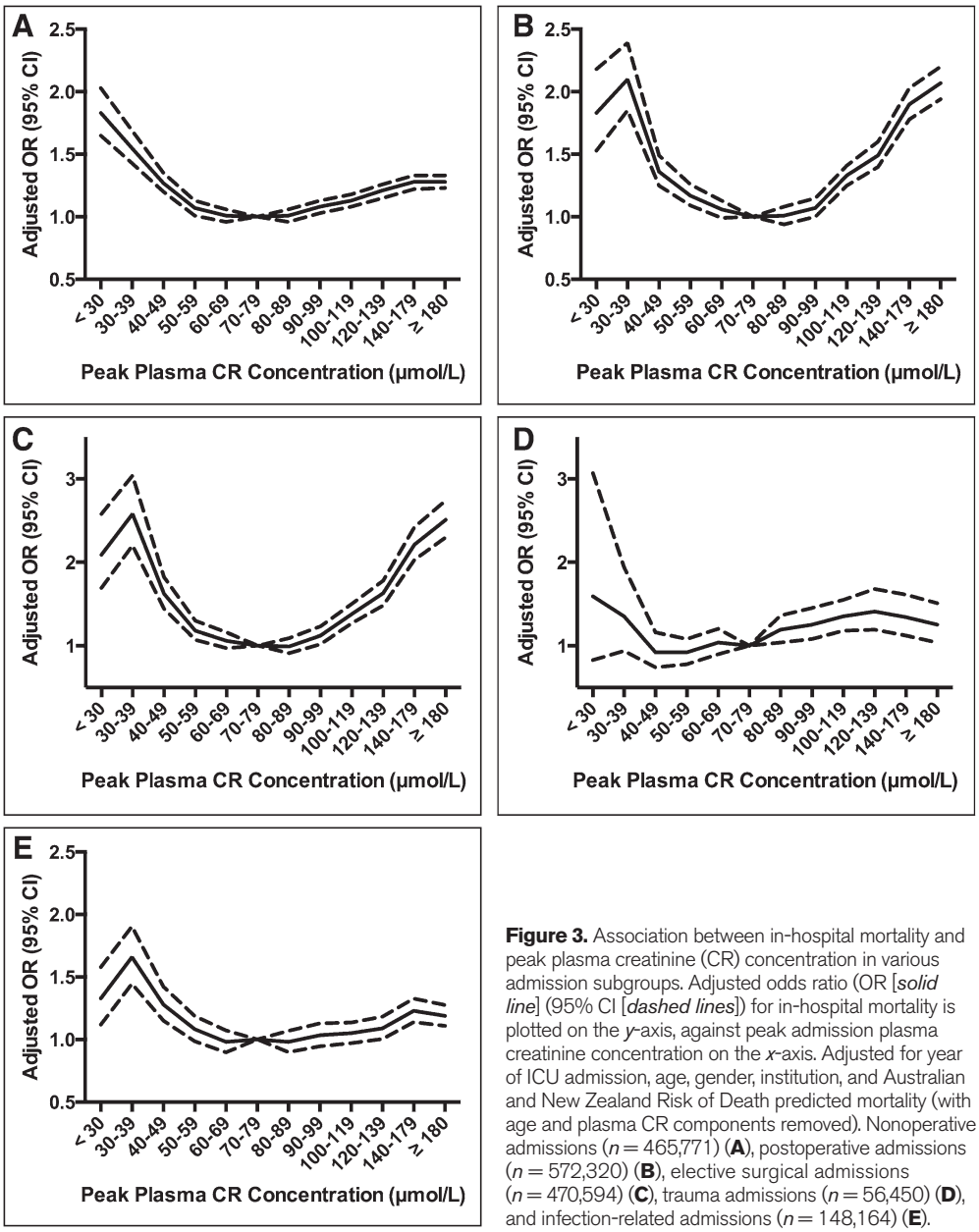

Figure 3. Association between in-hospital mortality and peak plasma creatinine (CR) concentration in various admission subgroups. Adjusted odds ratio (OR [*solid line*] (95% CI [*dashed lines*]) for in-hospital mortality is plotted on the *y*-axis, against peak admission plasma creatinine concentration on the *x*-axis. Adjusted for year of ICU admission, age, gender, institution, and Australian and New Zealand Risk of Death predicted mortality (with age and plasma CR components removed). Nonoperative admissions ($n = 465,771$) (**A**), postoperative admissions ($n = 572,320$) (**B**), elective surgical admissions ($n = 470,594$) (**C**), trauma admissions ($n = 56,450$) (**D**), and infection-related admissions ($n = 148,164$) (**E**).

admission imply a steadily increasing adjusted mortality risk, compared with a peak plasma creatinine concentration of 70–79 µmol/L (Table 2). In cases where this value is markedly low (< 30 µmol/L), the adjusted odds of dying in-hospital is over two-fold higher than the reference category (Fig. 2) and exceeds the risk implied with elevated (≥ 180 µmol/L) values. Importantly, low peak plasma creatinine concentrations were still predictive of greater in-hospital mortality, even with the inclusion of height and weight in regression modeling.

The causes of low plasma creatinine concentrations are generally well known and include decreased production (such as reduced muscle mass, aging, and female gender) and increased clearance, as seen in pregnancy, augmented renal clearance (ARC), and chronic liver disease. Although advanced age is clearly a risk factor for adverse outcomes in ICU, the association between low peak plasma creatinine and greater in-hospital mortality was independent of this covariate (Table 2). This was also the case with gender. Albeit obstetric ICU admissions are not infrequent in certain settings (15), maternal mortality in Australia has been reported at just 6.8 per 100,000 deliveries (16) and is clearly not sufficient to explain our study findings. Equally, although ARC is undoubtedly associated with suboptimal antibacterial exposures for renally cleared drugs in the ICU (17, 18), more recent work suggests that the clinical implications of this phenomenon are uncertain (19). As such, it seems unlikely that ARC alone accounts for the higher adjusted mortality risk seen with lower plasma creatinine concentrations in the current analysis.

More plausibly, low plasma creatinine concentrations are likely a marker of reduced skeletal muscle mass (20), which has important prognostic implications in critical illness. Weijs et al (21) explored this concept in their single-center retrospective analysis of 240 mechanically ventilated adults, whereby skeletal muscle area at the level of the third lumbar vertebra (L3) was correlated against survival. Regression analysis identified this variable as highly predictive for hospital mortality, whereas BMI was not. It was also noted that a greater proportion of patients with low-muscle area were subsequently discharged to a nursing home (21). Moisey et al (22) observed a similar finding in 149 critically ill elderly trauma patients, in which sarcopenia or low muscle mass was associated with both significantly decreased ventilator-free and ICU-free days. Although neither article reported plasma creatinine concentrations, these data reinforce that baseline skeletal muscle mass may be a crucial predictor of clinical outcomes in the ICU, and potentially reflected in admission creatinine values.

While a logical conclusion, our data are limited in extending this hypothesis. Of note, is the observation that lower plasma creatinine concentrations were associated with higher in-hospital mortality over a variety of admission subtypes. Given the heterogeneity in management between patient groups, this suggests that this association is potentially driven more by baseline patient

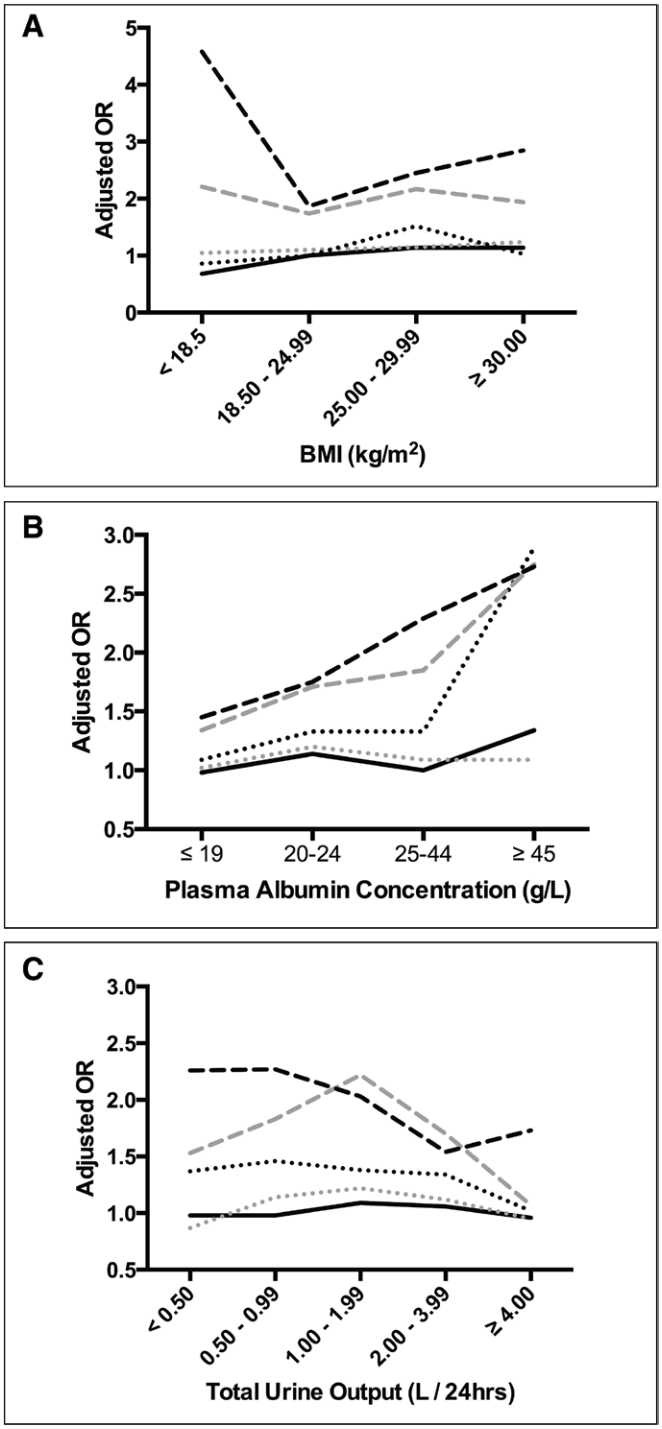

Figure 4. Association between in-hospital mortality and peak admission plasma creatinine (CR) concentration according to body mass index (BMI), plasma albumin concentration, and total 24-hr urine output. Adjusted odds ratio (OR) for in-hospital mortality are plotted on the *y*-axis, against categories of BMI (**A**), plasma albumin concentration (**B**), and total 24-hr urine output (**C**) on the *x*-axis. Adjusted for year of ICU admission, age, gender, institution, and Australian and New Zealand Risk of Death predicted mortality (with age and plasma CR components removed). *Black dashed line* = peak plasma CR < 30 μmol/L, *gray dashed line* = 30–39 μmol/L, *black dotted line* = 40–49 μmol/L, *gray dotted line* = 50–59 μmol/L, *black solid line* = 60–69 μmol/L.

characteristics, as distinct to some component of the critical insult or therapy provided. Having said this, IV fluid therapy remains a key intervention in both nonoperative and postoperative cases (23, 24), and whether systematic differences truly exist between these groups on this basis is uncertain. Unfortunately, we are unable to explore this further in our dataset. It is notable that a less robust association was apparent in trauma patients, although this group accounted for only 5% of the patient cohort, and therefore, it is difficult to draw any definitive conclusions.

An intriguing observation appears to be the possible relationship between low peak admission plasma creatinine, plasma albumin concentrations, and in-hospital mortality (Fig. 4). Specifically, with plasma creatinine concentrations less than 50 μmol/L, adjusted in-hospital mortality risk appears to increase with rising admission albumin values. The biological mechanisms potentially implicated remain uncertain; however, the most plausible explanation would appear to be related to the importance of skeletal muscle mass/physical activity. In this manner, baseline hypoalbuminemia (< 25 g/L) in critical illness is an independent risk factor for greater in-hospital mortality (25), either as a marker of a greater inflammatory burden (26), protein malnutrition, or fluid overload (27). Given that the bulk of plasma creatinine is generated by skeletal muscle metabolism (1), a low value in the setting of adequate albumin levels would imply marked physical deconditioning/muscle wasting as the primary cause. It should be noted that there were relatively few patients in this subgroup however (Appendix A, Supplemental Digital Content 1, http://links.lww.com/CCM/B458), leading to particularly wide CIs (Table 4), and as such, these data should be viewed with caution.

The other potential mechanism explaining our study findings is the impact of excessive fluid therapy. Current evidence stresses the adverse effects of a cumulative positive fluid balance in critical illness, particularly in sepsis (28), acute lung injury (29), and renal failure (30). While fluid balance data are lacking in the ANZICS-APD, the observed relationship between 24-hour total urine output, low admission peak plasma creatinine concentrations, and in-hospital mortality (Fig. 4) hints at a possible causative interaction. In this fashion, worsening oliguria appears to be associated with a greater mortality risk, particularly with very low plasma creatinine concentrations. This somewhat paradoxical finding can be easily rationalized as either representing iatrogenic fluid overload (resulting in dilution of plasma creatinine) or reduced skeletal muscle mass (with decreased creatinine production), in the setting of oliguric acute kidney injury (AKI).

Oliguria is a key risk factor for fluid overload, which can in turn "conceal" any rise in plasma creatinine concentrations (31), and leads to delays in diagnosing AKI when using standard plasma creatinine-based definitions (32). Lassnigg et al (33) explored this concept by examining changes in plasma creatinine concentrations (within 48 hr of ICU admission) and 30-day mortality in patients undergoing cardiac surgery. A fall in plasma creatinine concentrations, associated with greater fluid volume replacement and/or blood transfusion, was noted to predict inferior outcomes (33). Similarly, Cerdá et al (34) reported that lower plasma creatinine concentrations were associated with worse outcomes in oligoanuric patients commencing renal replacement therapy and were correlated with greater weight gain and lower urine output.

TABLE 3. Crude and Illness Severity Adjusted Odds Ratio (95% CI) for In-Hospital Mortality According to Peak Admission Plasma Creatinine in Those Patients With Height and Weight Data

Peak Plasma Creatinine (μmol/L)	Number in Category	In-Hospital Mortality Number (%)	Adjusted OR for In-Hospital Mortality (95% CI)
< 30	247	24 (9.7)	2.75 (1.69–4.46)
30–39	1,384	96 (6.9)	2.06 (1.59–2.65)
40–49	5,059	206 (4.1)	1.16 (0.96–1.40)
50–59	10,619	407 (3.8)	1.17 (1.01–1.36)
60–69	15,004	540 (3.6)	1.05 (0.92–1.21)
70–79	14,632	541 (3.7)	1.00 (Reference)
80–89	11,968	491 (4.1)	1.04 (0.90–1.20)
90–99	8,550	435 (5.1)	1.17 (1.01–1.36)
100–119	10,724	772 (7.2)	1.24 (1.08–1.42)
120–139	5,614	587 (10.5)	1.39 (1.20–1.62)
140–179	5,478	855 (15.6)	1.67 (1.46–1.92)
≥ 180	7,351	1,698 (23.1)	1.47 (1.30–1.67)
Covariates in Adjusted Analysis			
	Adjusted OR for In-Hospital Mortality (95% CI)		***p***
Peak plasma creatinine concentration	See above		< 0.01
Height	1.001 (0.998–1.004)		0.55
Weight	0.99 (0.99–1.00)		< 0.01
Year of ICU admission			0.02
2005	0.22 (0.04–1.26)		
2006	0.73 (0.42–1.27)		
2007	1.00 (0.76–1.31)		
2008	1.06 (0.82–1.38)		
2009	0.69 (0.54–0.88)		
2010	1.03 (0.92–1.15)		
2011	0.97 (0.88–1.07)		
2012	0.94 (0.87–1.02)		
Age	1.05 (1.05–1.06)		< 0.01
Male gender	1.06 (0.98–1.14)		0.17
Institution	–		< 0.01
Australian and New Zealand Risk of Death predicted mortality	1.068 (1.067–1.070)		< 0.01

OR = odds ratio.

In-hospital mortality risk is reported relative to a peak admission plasma creatinine of 70–79 μmol/L. Year of ICU admission (referenced against 2013), age (as per Acute Physiology and Chronic Health Evaluation III scoring system), gender, institution (entered as site identification number), height (m), weight (kg), and Australian and New Zealand Risk of Death predicted mortality (with age and plasma creatinine components removed) were included as covariates. The dash indicates that no OR was calculated.

Indeed, more recent data confirm that oliguria and fluid overload are independent risk factors for greater mortality in the critically ill (35), although whether this solely accounts for our study findings remains uncertain. Indeed, data from Pickering et al (36) suggest that both creatinine and volume kinetics are key factors in explaining the absence of elevated plasma creatinine

TABLE 4. Illness Severity Adjusted Odds Ratio (95% CI) for In-Hospital Mortality According to Admission Peak Plasma Creatinine and Body Mass Index, Plasma Albumin Concentration, and Total 24-Hour Urine Output

Peak Plasma Creatinine (μmol/L)	Adjusted OR for In-Hospital Mortality (95% CI)				
	Body mass index (kg/m^2)				
	< 18.50	18.50–24.99	25.00–29.99	≥ 30.00	
< 30	4.58 (1.49–14.13)	1.87 (0.79–4.42)	2.45 (0.81–7.48)	2.85 (0.98–8.29)	
30–39	2.21 (1.10–4.42)	1.74 (1.18–2.56)	2.17 (1.27–3.71)	1.94 (0.97–3.87)	
40–49	0.86 (0.46–1.58)	1.00 (0.75–1.33)	1.52 (1.06–2.17)	1.03 (0.63–1.67)	
50–59	1.05 (0.60–1.82)	1.10 (0.88–1.39)	1.15 (0.87–1.54)	1.24 (0.90–1.70)	
60–69	0.68 (0.38–1.23)	1.00 (0.81–1.24)	1.14 (0.89–1.46)	1.14 (0.85–1.52)	
	Plasma albumin concentration (g/L)				
	≤ 19	20–24	25–44	≥ 45	
< 30	1.45 (1.18–1.79)	1.75 (1.45–2.12)	2.29 (2.04–2.57)	2.73 (1.12–6.65)	
30–39	1.34 (1.14–1.58)	1.71 (1.48–1.98)	1.85 (1.68–2.04)	2.75 (0.90–8.42)	
40–49	1.09 (0.96–1.23)	1.33 (1.19–1.48)	1.33 (1.24–1.42)	2.89 (1.68–4.97)	
50–59	1.02 (0.92–1.14)	1.20 (1.09–1.32)	1.09 (1.04–1.16)	1.09 (0.64–1.86)	
60–69	0.98 (0.88–1.08)	1.14 (1.05–1.25)	1.00 (0.95–1.05)	1.34 (0.86–2.10)	
	Total urine output (L/24 hr)				
	< 0.50	0.50–0.99	1.00–1.99	2.00–3.99	≥ 0.40
< 30	2.26 (1.71–2.97)	2.27 (1.83–2.83)	2.03 (1.74–2.36)	1.54 (1.27–1.86)	1.73 (1.17–2.57)
30–39	1.53 (1.14–2.05)	1.83 (1.52–2.20)	2.22 (1.98–2.49)	1.70 (1.49–1.94)	1.07 (0.80–1.42)
40–49	1.37 (1.07–1.74)	1.46 (1.28–1.67)	1.38 (1.27–1.50)	1.34 (1.23–1.47)	1.02 (0.85–1.23)
50–59	0.87 (0.70–1.08)	1.14 (1.02–1.27)	1.22 (1.14–1.30)	1.12 (1.03–1.21)	0.95 (0.81–1.11)
60–69	0.98 (0.80–1.18)	0.98 (0.88–1.09)	1.09 (1.02–1.16)	1.06 (0.98–1.13)	0.96 (0.83–1.11)

OR = odds ratio.

In-hospital mortality risk is reported relative to a peak admission plasma creatinine of 70–79 μmol/L. Year of ICU admission (referenced against 2013), age (as per Acute Physiology and Chronic Health Evaluation III scoring system), gender, institution (entered as site identification number), and Australian and New Zealand Risk of Death predicted mortality (with age and plasma creatinine components removed) were also included as covariates in adjusted analysis.

concentrations in some critically ill patients, despite a reduction in glomerular filtration. As such, our study findings may simply reflect occult AKI, where plasma creatinine concentrations remain low due to the combination of reduced creatinine production and fluid overload.

This analysis has a number of strengths and weaknesses. Albeit data collection is undertaken prospectively, this work represents a retrospective cohort study. Data are entered on a voluntary basis, and some data points were therefore missing, although this is likely to be on a random basis. Anthropometric measures were available in less than 10% of cases, and in those with available data, only a small fraction were "underweight." In this respect, a more complete anthropometric dataset, including indirect measures of muscle mass, may yield more information on the interaction between body composition, plasma creatinine concentrations, and clinical outcomes. Equally no data are available for the period prior to ICU admission or beyond the first 24 hours, leading to uncertainty about the influence of ancillary interventions and temporal associations. Specifically, information on fluid balance, feeding, functional status, and physical therapy are lacking, all of which are likely to intimately influence these results.

The major strengths of this analysis are the size and distribution of the cohort. We have analyzed data from over 1 million ICU admissions, from an ethnically diverse, widely dispersed population, such that these data have excellent external validity across our region. Equally, any interinstitutional variability in plasma creatinine assays, which is known to be more pronounced at lower concentrations, is unlikely to have confounded the results. In addition, risk adjustment has utilized a locally generated prediction model, unique to the Australia and New Zealand setting.

CONCLUSIONS

In conclusion, this retrospective cohort study has demonstrated an independent association between low peak plasma creatinine concentrations measured in the first 24 hours post-ICU

admission and increased risk adjusted in-hospital mortality. In those where anthropometric data were available, this relationship was independent of these covariates. The mechanisms underlying this association remain uncertain, but may reflect either reduced skeletal muscle mass, fluid overload, or a combination of both. Importantly, given the ubiquity with which plasma creatinine concentrations are measured, and the strong association with adverse outcomes, low values may be a potentially useful risk stratification tool in future research and clinical practice. Additional research should also seek to further robustly define the causative mechanisms that may be implicated.

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