Advanced age affects the outcome-predictive power of RIFLE classification in geriatric patients with acute kidney injury

Chia-Ter Chao[1,11], Vin-Cent Wu[1,11], Chun-Fu Lai[1], Chih-Chung Shiao[2], Tao-Min Huang[3,4], Pei-Chen Wu[5], I-Jung Tsai[6], Chun-Cheng Hou[7], Wei-Jie Wang[8], Hung-Bin Tsai[9], Yu-Feng Lin[9], Wen-Chih Chiang[1], Shuei-Liong Lin[1], Pi-Ru Tsai[10], Wen-Je Ko[9,10], Ming-Shiou Wu[1] and Kuan-Dun Wu[1], for the NSARF group

[1]Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Division of Nephrology, Department of Internal Medicine, Saint Mary's Hospital, and Saint Mary's Medicine, Nursing, and Management College, Yilan, Taiwan; [3]Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin County, Taiwan; [4]Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [5]Division of Nephrology, Department of Internal Medicine, Da Chien General Hospital, Miaoli, Taiwan; [6]Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [7]Department of Internal Medicine, Min-Sheng General Hospital, Tao-Yuan, Taiwan; [8]Division of Nephrology, Department of Internal Medicine, Taoyuan General Hospital, Tao-Yuan, Taiwan; [9]Department of Traumatology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan and [10]Department of Surgery, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

The RIFLE (risk, injury, failure, loss, and end-stage) classification is widely used to gauge the severity of acute kidney injury, but its efficacy has not been formally tested in geriatric patients. To correct this we conducted a prospective observational study in a multicenter cohort of 3931 elderly patients (65 years of age or older) who developed acute kidney injury in accordance with the RIFLE creatinine criteria after major surgery. We studied the predictive power of the RIFLE classification for in-hospital mortality and investigated the potential interaction between age and RIFLE classification. In general, the survivors were significantly younger than the nonsurvivors and more likely to have hypertension. In patients 76 years of age and younger, RIFLE-R, -I, or -F classifications were significantly associated with increased hospital mortality in a stepwise manner. There was no significant difference, however, in hospital mortality in those over 76 years of age between patients with RIFLE-R and RIFLE-I, although RIFLE-F patients had significantly higher mortality than both groups. Thus, the less severe categorizations of acute kidney injury per RIFLE classification may not truly reflect the adverse impact on elderly patients.

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Correspondence: *Ming-Shiou Wu, Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Zhong-Zheng, Taipei 100, Taiwan. E-mail: mhw1001@gmail.com or Wen-Je Ko, Department of Traumatology, National Taiwan University Hospital, 7 Chung-Shan South Road, Zhong-Zheng District, Taipei 100, Taiwan. E-mail: kowj@ntu.edu.tw*

[11]These authors contributed equally to this work.

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Acute kidney injury (AKI) is common in critically ill patients, with a prevalence ranging from 2 to 25%.[1–3] It is defined as a significant increase in serum creatinine (sCr) or a decrease in urine output. AKI is associated with significant morbidity and mortality for patients in the intensive care unit (ICU), across the course of hospitalization, and even years after hospital discharge.[4,5] Aging predisposes the kidney to further injury, presumably from the interplay of intrinsic renal degeneration and multiple comorbidities.[6,7] Elderly patients are therefore at a higher risk of developing AKI and subsequent end-stage renal disease.[8] This risk is especially pronounced because of the increasing elderly population in the current society, along with polypharmacy and susceptibility to nephrotoxic agents in elderly populations.[6,7] Baraldi *et al.*[9] reported that in an unselected hospital population patients >65 years of age had a 10-fold increase in the incidence of AKI, significantly lower rates of renal recovery, and a higher risk of dialysis dependence when compared with patients aged <65 years. However, the geriatric population is heterogeneous in terms of the aging process itself and diagnostic diversity, which complicates the precision of geriatric research, resulting in few studies to date that specifically focus on geriatric AKI.

Since its introduction by the ADQI group (Acute Dialysis Quality Initiative), the RIFLE (risk, injury, failure, loss, and end-stage) classification has been widely used to detect changes in renal function and has been proven as a fair predictor of prognosis.[10] The RIFLE classification has shown fair predictive efficacy for both ICU and in-hospital outcomes after AKI. However, the RIFLE classification reportedly fails in discrimination between RIFLE-R and RIFLE-I (RIFLE-risk and RIFLE-injury) patients treated with continuous renal replacement therapy.[11] Application of the RIFLE classification system to geriatric AKI patients has not been tested in previous studies, and analyses associated with age and prognosis have yielded conflicting results.[7,9,12,13] We hypothesized that age itself may have an important role in determining elderly AKI patient outcomes. Our aim was to clarify the features of AKI in the elderly postoperative ICU patients and, in particular, to analyze the effect of age on RIFLE classification.

RESULTS

Eligible patients for our study were recruited from the NSARF (*N*ational Taiwan University Hospital *S*tudy Group on *A*cute *R*enal *F*ailure) cohort and entered into the analysis (Figure 1). After screening 17,787 patients, 3931 elderly patients (defined as age ⩾65 years) with postoperative status were selected (mean age 75.7 ± 6.7 years, 2237 male (56.9%)) and categorized into RIFLE-R ($n = 1600$), RIFLE-I ($n = 859$), and RIFLE-F (RIFLE-failure; $n = 1472$) groups. Overall, 2126 patients (54.1%) had their baseline sCr determined by nadir values obtained during index hospitalization, 950 patients (24.1%) had a previous admission sCr value within the past year as baseline, and 855 patients (21.8%) had their baseline sCr estimated by the Modification of Diet in Renal Disease (MDRD) equation.

The demographic data and comorbidity profiles are shown in Table 1. Nearly half of the included cohort had underlying hypertension and a history of malignancy (47.1%), and 22.6% had been diagnosed with renal insufficiency. Most of these geriatric patients were admitted for abdominal surgery (48.5%), and 24.6% were admitted for cardiovascular surgery.

RIFLE classification and geriatric AKI prognosis

As shown in Table 1, there was no difference of age and gender among all the groups who had sustained varying degrees of AKI during the postoperative period. There were fewer patients with hypertension (RIFLE-F vs. -I vs. -R, 45.1% vs. 46.5% vs. 50.2%; $P = 0.016$), coronary artery disease (26.8% vs. 43.5% vs. 47.5%; $P < 0.001$), and malignancy (43.2% vs. 46.2% vs. 51.2%; $P < 0.001$) in the elderly patients who developed RIFLE-F AKI. However, there were more incidents of chronic hepatitis (RIFLE-F vs. -I vs. -R, 8.1% vs. 7.1% vs. 5.4%; $P = 0.013$) and previous renal insufficiency (34.6% vs. 17.8% vs. 14.0%; $P < 0.001$) in this group.

Comparison between survivors and nonsurvivors

Among the 3931 patients, 783 (19.9%) died during index hospitalization (27 days, interquartile range 16–52; Table 2). Survivors were significantly younger (age 75.5 vs. 76.5; $P < 0.001$) and more likely to have hypertension (50.2% vs.

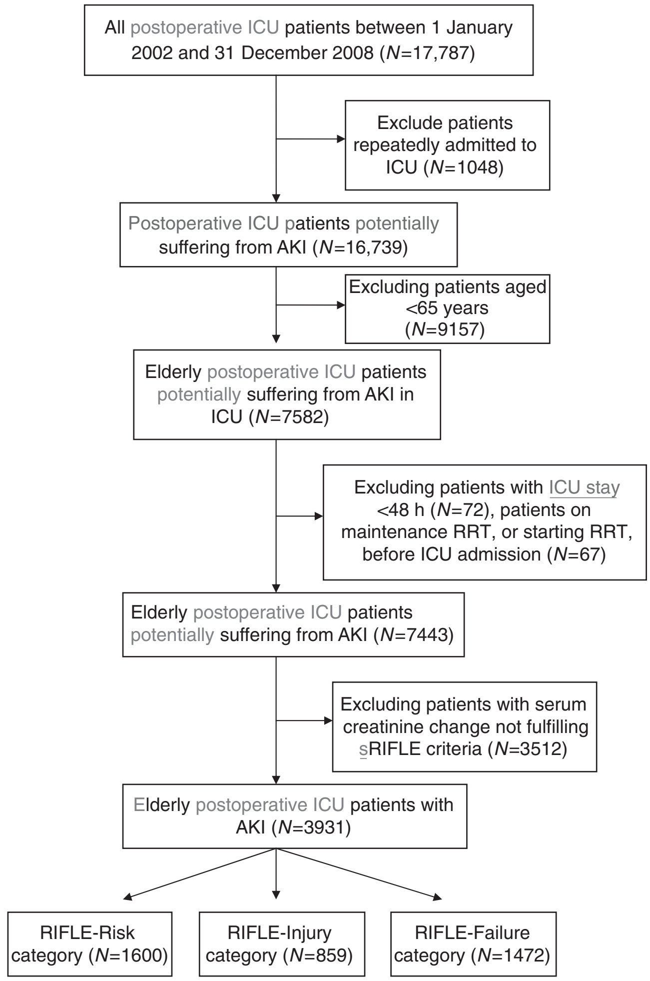

Figure 1 | Flowchart of the recruitment of study patients. AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy.

36.6%; $P < 0.001$), coronary artery disease (41.1% vs. 30.2%; $P < 0.001$), and malignancy (48.3% vs. 42.5%; $P = 0.004$). Nonsurvivors had more underlying renal insufficiency (31.9% vs. 20.2%; $P < 0.001$) and liver cirrhosis (6.7% vs. 4.7%; $P = 0.028$), along with higher APACHE-II (Acute Physiology and Chronic Health Evaluation II) scores at ICU admission (16.4 vs. 11.9; $P < 0.001$). The in-hospital mortality rates for the RIFLE-R, RIFLE-I, and RIFLE-F groups were 8.5%, 14.1%, and 35.9%, respectively. We constructed Kaplan–Meier survival curves stratified by RIFLE categories to assess in-hospital mortality (Figure 2). The in-hospital mortality rates for the RIFLE-R and RIFLE-I AKI groups were similar (log-rank test $P = 0.455$), whereas both groups had lower unadjusted mortality rates than the RIFLE-F AKI group ($P < 0.001$).

A logistic regression analysis was subsequently performed to identify the independent predictors for in-hospital mortality (Table 3). After adjustment, the RIFLE-F and RIFLE-I AKI groups (compared with the RIFLE-R AKI group) were significantly associated with higher in-hospital mortality rates (for RIFLE-F vs. -R: odds ratio (OR), 4.20;

Table 1 | Features of patients sustaining different levels of acute kidney injury, classified according to the RIFLE criteria

Variables[a]	Total (3931)	RIFLE-R (1600) Sum	RIFLE-R Younger-old (902)	RIFLE-R Older-old (698)	RIFLE-R *P*-value	RIFLE-I (859) Sum	RIFLE-I Younger-old (459)	RIFLE-I Older-old (401)	RIFLE-I *P*-value	RIFLE-F (1472) Sum	RIFLE-F Younger-old (816)	RIFLE-F Older-old (656)	RIFLE-F *P*-value	*P*-value[b]
Demographic profile														
Age (years)	75.7 ± 6.7	75.4 ± 6.6	70.7 ± 3.2	81.4 ± 4.1	<0.001	75.9 ± 6.9	70.6 ± 3.2	81.8 ± 4.3	<0.001	75.8 ± 6.7	70.9 ± 3.1	81.7 ± 4.1	<0.001	0.120
Sex (male)	56.9%	56.6%	58.9%	53.9%	0.04	55.7%	55.1%	56.2%	0.67	58.1%	58.8%	57.2%	0.58	0.499
Comorbidities														
Hypertension	47.5%	50.2%	49.9%	50.3%	0.875	46.5%	43.9%	49.8%	0.086	45.1%	43.6%	47.6%	0.127	0.016
Diabetes mellitus	28.9%	28.7%	31.2%	25.5%	0.012	29.3%	28.8%	30.1%	0.682	29.0%	33.3%	24.2%	<0.001	0.946
CAD	38.9%	47.5%	48.5%	46.3%	0.387	43.5%	45.0%	41.8%	0.347	26.8%	26.3%	27.4%	0.632	<0.001
Heart failure	12.1%	10.6%	9.8%	11.7%	0.222	15.6%	14.6%	16.7%	0.412	11.6%	12.9%	10.2%	0.118	0.001
Atrial fibrillation	10.3%	9.5%	7.3%	12.5%	<0.001	13.4%	12.0%	15.2%	0.176	9.2%	7.7%	11.2%	0.024	0.002
Liver cirrhosis	5.1%	4.2%	5.3%	2.7%	0.01	6.0%	7.6%	4.2%	0.036	5.6%	7.5%	3.2%	<0.001	0.074
Hepatitis	6.8%	5.4%	6.7%	3.7%	0.008	7.1%	8.7%	5.2%	0.046	8.1%	11.2%	4.1%	<0.001	0.013
COPD	5.8%	6.2%	5.6%	6.9%	0.305	6.4%	4.4%	8.7%	0.009	5.1%	4.2%	6.3%	0.07	0.361
Malignancy	47.1%	51.2%	51.9%	50.3%	0.527	46.2%	47.2%	45.0%	0.531	43.2%	42.5%	44.2%	0.445	<0.001
Renal insufficiency	22.6%	14.0%	11.9%	15.7%	0.021	17.8%	17.2%	18.4%	0.658	34.6%	35.0%	34.0%	0.85	<0.001
Operation category														
Cardiovascular	24.6%	25.3%	27.7%	22.5%	0.024	27.7%	31.7%	23.3%	0.007	21.5%	23.9%	18.9%	0.03	0.125
Abdominal	48.5%	47.5%	39.8%	57.4%	<0.001	47.6%	39.9%	56.3%	<0.001	50.3%	46.4%	55.3%	0.001	0.269
Thoracic	9.8%	10.4%	13.2%	6.7%	<0.001	8.7%	9.3%	8.0%	0.5	9.9%	10.8%	8.7%	0.209	0.399
Neurosurgery	12.7%	14.1%	16.5%	10.9%	0.002	12.0%	14.1%	9.8%	0.059	11.6%	12.4%	10.3%	0.255	0.113
Miscellaneous[c]	4.4%	2.7%	2.8%	2.5%	0.657	4.0%	5.0%	2.6%	0.071	6.7%	6.5%	6.8%	0.868	0.015

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RIFLE, risk, injury, failure, loss, and end-stage; RIFLE-F, RIFLE-failure; RIFLE-I, RIFLE-injury; RIFLE-R, RIFLE-risk.

[a]All continuous variables were expressed as mean ± s.d., whereas dichotomized variables were expressed as frequency and percentages.

[b]One-way analysis of variance (ANOVA) was used to compare difference among the sum of three groups (RIFLE-R, RIFLE-I, and RIFLE-F).

[c]Includes gynecologic, orthopedic, and urologic surgery.

95% confidence interval (CI), 3.31–5.33; $P<0.001$; for RIFLE-I vs. -R: OR, 1.51; 95% CI, 1.15–1.99; $P=0.003$). Baseline hypertension (OR, 0.58; 95% CI, 0.48–0.69; $P<0.001$) was predictive of lower rates of in-hospital mortality, whereas pre-existing renal insufficiency (OR, 1.42; 95% CI, 1.14–1.77; $P=0.002$) or liver cirrhosis (OR, 1.64; 95% CI, 1.00–2.67; $P=0.047$) was predictive of a higher risk of death. A sensitivity analysis based upon patients with available preadmission or admission sCr data (78.2% of total cohort) yielded similar results (for RIFLE-F vs. -R: OR, 3.69, 95% CI, 3.25–3.90; $P<0.001$; for RIFLE-I vs. -R: OR, 1.45, 95% CI, 1.09–1.92; $P=0.01$).

Aging, RIFLE classification, and geriatric AKI prognosis

As depicted in Figure 3, age >76 years was identified as a risk factor for mortality by the Generalized Additive Model plot. Therefore, we chose to use the cutoff value of 76 years of age to divide our patient population into two subgroups to investigate the relationship between age and RIFLE predictability (Table 1). One group of patients was ⩽76 years of age (younger-old, $n=2177$) and the other group of patients was >76 years of age (older-old, $n=1754$).

To further determine the modification effect of age upon RIFLE classification, we divided the entire elderly AKI cohort into six subgroups according to RIFLE grade (R, I, and F) and age (⩽76 and >76). Logistic regression analysis to identify in-hospital mortality using the variable age × RIFLE and all the other variables included in Table 3 was performed to elucidate the interaction between age and the RIFLE grading. The RIFLE classification performed differently between the two age strata. In younger-old patients (aged ⩽76 years), the RIFLE-R, -I, and -F AKI classifications significantly predicted increasingly worse outcomes (RIFLE-I vs. -R: OR, 1.71; 95% CI, 1.13–2.57; $P=0.011$; RIFLE-F vs. -R: OR, 4.22; 95% CI, 2.98–5.99; $P<0.001$; Figure 4). However, in older-old patients (aged >76 years), the difference between RIFLE-R and RIFLE-I AKI was insignificant (RIFLE-I vs. -R: OR, 1.32; $P=0.172$). Older-old patients with a RIFLE-F AKI still had a significant higher mortality rate (RIFLE-F >76 vs. -R <76: OR, 6.33; $P<0.001$).

DISCUSSION

In our study, we investigated a large cohort of elderly patients suffering from postoperative AKI. We focused on the predictive power of RIFLE classification and age for hospital mortality, as well as the potential interactions between them. To our knowledge, this study is the first one to specifically focus on a geriatric population with AKI by the RIFLE classification. In our cohort, the in-hospital mortality rate of the younger-old patients was significantly lower than that of the older-old patients (18.3% vs. 21.6%, $P=0.025$). We found that age modified the predictive power of RIFLE classification in elderly AKI patients. Age of 76 years was an important marker for RIFLE predictability in our elderly cohort; the predictive power of RIFLE classification was not

Table 2 | Comparison between survivors and nonsurvivors

Variables[a]	Total (3931)	Survivors (3148)	Nonsurvivors (783)	*P*-value
Demographic profile				
Age (years)	75.7 ± 6.7	75.5 ± 6.6	76.5 ± 6.9	< 0.001
Sex (male)	56.9%	56.6%	58.3%	0.409
Comorbidities				
Hypertension	47.5%	50.2%	36.6%	0.001
Diabetes mellitus	28.9%	29.6%	26.1%	0.056
CAD	38.9%	41.1%	30.2%	< 0.001
Heart failure	12.1%	11.8%	13.3%	0.271
Atrial fibrillation	10.3%	10.7%	8.4%	0.058
Liver cirrhosis	5.1%	4.7%	6.7%	0.028
Hepatitis	6.8%	6.4%	8.1%	0.107
COPD	5.8%	6.1%	4.7%	0.151
Malignancy	47.1%	48.3%	42.5%	0.004
Renal insufficiency	22.6%	20.2%	31.9%	< 0.001
Operation category				
Cardiovascular	24.6%	24.8%	23.9%	0.254
Abdominal	48.5%	49.1%	46.2%	0.164
Thoracic	9.8%	9.8%	9.8%	0.953
Neurosurgery	12.7%	12.9%	12.0%	0.52
Miscellaneous[b]	4.4%	3.4%	8.1%	0.006
RIFLE category				0.001
Risk	40.7%	46.5%	17.3%	
Injury	21.9%	23.5%	15.5%	
Failure	37.4%	30.0%	67.2%	
Treatment				
Hemodialysis	6.0%	6.0%	6.0%	0.952
Tracheostomy	8.3%	8.3%	8.5%	0.887
CPB	9.5%	10%	7.6%	0.048
IABP	2.5%	2.1%	3.8%	0.009
PCI	0.1%	0.1%	0.1%	0.708
Pacemaker implant	0.8%	0.7%	1.5%	0.032
Pericardiocentesis	0.5%	0.3%	0.9%	0.086
CPR	3.4%	2.1%	9.0%	0.001
ICP monitoring	2.6%	2.8%	1.6%	0.092
ECMO	0.7%	0.4%	1.6%	0.001
TPN	4.6%	4.6%	4.4%	0.901
APACHE-II score at ICU admission	12.8 ± 7.8	11.9 ± 7.0	16.4 ± 9.5	0.001
Length of hospital stay (days)	42.0 ± 48.3	41.9 ± 47.4	42.5 ± 51.9	0.019

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation II; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon counterpulsation; ICP, intracranial pressure; ICU, intensive care unit; PCI, percutaneous coronary intervention; RIFLE, risk, injury, failure, loss, and end-stage; TPN, total parenteral nutrition.

[a]All continuous variables were expressed as mean ± s.d., whereas dichotomized variables were expressed as frequency and percentages.

[b]Includes gynecologic, orthopedic, and urologic surgery.

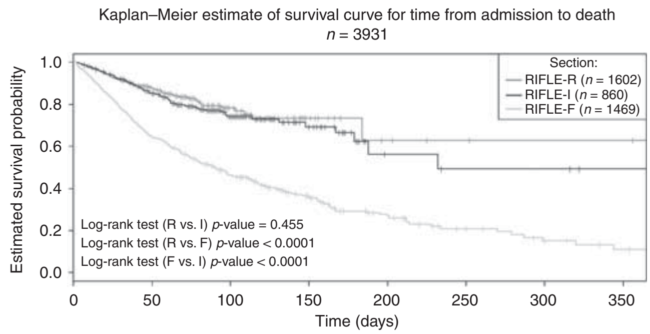

Figure 2 | The Kaplan–Meier survival curve of the study patients divided into RIFLE-R, -I, and -F groups. RIFLE, risk, injury, failure, loss, and end-stage; RIFLE-F, RIFLE-failure; RIFLE-I, RIFLE-injury; RIFLE-R, RIFLE-risk.

as conclusive in the higher age stratum, with a loss of differentiation between the RIFLE-R and -I groups in older-old patients. Ricci *et al.*[14] performed a literature review and analyzed the predictability of RIFLE classification for AKI patient outcomes without age or AKI origin stratification. They discovered that risk for patient mortality increased stepwise: a 1.7-fold and 2.7-fold increased risk for RIFLE-I vs. -R and RIFLE-F vs. -R, respectively. Our results differed from their findings, in that RIFLE-I and RIFLE-F AKI predicted a 1.5-fold and 4.2-fold increased risk of hospital mortality, respectively, when compared with RIFLE-R. This implied that elderly patients who suffered from a more severe AKI (RIFLE-F) might have a poorer outcome than the general population. Elderly patients therefore warrant special attention rather than being grouped together with the general population.

Registry data and large cohort studies regarding the in-hospital mortality of elderly ICU patients showed conflicting results, ranging from 18 to 40% because of the heterogeneous definition of the elderly, the ICU settings, patient selection biases, and voluntary therapy withdrawal in this population.[15–17] The overall outcome for our elderly cohort (mortality rate 19.9%) is slightly lower despite the significantly advanced age (mean 75.7 ± 6.7) and the compounded effects of AKI. This lower mortality rate may partially stem from the selection of elderly patients for surgery and the high percentage of elective surgeries in our patients (67.4%).[18,19]

The effects of aging on postoperative critical patients are also heterogeneous. Prospectively designed cohort studies suggested that ICU and in-hospital mortality greatly increased when ICU patients were older (> 70–75 years of age) compared with younger ones (< 65 years of age).[18,20] Ried *et al.*[21] also identified increased rates of short-term mortality in patients > 70 years of age with postoperative AKI. Consequently, age might have an important role in determining hospitalization outcomes of postoperative ICU patients with AKI. The limit of 76 years that we identified could have important implications for future studies on geriatric issues.

The aging process is accompanied by both physiological and structural changes, including reduction of glomerular filtration rate (GFR), impairment of autoregulation, rise in comorbidity factors (especially cardiovascular diseases), and an increased susceptibility to nephrotoxic agents.[6] The renal reserve of the elderly is also reduced.[22] Consequently, advanced age will undoubtedly accentuate the susceptibility of kidneys to most insults. In addition, as sCr levels are

Table 3 | Predictors of in-hospital mortality by multiple logistic regression analysis with stepwise variable selection method

Covariate[a,b]	Regression coefficient	Standard error	*P*-value	Odds ratio	95% Confidence interval
Age (every 1-year increment above 65 years)	0.027	0.007	<0.001	1.03	1.01–1.04
Sex (male)	0.192	0.098	0.05	1.21	1.00–1.47
Baseline renal insufficiency	0.353	0.112	0.002	1.42	1.14–1.77
Baseline HTN	−0.546	0.093	<0.001	0.58	0.48–0.69
Baseline cirrhosis	0.494	0.249	0.047	1.64	1.00–2.67
RIFLE-F vs. -R	1.435	0.122	<0.001	4.20	3.31–5.33
RIFLE-I vs. -R	0.413	0.140	0.003	1.51	1.15–1.99
Treatment—hemodialysis	−0.355	0.191	0.064	0.70	0.48–1.02
Treatment—CPR	1.804	0.202	<0.001	6.07	4.09–9.02
Treatment—pacemaker implant	0.828	0.413	0.045	2.29	1.02–5.15
Treatment—pericardiocentesis	1.329	0.528	0.012	3.78	1.34–10.64

Abbreviations: CPR, cardiopulmonary resuscitation; HTN, hypertension; RIFLE, risk, injury, failure, loss, and end-stage; RIFLE-F, RIFLE-failure; RIFLE-I, RIFLE-injury; RIFLE-R, RIFLE-risk.

[a]Multivariate logistic regression model: n=3931, adjusted generalized R^2=0.231, estimated area under the receiver operating characteristic (AUROC) curve=0.772.

[b]Variables included in the analysis comprised age, sex, severity of renal injury (RIFLE-F and RIFLE-I, with RIFLE-R as comparator), baseline renal insufficiency, hypertension, cirrhosis, institution of hemodialysis, CPR, pacemaker implantation, and pericardiocentesis.

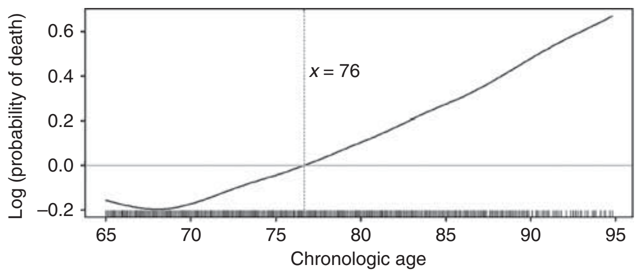

Figure 3 | The probability of in-hospital mortality associated with the chronologic age of the patients at admission to the ICU as constructed with the generalized additive model (GAM). Adjusted by sex, RIFLE category, baseline renal insufficiency, hypertension, liver cirrhosis, treatment with hemodialysis, CPR, ECMO, TPN, pacemaker implantation, and pericardiocentesis. CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RIFLE, risk, injury, failure, loss, and end-stage; TPN, total parenteral nutrition.

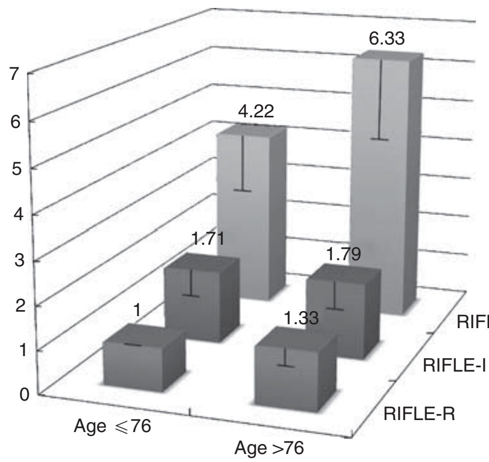

Figure 4 | The odds ratio for hospital mortality among patients stratified by patient age and RIFLE (risk, injury, failure, loss, and end-stage) categorization (with patients aged ⩽76 years and RIFLE-R category acute kidney injury as comparator). RIFLE-F, RIFLE-failure; RIFLE-I, RIFLE-injury; RIFLE-R, RIFLE-risk.

influenced by factors such as the creatinine production rate and nonrenal issues (muscle mass, nutrition), which are more often compromised in the elderly, aging also affects the diagnostic probability of AKI.[23] Furthermore, more pre-existing renal insufficiency in elderly patients also delay the time frame of sCr elevation,[24] although this might occur less often in our elderly cohort, owing to our maximal sCr definition. Finally, in critically ill patients, sepsis and fluid accumulation disproportionately affect older patients, which further 'mask' the increases in sCr, rather than delay it.[25,26] Creatinine-based diagnosis of AKI may inadvertently delay or even mask the recognition of renal injury onset,[27,28] especially in older patients. Thus, minor AKI in the elderly may not trigger and be recognized as early-stage RIFLE classification. This has two important implications. First, the RIFLE-R group in older-old patients actually blends in with the RIFLE-I group (if AKI is defined by other markers instead of sCr). Second, this late diagnosis will undoubtedly expose this vulnerable population to a higher degree of nephrotoxic injury and delay the institution of nephro-protective measures (Figure 5). As a result, the combination of susceptible kidneys, prolonged nephrotoxic damage, and possibly incorrect RIFLE classification will lead to higher rates of mortality in elderly patients with milder classifications of AKI, culminating in the poor differentiation between the mortality of the older-old and the younger-old patients. We therefore emphasized that older-old patients (>76 years old) may need to rigorously avoid potentially nephrotoxic drugs or metabolic factors even if the sCr is only mildly elevated.

The observation that aging effect on the prognosis of patients with RIFLE-I insult diminished mildly may have several reasons: first, the elderly have less muscle mass, manifesting as low sCr levels. Sarcopenia, a syndrome with low muscle mass, reportedly associates with lower survival in patients undergoing major surgery.[29] This phenomenon may potentially blur the difference between each grade of RIFLE classification. Second, as in Table 3, liver cirrhosis was identified as a potential predictor of poor prognosis in our elderly cohort, and older-old patients with RIFLE-I injury had significantly less baseline liver cirrhosis (older-old vs. younger-old, 4.2% vs. 7.6%; $P=0.036$) and chronic hepatitis (older-old vs. younger-old, 5.2% vs. 8.7%; $P=0.046$; Table 1). This difference in comorbidities might also explain partially the diminished difference between older-old and younger-old patients with RIFLE-I AKI.

The accentuation of prognostic difference between the older-old and the younger-old patients in RIFLE-F category AKI is another important finding (Figure 4). Delayed diagnosis of AKI in the elderly patients potentially inflicted further damage and postponed appropriate nephroprotective measures. As older-old patients might have even less muscle mass than their younger-old counterparts, the time needed to develop RIFLE-F-grade AKI could be further lengthened. This means an even longer window for nephrotoxic insults and shorter period for appropriate actions, translating into a larger prognostic difference between the two RIFLE-F subgroup patients. In addition, the policy of dialysis institution in elderly patients with RIFLE-F injury also merits attention. The initiation of dialysis, whether life saving or not, in the elderly patients has been debated recently.[30] Treatment with hemodialysis was borderline associated with better hospitalization survival (Table 3). We also found that older-old patients with RIFLE-F injury were significantly less likely to receive dialysis than the younger-old patients during hospitalization (the former vs. the latter, 7.2% vs. 10.4%; $P=0.031$). This could be another reason why the mortality difference between the older-old and the younger-old patients during severer AKI is even greater.

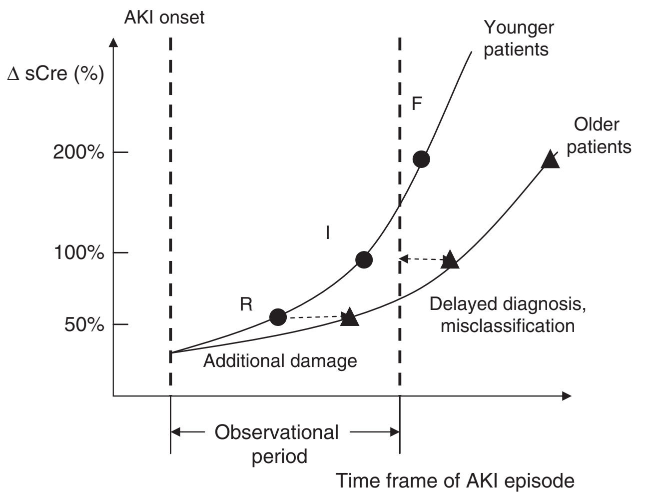

Figure 5 | A diagram that illustrates creatinine kinetics and the potential implications for its use in the diagnosis of elderly patients with acute kidney injury (AKI). RIFLE, risk, injury, failure, loss, and end-stage; RIFLE-F, RIFLE-failure; RIFLE-I, RIFLE-injury; RIFLE-R, RIFLE-risk; sCre, serum creatinine.

In light of our findings, older-old patients with AKI and lower levels of sCr change should be managed more cautiously. Nephroprotective strategies including avoidance of nephrotoxic drugs and procedures; optimization of hemodynamic status; evidence-based therapy such as acetylcysteine use and hydration before contrast-enhanced computed tomography; organ-specific intervention such as coronary revascularization for coronary vasculopathy; and nutritional counseling should be provided. We suggest that the RIFLE classification system may need modification, especially when applied to elderly AKI patients >76 years of age.

Our analysis also revealed several other independent factors that were predictive of increased rates of in-hospital mortality, such as pre-existing renal insufficiency, cirrhosis, and various procedures that patients had undergone (Table 3). These findings are comparable to the results of others.[15,18,31] This suggests that geriatric patients are especially prone to develop AKI when critically ill and that the use of invasive procedures will incur further iatrogenic damage, such as hospital-acquired infections, thus increasing the risk of mortality.[6,7,18]

Our study had certain limitations. First, this study was observational in nature and was likely to have an unequal distribution of variables between the groups. However, this potential limitation was mitigated by the large number of participants and the relatively homogeneous population (all postoperative AKI cases). Second, the definition of baseline sCr might be a concern in this study, as part of it came from assuming an estimated GFR of 75 ml/min using the MDRD equation. Our data suggested that the effect was small, as the overall proportion of sCr from estimation was low (21.8%), and the percentage between the older-old and the younger-old patients was balanced (Table 4). We further performed sensitivity analysis based upon patients with preadmission or admission sCr, and the results were consistent with our findings. Third, the definition of AKI in our study was based on sCr. We did not collect other more accurate biomarkers, such as cystatin C or neutrophil gelatinase–associated lipocalin, for cross-reference. Fourth, we did not include elderly patients with subclinical elevations in sCr (change <50%) after surgery, although previous studies have found that this population is also at risk for adverse outcomes.[32]

Table 4 | Proportions of different baseline serum creatinine sources between age strata

Baseline serum creatinine sources	Age ⩽76	Age >76	*P*-value[a]
Nadir during index admission	1125 (51.7%)	1001 (57.1%)	0.462
Nadir during previous admission within recent 1 year	630 (28.9%)	320 (18.2%)	0.167
Calculated from MDRD formula assuming eGFR 75 ml/min	422 (19.4%)	433 (24.7%)	0.128

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
[a]Compared with Student's *t*-test.

Finally, there are studies demonstrating the impact of postoperative AKI duration upon patient outcomes.[33] We could not derive this conclusion, as AKI duration was not recorded in our database. Cohort studies using different classifications of AKI or different biomarkers for detecting AKI in geriatric populations are warranted to confirm our findings.

In conclusion, we showed that age was an independent risk factor for mortality in geriatric patients. The older-old age (>76 years) compromised the ability of RIFLE to predict AKI prognosis in geriatric critically ill patients. Even mild elevations in sCr (RIFLE-R group) might associate with higher rates of mortality as in patients with RIFLE-I AKI in the older-old group. These slight increases in sCr may only be the tip of the iceberg, suggesting that there is already a high risk of adverse outcomes for certain populations of the elderly.

MATERIALS AND METHODS

This prospective study was conducted using the NSARF database.[34,35] The institutional review board of the National Taiwan University Hospital approved the study (no. 31MD03) and waived the need for informed consent, because there was no breach of privacy or interference with decision-making processes related to patient care.

Patients were eligible for enrollment if they were $\geqslant$65 years of age and had major surgery with postoperative AKI in ICUs between 1 January 2002 and 31 December 2008. Exclusion criteria included patients on maintenance dialysis (defined as >3 months of renal replacement therapy) or patients who had received renal replacement therapy before admission into the ICU admission and stayed in the ICU for <48 h. As with other studies,[36–38] we used the sRIFLE classification system in which only creatinine levels are used to classify patients. AKIs were stratified by the maximum sRIFLE classification during hospitalization.[39] The baseline sCr was the nadir value obtained from the previous admission for those who had more than one admission within 1 year before the index admission;[36] the nadir sCr value obtained during hospitalization and excluded from the emergency department measurement;[34,39,40] or the estimated sCr obtained by solving the MDRD equation with the assumption of a baseline eGFR of 75 ml/min per 1.73 m^2 if a baseline value was unavailable.[10] Study participants were prospectively followed up until their discharge from the index hospitalization or until death. Information concerning baseline demographic data, comorbidities, and types of surgery were collected and recorded. Diabetes mellitus was defined as the previous use of insulin or oral hypoglycemic agents. Hypertension was defined as the previous use of antihypertensive agents or a blood pressure >140/90 at the time of hospitalization. Coronary artery disease was defined according to previous coronary angiography or positive electrocardiographic findings. Heart failure was defined using the New York Heart Association functional class III or IV status. Atrial fibrillation was coded if there were more than two previous episodes of electrocardiographic evidence of atrial fibrillation. Hepatitis was defined as abnormal liver function with serologic evidence of hepatitis B or C. Cirrhosis was identified using compatible image findings, such as sonography or computed tomography. Chronic obstructive pulmonary disease was documented by certified pulmonologists. Renal insufficiency was defined as a baseline estimated GFR of <60 ml/min per 1.73 m^2.

Treatments during the ICU stay, including hemodialysis, tracheostomy, cardiopulmonary bypass, Swan–Ganz catheterization, intra-aortic balloon counterpulsation, coronary intervention, pacemaker implantation, intracranial pressure monitoring, extracorporeal membrane oxygenation, cardiopulmonary resuscitation, pericardiocentesis, and total parenteral nutrition, were also recorded. Severity scores, including APACHE-II scores,[41] were recorded at the time of ICU admission. The outcome of this study was in-hospital mortality, and survival periods were calculated from the date of ICU admission to patient death (in nonsurvivors) or hospital discharge (in survivors).

Statistical analysis

Statistical analysis was performed with the R 2.12.1 (R Foundation for statistical computing, Vienna, Austria) software. Continuous variables were expressed as the mean ± s.d. unless otherwise specified and compared with Student's *t*-test. Categorical variables were expressed as numbers (percentages) and analyzed using Fisher's exact test with Bonferroni correction. One-way analysis of variance was used for trend analysis if there were more than two groups. Kaplan–Meier survival curves were constructed and stratified according to the RIFLE classifications to display the relationship between AKI severity and mortality, with comparison by the log-rank test. Generalized Additive Models were applied to measure the probability of death by chronologic age. We subsequently analyzed the potential predictors of in-hospital mortality with the stepwise selection method of the multiple logistic regression models. All variables with a *P*-value of $\leqslant$0.1 in univariate analysis were selected and entered into the logistic regression analysis. Basic model-fitting techniques, goodness-of-fit assessments, and regression diagnostics were used in our regression analysis to ensure the quality of results. In all statistical analyses, a two-sided $P<0.05$ was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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