Retrospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Association between frailty and acute kidney injury after cardiac surgery: unraveling the moderation effect of body fat through an international, retrospective, multicohort study

Yun-Xiao Bai, MD[a,b,c], Zi-Hao Wang, MD[d], Yong Lv, MD[a,b,c], Jie Liu, MD[a,b,c], Zhen-Zhen Xu, MD[a,b,c], Yi-Qi Feng, MD[a,b,c], Guo-Yang Liu, MD[a,b,c], Ping Yin, PhD[e], Yan-Ting Wang, MD[a,b,c,*], Nian-Guo Dong, PhD, MD[d,*], Qing-Ping Wu, PhD, MD[a,b,c,*]

Background: Acute kidney injury (AKI) is a common and serious complication after cardiac surgery that significantly affects patient outcomes. Given the limited treatment options available, identifying modifiable risk factors is critical. Frailty and obesity, two heterogeneous physiological states, have significant implications for identifying and preventing AKI. Our study investigated the interplay among frailty, body composition, and AKI risk after cardiac surgery to inform patient management strategies.

Material and methods: This retrospective cohort study included three international cohorts. Primary analysis was conducted on adult patients who underwent cardiac surgery between 2014 and 2019 at Wuhan Union Hospital, China. We tested the generalizability of our findings with data from two independent international cohorts, the Medical Information Mart for Intensive Care IV (MIMIC-IV) and the eICU Collaborative Research Database. Frailty was assessed using a clinical lab-based frailty index (FI-LAB), while total body fat percentage (BF%) was calculated based on a formula accounting for BMI, sex, and age. Logistic regression models were used to analyze the associations between frailty, body fat, and AKI, adjusting for pertinent covariates.

Results: A total of 8785 patients across three international cohorts were included in the study. In the primary analysis of 3569 patients from Wuhan Union Hospital, moderate and severe frailty were associated with an increased AKI risk after cardiac surgery. Moreover, a nonlinear relationship was observed between BF% and AKI risk. When stratified by the degree of frailty, lower body fat correlated with a decreased incidence of AKI. Extended analyses using the MIMIC-IV and eICU cohorts ($n=3951$ and $n=1265$, respectively) validated these findings and demonstrated that a lower total BF% was associated with decreased AKI incidence. Moderation analysis revealed that the effect of frailty on AKI risk was moderated by the BF%. Sensitivity analyses demonstrated results consistent with the main analyses.

Conclusion: Higher degrees of frailty were associated with an elevated risk of AKI following cardiac surgery, and total BF% moderated this relationship. This research underscores the significance of integrating frailty and body fat assessments into routine cardiovascular care to identify high-risk patients for AKI and implement personalized interventions to improve patient outcomes.

Keywords: acute kidney injury, body fat percentage, cardiac surgery, frailty

[a]Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [b]Institute of Anesthesia and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [c]Key Laboratory of Anesthesiology and Resuscitation (Huazhong University of Science and Technology), Ministry of Education, China, [d]Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China and [e]Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Yun-Xiao Bai, Zi-Hao Wang, and Yong Lv contributed equally to this work and shared the first authorship.

Yan-Ting Wang, Nian-Guo Dong, Qing-Ping Wu contributed equally to this work and share the corresponding author.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, People's Republic of China. Tel.: +861 737 126 6089. E-mail: wyt_cherish@163.com (Y.T. Wang); Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, People's Republic of China. Tel.: +861 397 118 1551. E-mail: dongnianguo@hotmail.com (N.G. Dong); Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, People's Republic of China. Tel.: +861 397 160 5283. E-mail: wqp1968@163.com (Q.P. Wu).*

International Journal of Surgery (2025) 111:761–770

Received 16 April 2024; Accepted 10 June 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 2 July 2024

http://dx.doi.org/10.1097/JS9.0000000000001861

Introduction

Acute kidney injury (AKI) is a prognostically significant complication following cardiac surgery, with a prevalence ranging from 15 to 42%[1–3]. There is a direct, independent association between AKI and both short-term and long-term morbidity[4], as well as mortality[5,6], and the adjusted risk of 30-day mortality in severe AKI patients is increased by approximately eight-fold[7]. Yet there are no proven interventions for AKI after cardiac surgery other than supportive measures[8,9], making the identification of modifiable risk factors a reasonable and critical strategy for personalized patient management.

Frailty is a heterogeneous clinical condition[10], characterized by a decline in function across multiple physiologic systems, resulting in increased vulnerability to stressors[11], which increases the likelihood of iatrogenic complications, prolonged length of hospital stay, and early mortality[12–14]. Owing to the heterogeneity of frailty, patients with the same frailty status could present different features regarding the risk of adverse outcomes[15]. Although the concept of frailty has been well recognized as an aging-related process, frailty is not inevitably a consequence of aging and can exist in individuals younger than 65 years, especially those with comorbidities[16]. Beyond being a risk factor for frailty, there is a bidirectional causality between comorbidity and frailty, underlining their mutual risk association[10]. Thus, consideration of comorbidities should be integral to supporting early identification and promoting informed decision-making when assessing frailty.

The obesity paradox, an observation suggesting that obesity may confer a protective effect in certain chronic disease populations, adds complexity to the narrative[17]. However, this paradox remains contentious, largely because most studies have used BMI as the sole obesity measure, which does not accurately reflect fat distribution[18,19]. It is adiposity rather than excess body weight, which is the real culprit behind obesity-related complications[19]. The benefits of the obesity paradox could be a result of reverse causality or collider bias, reflecting poorer survival outcomes in underweight and frail patients.

Our study sought to bridge these gaps by investigating the association between different degrees of frailty and the risk of AKI following cardiac surgery, with a special focus on the potential moderating role of total body fat percentage (BF%). This approach acknowledges the intricate interplay between frailty, body composition, and AKI risk, and aims to unveil insights that could inform targeted interventions and refine patient management strategies.

HIGHLIGHTS

- Frail patients were associated with an increased risk of developing acute kidney injury (AKI) after cardiac surgery.
- Cardiac patients with a lower total body fat percentage (BF %) had decreased AKI risk after adjustment for potential confounding factors, while those with a higher total BF% had elevated AKI risk.
- This study demonstrated a consistent protective effect in cardiac patients with a lower BF% than those with the median total BF% levels across all three international cohorts.
- It has been validated in three international cohorts to underscore the significance of integrating frailty and body fat assessments into routine cardiovascular care to identify high-risk patients for AKI and implement personalized interventions to improve patient outcomes.

Methods

Study design and inclusion population

This retrospective cohort study was conducted at Wuhan Union Hospital, a major academic medical center in central China. This study adhered to STROBE reporting guidelines and was approved by the institutional Ethics Committee (No. 2024–0554). This study has been registered in Research Registry (ID: researchregistry10191).

The requirement for informed consent was waived due to the retrospective and anonymous nature of the data. This study adhered to the strengthening the reporting of cohort, cross-sectional and, case–control studies in surgery (STROCSS) guidelines (Supplemental Digital Content 1, http://links.lww.com/JS9/C983)[20].

All adult patients admitted to the hospital and who underwent cardiac surgery between January 2014 and December 2019 were identified. The study excluded participants who met any of the following criteria: (1) underwent noncardiac surgeries; (2) required a second thoracotomy after surgery; (3) died or were discharged within 48 h after surgery; (4) preoperative serum creatinine (Scr) values of 4 mg/dl or higher; (5) had missing clinical data; and (6) had insufficient laboratory tests to evaluate their frailty status. Cardiac surgeries include coronary artery bypass graft (CABG), valve repair or replacement (single or multiple), and combined surgeries.

We further extended our analysis to enhance the generalizability of our findings by leveraging data from two international cohorts with distinct ethnic characteristics sourced from the Medical Information Mart for Intensive Care IV (MIMIC-IV) and the eICU Collaborative Research Database (eICU)[21,22]. Access to both databases was approved by the Massachusetts Institute of Technology Affiliates (ID: 61043182). The creation of the MIMIC database was approved by the Institutional Review Boards at the Beth Israel Deaconess Medical Center (2001-P-001699/14) and Massachusetts Institute of Technology (No. 0403000206), which waived the need for informed consent and approved the data-sharing initiative. The eICU dataset was exempt from ethical approval because it met the safe harbor standards established by an independent privacy expert (Privacert) (Health Insurance Portability and Accountability Act Certification no. 1031219-2).

Definitions of study outcomes

The primary outcome was AKI after cardiac surgery in all cohort studies, defined according to the Scr criteria of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[23]. The Baseline Scr value was determined based on the most recent available Scr level before the surgery. AKI was defined by any of the following criteria: a postoperative SCr within 48 h $\geq$ 0.3 mg/dl above the baseline SCr, or a postoperative SCr within 7 days $\geq$ 1.5 times the baseline SCr. For analysis purposes, patients who died before postoperative day 7 and did not develop any-stage AKI were presumed to be devoid of AKI.

Definitions of other variables

Baseline characteristics, including age, sex, ethnicity, BMI, admission type, surgery type, baseline Scr, and comorbidities, were determined according to the WHO International Classification of Diseases Ninth Revision (ICD-9) and Tenth Revision (ICD-10). Vasopressor medications prior to cardiac surgery, such as norepinephrine, epinephrine, dopamine, vasopressin, and phenylephrine, were obtained.

In all cohorts, frailty was assessed using a clinical lab-based frailty index (FI-LAB)[24], comprising up to 23 variables based on 21 routine blood tests and measured systolic and diastolic blood pressures. FI-LAB has consistently demonstrated good predictive ability for mortality and various adverse outcomes across diverse populations[25]. Initially, each variable was assigned a binary code of '0' or '1', where 0 indicates values within normal cut-offs and '1' indicates values above or below the normal cut-off values. Subsequently, the FI-LAB score was calculated exclusively for individuals with more than 70% of the laboratory variables available. The FI-LAB score for each individual was determined by dividing the number of deficits by the total number of deficits measured. All patients were categorized as nonfrail (< 0.1), mildly frail (0.1–0.2), moderately frail (0.2–0.35), and severely frail (> 0.35).

In all cohorts, total BF% was determined using the formula developed by Deurenberg *et al.*[26], which calculates body fat using the equation: $(1.20 \times \text{BMI}) + (0.23 \times \text{age}) - (10.8 \times \text{sex}) - 5.4$, where the female is represented as 0 and male as 1 for sex, with age in years. Owing to variations in the distribution of BF% among different cohorts and the potential influence of local demographics, coupled with the lack of consensus on defining obesity thresholds, previously established reference cutoffs may have limited applicability. Therefore, we categorized the patients into five quintiles based on their total BF% to account for these factors.

Statistical analysis

The institutional review board granted approval for the statistical analysis plan, and the analysis was performed with the guidance and supervision of a statistics professor. A formal sample size calculation was not performed. Instead, we aimed to include all eligible patients from our database to increase statistical power. We also took precautions to avoid overfitting by ensuring at least 10 events for each variable were included in the multivariable model.

Quantitative variables were presented as median and interquartile range (IQR), whereas qualitative variables were presented as frequencies and percentages. Group comparisons were conducted using the χ^2 test or Fisher's exact test for qualitative variables and the Mann–Whitney *U*-test for quantitative variables, as deemed appropriate.

Logistic regression models were used to compute the odds ratio (OR) and 95% CI to evaluate the association between frailty status and the risk of AKI following cardiac surgery. The association between total BF% and AKI was evaluated using locally weighted regression scatter plot smoothing (LOWESS) and restrictive cubic spline (RCS) analyses. Furthermore, the association between body fat status and the risk of AKI following cardiac surgery across different frailty statuses was tested using logistic regression models. All models were multivariable-adjusted, controlling for age, sex, chronic kidney disease, coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, vasopressor use before surgery, baseline Scr, and baseline blood urea nitrogen (BUN).

The moderating effects of total BF% on the relationship between frailty and AKI were examined using moderating analysis. All statistical analyses were performed using R software (version 4.3.1). Statistical significance was defined as a two-sided *P*-value of <0.05 was considered statistically significant.

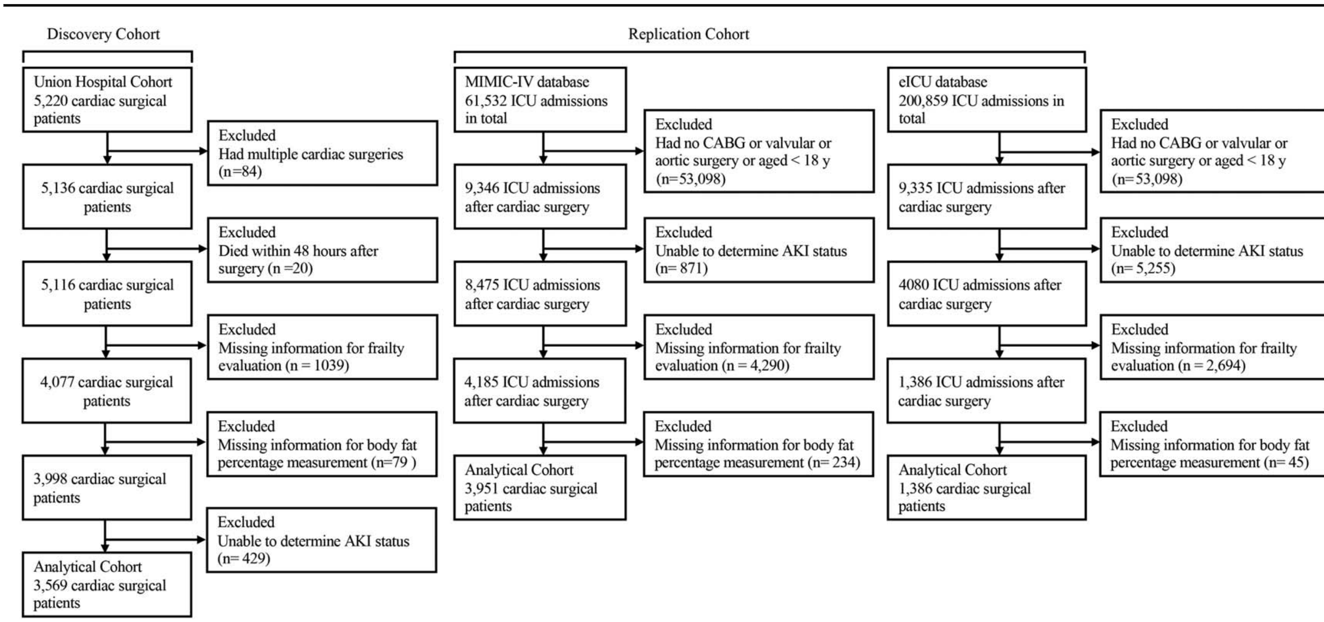

Figure 1. Flow diagram of the selection process of the eligible population. AKI, acute kidney injury; CABG, coronary artery bypass grafting; eICU, eICU Collaborative Research Database; MIMIC-III, Medical Information Mart for Intensive Care III.

Table 1

Baseline characteristics from Wuhan union cohort.

Variables	Overall (n = 3569)	AKI (n = 897)	Non-AKI (n = 2672)	P
Age, years	54 (45–62)	58 (50–65)	53 (44–61)	< 0.001
Sex (male), n (%)	1966 (55.09)	611 (68.12)	1355 (50.71)	< 0.001
BMI, kg/m²	23.11 (21.01–25.45)	24.21 (21.64–26.30)	22.86 (20.81–25.14)	< 0.001
Body fat percentage, %	28.292 (23.894– 33.506)	27.36 (23.45–32.60)	28.27 (23.58–33.49)	0.630
Smoking history, n (%)	998 (27.96)	323 (36.01)	675 (25.26)	< 0.001
Drinking history, n (%)	758 (21.24)	252 (28.09)	506 (18.94)	< 0.001
Hypertension, n (%)	964 (27.01)	358 (39.91)	606 (22.68)	< 0.001
Diabetes, n (%)	314 (8.8)	108 (12.04)	206 (7.71)	< 0.001
CHD, n (%)	965 (27.04)	350 (39.02)	615 (23.02)	< 0.001
COPD, n (%)	53 (1.49)	17 (1.9)	36 (1.35)	0.310
History of myocardial infarction, n (%)	110 (3.08)	46 (5.13)	64 (2.4)	< 0.001
History of cerebral infarction, n (%)	186 (5.21)	59 (6.58)	127 (4.75)	0.041
Chronic kidney failure, n (%)	118 (3.31)	58 (6.47)	60 (2.25)	< 0.001
History of malignant tumor, n (%)	18 (0.5)	0	18 (0.67)	0.028
Atrial fibrillation, n (%)	698 (19.56)	152 (16.95)	546 (20.43)	0.026
Cardiac surgery history, n (%)	161 (4.51)	49 (5.46)	112 (4.19)	0.135
NYHA class II–IV, n (%)	946 (26.51)	247 (27.54)	699 (26.26)	0.445
Ejection fraction, %	62 (57–66)	62 (58–66)	61 (56–66)	0.105
Preoperative use of vasoactive agents, n (%)	94 (2.63)	33 (3.68)	61 (2.28)	0.032
Emergency admission, n (%)	67 (1.88)	35 (3.9)	32 (1.2)	< 0.001
Type of surgery, n (%)				
CABG	334 (9.36)	112 (12.49)	222 (8.31)	< 0.001
Valve	2104 (58.95)	421 (46.93)	1683 (62.99)	< 0.001
Aortic	241 (6.75)	90 (10.01)	151 (5.65)	< 0.001
Combined surgery	890 (24.94)	274 (30.54)	616 (23.05)	< 0.001
EUROSCORE II, %	1.745 (1.23–2.74)	2.03 (1.30–3.52)	1.690 (1.20–2.63)	< 0.001
CPB duration, min	109 (85–139)	119 (90–157)	105 (84–133)	< 0.001
Aortic cross clamp duration, min	72 (53–95)	77 (56–105)	71 (52–91)	< 0.001
Surgery duration, h	4 (3.28–5)	4.48 (3.58–5.50)	3.9 (3.17–4.67)	< 0.001
Preoperative Hb, g/l	129 (118–140)	129 (117–140)	129 (118–140)	0.268
AST, U/l	21 (17–27)	21 (17–28)	21 (17–27)	0.203
ALT, U/l	20 (14–31)	21 (15–32)	20 (14–30)	< 0.001
Preoperative SCr, mg/dl	72.2 (61.4–85.2)	77.3 (64.8–92.6)	70.4 (60.6–82.8)	< 0.001
BUN, mmol/l	5.72 (4.62–6.97)	6.11 (5.01–7.47)	5.61 (4.51–6.84)	< 0.001
eGFR, ml/min/1.73 m^2	95.73 (80.48–108.8)	91.39 (72.95–103.94)	97.39 (82.91–109.98)	< 0.001
Admission frailty index	0.23 (0.16–0.29)	0.24 (0.18–0.32)	0.21 (0.16–0.29)	< 0.001

All data are presented as n (%) or median [IQR]. Wilcoxon rank sum and Pearson χ^2 tests were used to perform univariable analyses for continuous and categorical variables.
AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; NYHA, New York heart association; SCr, serum creatinine.

Sensitivity analyses

Sensitivity analyses were conducted according to the following criteria: (i) Due to controversial FI cut-off values for defining frailty status[27], two other common cut-offs were used; cut-off 1, severely frail, mildly frail, and nonfrail were defined as FI > 0.21, 0.10 < FI ≤ 0.21, and FI ≤ 0.10, respectively; cut-off 2, severely frail, mildly frail, and nonfrail were defined as FI ≥ 0.25, 0.08 < FI < 0.25, and FI ≤ 0.08, respectively. (ii) To further explore the generalizability of our findings, we utilized a different widely used equation to measure body fat, namely, the formula developed by the Metabolic Research Laboratory from *Clínica Universidad de Navarra* (CUN-BAE)[28], which is also based on BMI, sex, and age.

Results

Primary analyses in Wuhan cohort

The primary analysis identified 3569 eligible cardiac surgical patients from the Wuhan Union Hospital cohort (male: 55.1%, median age: 54 years) (Figure 1). The baseline characteristics here are summarized in Table 1, while the baseline characteristics are summarized in Supplemental Table 1. (Supplemental Digital Content 2, http://links.lww.com/JS9/C984). In the Wuhan Union Hospital cohort, AKI patients tended to be older, more likely to be female, had a higher prevalence of smoking and drinking history, and exhibited a greater prevalence of comorbidities than participants who did not develop AKI following cardiac surgery. However, patients with AKI had a higher BMI but a similar BF% and a higher Frailty Index (FI) score at admission. Additionally, AKI participants exhibited elevated levels of ALT and Scr, lower eGFR, and experienced longer durations of CPB, aortic cross-clamp, and surgery than non-AKI participants.

Figure, 2A demonstrates the association between frailty status at admission and the risk of AKI after cardiac surgery. After adjusting for potential confounders, patients with moderate and severe frailty showed a significantly higher risk of AKI than robust cardiac patients (moderate frailty: OR 1.07, 95% CI: 1.01–1.13; severe frailty: OR 1.13, 95% CI: 1.06–1.20). As illustrated in Figure 2B, there was a nonlinear relationship

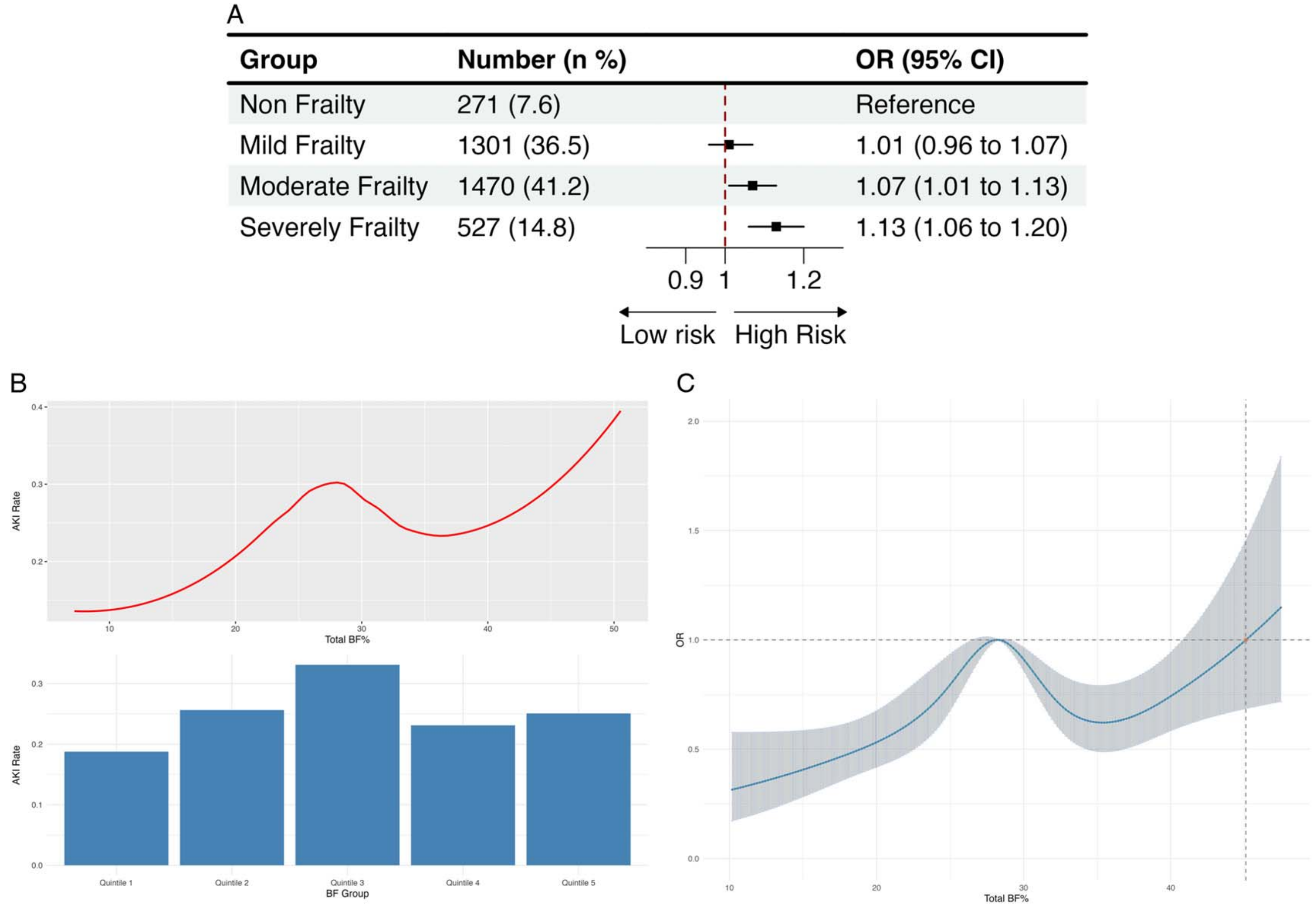

Figure 2. Association between frailty, body fat percentage, and AKI. (A) Association between different frailty status and AKI. (B) The LOWESS curve indicated a nonlinear association between total BF% and AKI. (C) The restricted cubic spline indicated a nonlinear association between total BF% and AKI. AKI, acute kidney injury; BF%, body fat percentage; OR, odds ratio.

between different quintiles of BF% and AKI after cardiac surgery (P for trend = 0.049), with RCS regression further validating this nonlinear relationship ($P < 0.001$) (Fig. 2C).

Figure 3 depicts the association of different quintiles of total BF % with the risk of AKI stratified by the degree of frailty. We found that patients with total BF% in Q1 had a statistically significantly lower risk of developing AKI following cardiac surgery across all frailty statuses than those with total BF% in Q3 after controlling for the potential covariates (all OR <1 and $P < 0.05$). Likewise, patients with total BF% in Q2 exhibited a significantly lower risk of developing AKI following cardiac surgery across all frailty statuses, except for nonfrailty status, compared to those with total BF% in Q3 (all OR <1 and $P < 0.05$). Furthermore, across all frailty subgroups, the OR for developing AKI after cardiac surgery was higher in patients with total BF% in Q2 than in those in Q1. Forest plots indicated decreasing trends in AKI risk with reduced Total BF% across different levels of frailty.

Extended analyses in the validation cohorts

The eligible population for the replication analyses was 3951 (male: 68.3%, mean age: 70 years) from the MIMIC-III database and 1265 (male: 68.1%, mean age: 68 years) from the eICU database. The baseline characteristics and outcomes of the enrolled patients are summarized in Supplemental, Table 1. In both cohorts, AKI patients had a higher BMI, BF%, and FI score at admission compared to participants who did not develop AKI following cardiac surgery. Patients in the MIMIC cohort had a higher prevalence of comorbidities, including coronary heart disease, chronic kidney failure, and diabetes, and were more likely to receive vasoactive agents before undergoing cardiac surgery.

Figure 4 demonstrates the association of different quintiles of total BF% with the risk of AKI, stratified by the degree of frailty, in the MIMIC and eICU cohorts. In the MIMIC cohort, patients with FI scores > 0.35, those with total BF% in Q1, and Q5 exhibited a higher risk of developing AKI compared to those with total BF% in Q3, with the OR for AKI development being significantly lower in Q1 than in Q5 (Q1, OR 1.60, 95% CI: 1.06–2.43; Q5, OR 1.99, 95% CI: 1.28–3.12). In the eICU cohort, among patients with FI scores > 0.35, those with total BF % in Q1 and Q2 displayed a lower risk of developing AKI than those with total BF% in Q3, with the OR for AKI development being significantly lower in Q1 than in Q2 (Q1, OR 0.45, 95% CI: 0.24–0.83; Q5, OR 0.56, 95% CI: 0.33–0.96). Extended analyses conducted in these two international cohorts further validated the decreased risk of AKI in patients with a reduced total BF%.

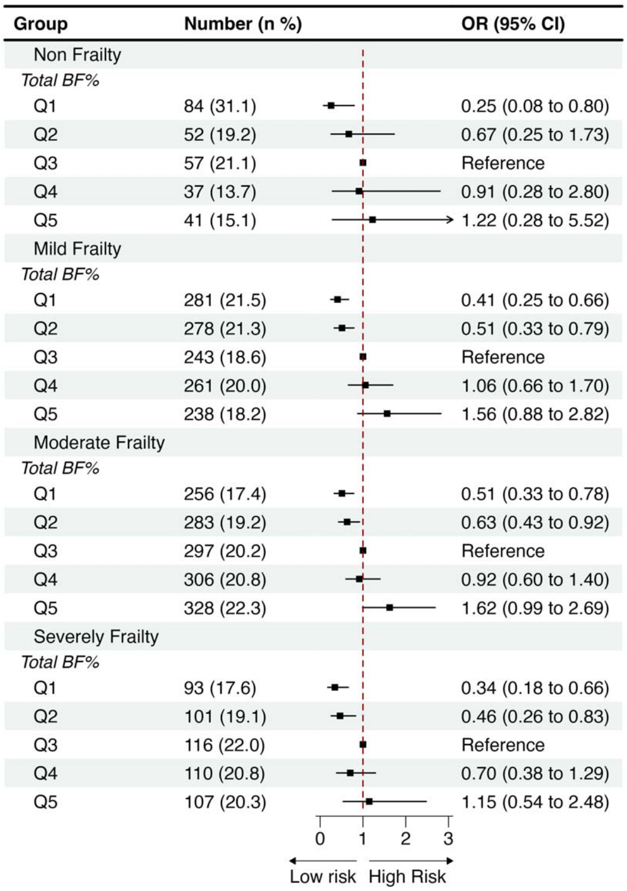

Figure 3. Association between body fat percentage and AKI when stratified by degrees of frailty in Wuhan Union Cohort. AKI, acute kidney injury; BF%, body fat percentage; OR, odds ratio;.

Body fat percentage moderated the effect of FI scores on acute kidney injury

We performed a moderation analysis to determine the relationship between total BF% and FI in AKI after cardiac surgery. A significant interaction was observed between total BF% moderated the effect of FI scores on AKI ($P = 0.033$ in total BF% Q1, $P = 0.027$ in total BF% Q4 (Wuhan cohort); $P = 0.001$ in total BF % Q1, $P = 0.049$ in total BF% Q5 (MIMIC cohort); $P = 0.038$ in total BF% Q2 (eICU cohort)). As the FI score increased, the risk of developing AKI also increased among the patients in the MIMIC cohort (Fig. 5). However, patients in the lower quintiles of total BF% (Q1) exhibited a decreased risk of developing AKI after cardiac surgery (Beta-coefficient: – 0.970, $P = 0.004$) compared to those with average total BF% (depicted by the black line). The differences among the slopes indicated that the different quintiles of total BF% moderated the relationship between FI scores and AKI.

Sensitivity analyses

The association between frailty status and AKI after cardiac surgery remained consistent even after adjusting for baseline FI score or using different FI cutoff values to define frailty status (SDC, Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/C984). Furthermore, the association of different quintiles of total BF% with the risk of AKI, stratified by the degree of frailty, remained consistent even after additional adjustment for baseline FI score or when two other FI cutoff values were applied to define frailty status (SDC, Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C984). The results were also consistent after further adjusting for the equation to measure total BF% in all cohorts, except the eICU cohort (SDC, Table 4, Supplemental Digital Content 2, http://links.lww.com/JS9/C984).

Discussion

In this study, spanning three international cohorts, we investigated the association between frailty status and the risk of AKI postcardiac surgery, with a particular focus on the moderating role of total BF%. In the primary analysis, we observed that higher degrees of frailty exhibited an elevated risk of developing AKI, a relationship significantly moderated by total BF% after adjusting for potential confounders, indicating that a lower BF% offered a protective effect compared with the median total BF% levels. Given the homogeneity of the ethnic background within the primary cohort, which consisted solely of Chinese individuals, we sought to bolster the robustness of our findings through validation in two additional international cohorts of multiethnic populations. These further analyses confirmed our initial observations, with lower and higher total BF%, respectively, decreasing and increasing AKI risk in severely frail cardiac patients after adjustment for potential confounding factors. These validations not only reinforced our initial observations, but also underscored the potential of BF% as a critical tool for clinicians. This supports early identification and informed decision-making in managing AKI risk among frail patient populations. Our methodological approach to verifying these associations across varied populations highlights the study's methodological rigor and the reliability of BF% as a significant factor in assessing AKI risk in frail patients.

Frailty is becoming an increasingly prevalent health condition as the global elderly population increases. Through a meta-analysis of 849 participants across three prospective cohort studies, Chien *et al.*[29] identified a significant association between frailty and an increased risk of AKI compared to the nonfrail group. Similarly, Aykut and Salman[30] conducted a retrospective analysis of 455 patients undergoing on-pump CABG, confirming a strong link between frailty and the subsequent development of AKI post-CABG. Reinforcing these findings, a recent national prospective cohort study demonstrated that frail patients face a more than two-fold risk of developing AKI compared to their nonfrail counterparts[31]. This correlation is underpinned by a pathophysiological perspective where inflammation, a cornerstone of biological ageing[32] and recognized as a significant contributor to cardiac surgery-related AKI, is a shared mechanism between frailty and the increased risk of AKI[33]. Our study echoes these findings, showing a consistent increase in AKI risk among frail patients as opposed to nonfrail patients, even after adjusting for clinically relevant confounders. The results of our study are consistent with previous observations and further support the argument that frailty is an independent risk factor for AKI, further underlining the critical need for targeted interventions in this vulnerable population.

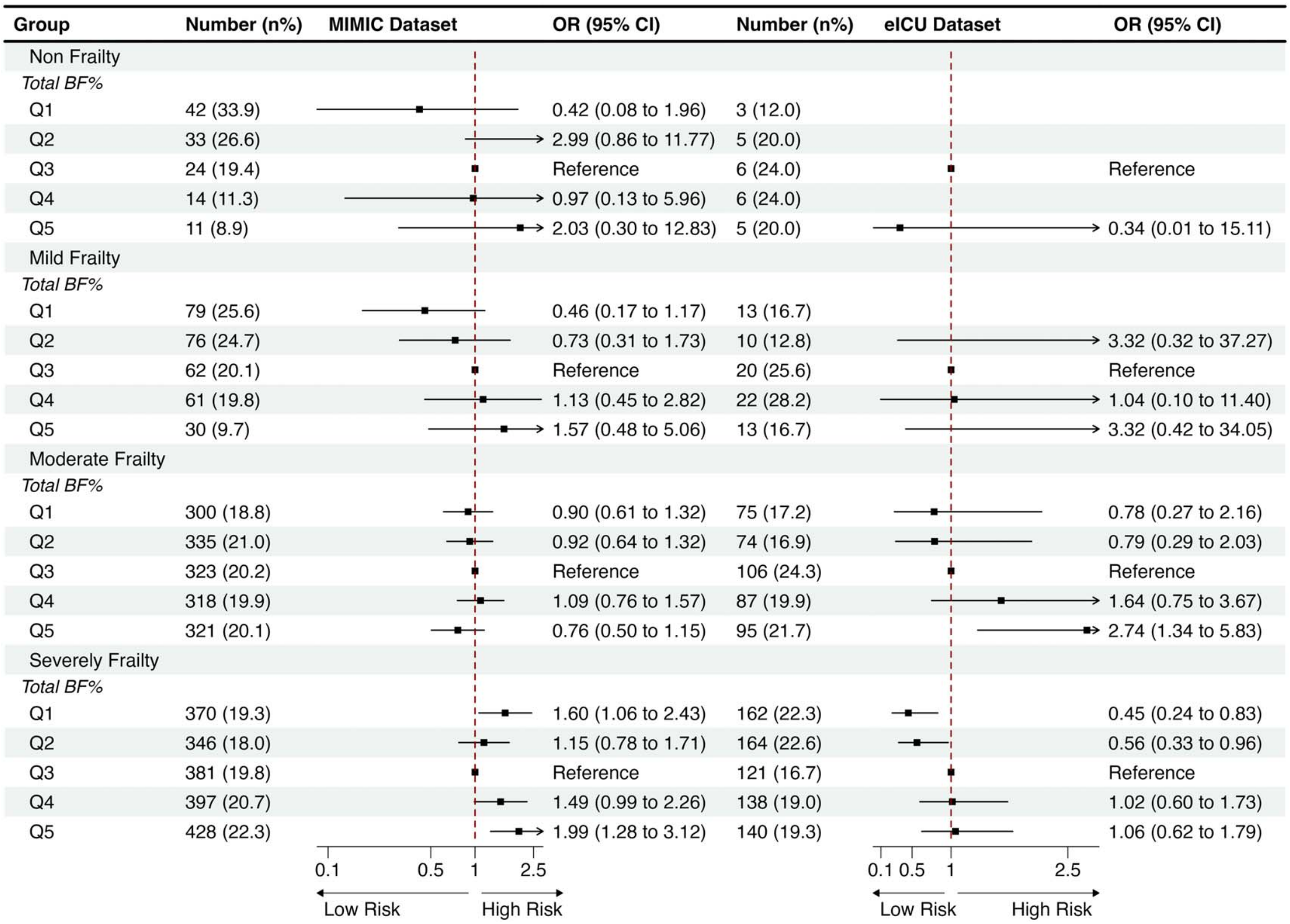

Figure 4. Association between body fat percentage and AKI when stratified by degrees of frailty in MIMIC- IV and eICU Cohort. AKI, acute kidney injury; BF%, body fat percentage; OR, odds ratio.

The finding that total-body BF% moderated the relationship between frailty and AKI incidence, with a protective effect at lower BF% and elevated AKI risk at higher BF%, aligns with a nuanced understanding of the role of body composition in health outcomes. This moderation effect suggests a complex interplay between adiposity and physiological resilience, where a lower BF % might confer protection against stressors that precipitate AKI in frail individuals. This moderation effect suggests a complex interplay between adiposity and physiological resilience, where an optimal range of BF% might confer protection against stressors that precipitate AKI in frail individuals. A large-scale study encompassing 320 252 adult participants highlighted a significant association between a BMI above 25 kg/m^2 and an elevated risk for end-stage renal disease, a relationship that was independent of diabetes and hypertension[34]. Furthermore, obesity can expedite the decline of kidney function in patients with diverse primary renal conditions and compromised renal function, including IgA glomerulonephritis, kidney transplantation, and diabetic nephropathy[35–37]. In summary, accumulating evidence has suggested a close relationship between obesity, a condition marked by an excessive accumulation of body fat, and the incidence and progression of kidney disease. Studies have indicated that adipose tissue, beyond its role in energy storage, functions as an endocrine organ releasing adipokines, which can have protective or detrimental effects on renal function depending on the balance of proinflammatory and anti-inflammatory factors[38,39]. Higher BF% is often associated with chronic low-grade inflammation[40], contributing to the pathophysiology of AKI by exacerbating renal hypoxia and endothelial dysfunction[41]. A pivotal stage in AKI involves mitochondrial swelling and increased permeability due to hypoxia, termed mitochondrial permeability transition, where fatty acids are identified as a significant contributor[42,43]. Conversely, lower BF % might reduce the burden of inflammation and preserve renal function[44], aligning with findings that healthier body composition, even in the context of ageing and frailty, can mitigate the risk of adverse health outcomes[45]. Echoing findings from both clinical and basic research on the significance of adipose tissue in affecting kidney diseases, a recent national study within the Chinese population revealed that higher immediate levels and patterns of increasing or persistently high visceral fat independently correlate with an elevated risk of renal damage[46]. The pathophysiological mechanisms at play suggest that fat accumulation, beyond serving as a mere marker of obesity, directly contributes to renal stress and injury, thereby offering a critical perspective for the early identification and facilitation of clinical decisions regarding preventative measures against kidney disease.

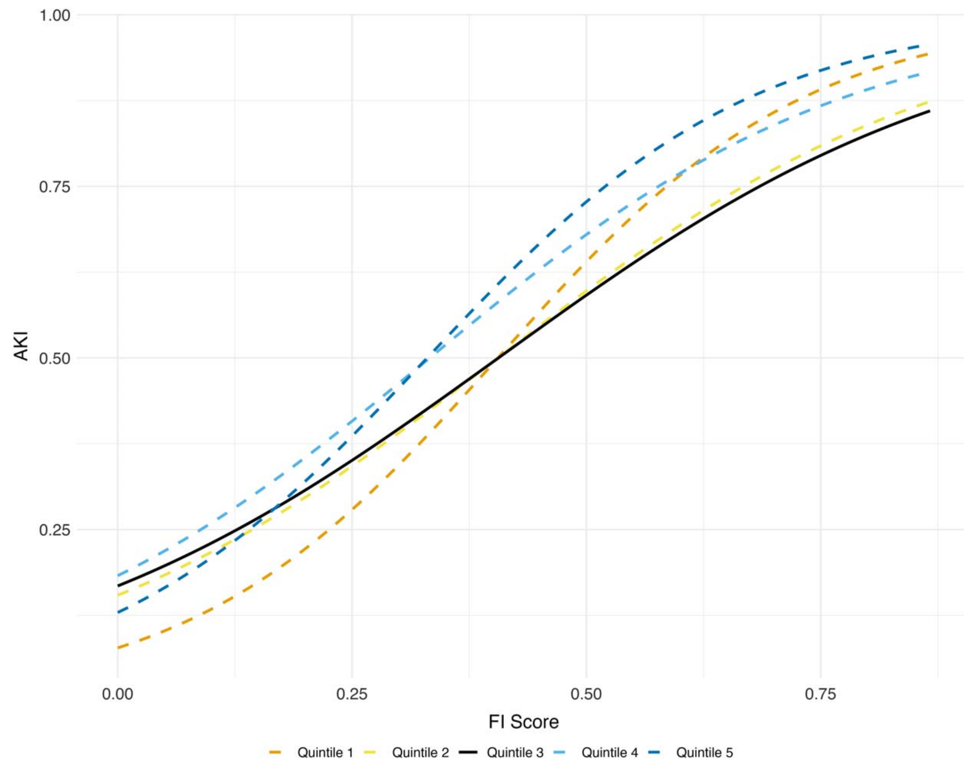

Figure 5. Moderation effect of total body fat percentage, represented as five quintiles, on the association between frailty index score and the risk of AKI. AKI, acute kidney injury; FI, frailty index.

Our study has significant clinical implications and advocates the integration of frailty assessment and body fat measurement into routine cardiovascular care. However, employing a comprehensive FI to evaluate patients' frailty levels could burden the already demanding clinical workflow, thereby limiting its practical application in clinical settings. Alternatively, assessing frailty through standard laboratory tests and blood pressure measurements does not add to the clinical workload, and research has shown that its predictive efficacy is comparable to that of the complete FI. We measured the patients' BF% using a formula-based on age, sex, and BMI, a straightforward tool that can be easily integrated into clinical routines. Studies indicate that this formula-based body fat estimation aligns well with measurements obtained using dual-energy X-ray absorptiometry (DXA), demonstrating good consistency. Our findings suggest that routine physical and laboratory examination results can effectively assess patients' frailty levels and BF%, thereby efficiently identifying those at a high-risk for AKI following cardiac surgery. This facilitates targeted early clinical decision-making, emphasizing the feasibility and effectiveness of these assessments in enhancing patient care without adding to the clinical burden.

This study has several strengths. To our knowledge, this study is the first to investigate total BF% as a moderator in the relationship between frailty and AKI risk after cardiac surgery, making a significant contribution to our understanding of these interactions. Furthermore, the results from the primary cohort were validated in two international cohorts with a large sample size, enhancing their applicability to diverse populations with multiethnic backgrounds. The consistency of the moderation effect across all the three international cohorts underscores the generalizability of our results. Comprehensive sensitivity analyses further confirmed the reliability of our conclusions. Notably, this research introduces a novel approach for the pre-emptive identification of acquired AKI risk in frail cardiac patients, providing intriguing prophylactic opportunities for personalized patient management.

Our study had certain limitations. First, frailty status was measured using the FI-lab, which lacks a measurement of physical ability and mental health. However, the accuracy of FI-lab has been shown to match that of the comprehensive FI[24,25], which is considered the gold standard. Moreover, we performed a sensitivity analysis to adjust for different cutoff values to redefine frailty status, yielding results consistent with our main analyses. Second, the measurement of total BF% was derived from an equation incorporating age, sex, and BMI rather than through DXA measurement. Nonetheless, the Deurenberg equation demonstrated moderate correlations with DXA-measured BF %[47,48]. Moreover, we conducted sensitivity analyses to reassess total BF% using the CUN-BAE equation, demonstrating excellent correlation with DXA-measured BF%. Remarkably, similar results were observed in the main analysis. Finally, several analyses were conducted without adjusting for multiplicity, potentially leading to an inflated type-I error.

Conclusions

This study revealed that higher degrees of frailty were associated with an elevated risk of AKI following cardiac surgery, and total BF% moderated this relationship. Lower total BF% was associated with a decreased risk of AKI, whereas higher total BF%

was associated with an increased risk of AKI. This study advocates incorporating frailty and body fat assessments into routine cardiovascular care to help identify high-risk patients for AKI and facilitate preventive measures.

Ethical approval

This study has been approved by the International Review Board of Union Hospital, Tongji Medical University, Huazhong University of Science and Technology (No. 2024-0554).

Consent

Due to the study's retrospective design, the requirement for informed consent was waived.

Source of funding

This study was supported by the National Key Research and Development Program of China (Grant No. 2023YFC2506901) and National Key Research and Development Program of China (Grant No.2018YFC2001903) and the National Natural Science Foundation of China (Grant No. 81873952) and the National Natural Science Foundation of China (Grant No. 81901948).

Author contribution

Y.B., Y.W., N.D., and Q.W.: proposed the idea and drafted the manuscript; J.L., Z.X., Y.F., and G.L.: completed the quality control of clinical data; Z.W. and Y.L.: contributed to data analysis; Y.B., Z.W., Y.L., Y.W., N.D., Q.W., J.L., Z.X., Y.F., and G.L.: collected clinical data; Y.B., Y.F., G.L., and Y.W.: conducted project integration; Y.B., Y.W., N.D., Q.W.: contributed to the conception of the study and helped perform the revision with constructive discussions. All authors read and approved the final version of the manuscript. All authors verified the underlying data of this study, had full access to all the data in the study and accepted responsibility for the decision to submit for publication.

Conflicts of interest disclosure

The author(s) have no potential conflicts of interest to disclose.

Research registration unique identifying number (UIN)

This study has been registered in Research Registry (ID: researchregistry10191).

Guarantor

Prof. Wu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Presentation

None.

Acknowledgements

Assistance with the study: none.

References

[1] Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol 2017;13: 697–711.
[2] Wang C, Gao Y, Tian Y, *et al*. Prediction of acute kidney injury after cardiac surgery from preoperative N-terminal pro-B-type natriuretic peptide. Br J Anaesth 2021;127:862–70.
[3] Bernardi MH, Schmidlin D, Ristl R, *et al*. Serum creatinine back-estimation in cardiac surgery patients: misclassification of AKI using existing formulae and a data-driven model. Clin J Am Soc Nephrol 2016;11: 395–404.
[4] Mao H, Katz N, Ariyanon W, *et al*. Cardiac surgery-associated acute kidney injury. Cardiorenal Med 2013;3:178–99.
[5] Hobson CE, Yavas S, Segal MS, *et al*. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009;119:2444–53.
[6] Hoste EAJ, Bagshaw SM, Bellomo R, *et al*. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intens Care Med 2015;41:1411–23.
[7] Chertow GM, Levy EM, Hammermeister KE, *et al*. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343–8.
[8] Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet 2019;394: 1949–64.
[9] Pickkers P, Darmon M, Hoste E, *et al*. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. Intens Care Med 2021;47:835–50.
[10] Hoogendijk EO, Afilalo J, Ensrud KE, *et al*. Frailty: implications for clinical practice and public health. Lancet 2019;394:1365–75.
[11] Dent E, Martin FC, Bergman H, *et al*. Management of frailty: opportunities, challenges, and future directions. Lancet 2019;394:1376–86.
[12] Yang X, Lupón J, Vidán MT, *et al*. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. J Am Heart Assoc 2018;7:e008251.
[13] Vermeiren S, Vella-Azzopardi R, Beckwée D, *et al*. Frailty and the prediction of negative health outcomes: a meta-analysis. J Am Med Dir Assoc 2016;17:1163.e1–17.
[14] Clegg A, Young J, Iliffe S, *et al*. Frailty in elderly people. Lancet 2013;381: 752–62.
[15] Wallace LMK, Theou O, Godin J, *et al*. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. Lancet Neurol 2019;18:177–84.
[16] Hanlon P, Nicholl BI, Jani BD, *et al*. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health 2018;3:e323–32.
[17] Tutor AW, Lavie CJ, Kachur S, *et al*. Updates on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2023;78:2–10.
[18] Bianchettin RG, Lavie CJ, Lopez-Jimenez F. Challenges in cardiovascular evaluation and management of obese patients: JACC state-of-the-art review. J Am Coll Cardiol 2023;81:490–504.

[19] Després JP, Carpentier AC, Tchernof A, *et al*. Management of obesity in cardiovascular practice: JACC focus seminar. J Am Coll Cardiol 2021; 78:513–31.
[20] Mathew G, Agha R, Albrecht J, *et al*. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.
[21] Johnson AEW, Bulgarelli L, Shen L, *et al*. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data 2023;10:1.
[22] Pollard TJ, Johnson AEW, Raffa JD, *et al*. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. Sci Data 2018;5:180178.
[23] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179–84.
[24] Howlett SE, Rockwood MR, Mitnitski A, *et al*. Standard laboratory tests to identify older adults at increased risk of death. BMC Med 2014;12:171.
[25] Blodgett JM, Theou O, Howlett SE, *et al*. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. Geroscience 2017;39:447–55.
[26] Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr 1991; 65:105–14.
[27] Kaskirbayeva D, West R, Jaafari H, *et al*. Progression of frailty as measured by a cumulative deficit index: a systematic review. Ageing Res Rev 2023;84:101789.
[28] Geng S, Chen X, Bai K, *et al*. Association of the clínica universidad de navarra-body adiposity estimator with type 2 diabetes: a retrospective cohort study. Int J Public Health 2023;68:1606063.
[29] Jiesisibieke ZL, Tung TH, Xu QY, *et al*. Association of acute kidney injury with frailty in elderly population: a systematic review and meta-analysis. Ren Fail 2019;41:1021–7.
[30] Aykut A, Salman N. Poor nutritional status and frailty associated with acute kidney injury after cardiac surgery: A retrospective observational study. J Card Surg 2022;37:4755–61.
[31] Tirupakuzhi Vijayaraghavan BK, Rashan A, Ranganathan L, *et al*. Prevalence of frailty and association with patient centered outcomes: a prospective registry-embedded cohort study from India. J Crit Care 2024; 80:154509.
[32] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018;15:505–22.
[33] Vives M, Hernandez A, Parramon F, *et al*. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis 2019;12:153–66.
[34] Hsu CY, McCulloch CE, Iribarren C, *et al*. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21–8.
[35] Berthoux F, Mariat C, Maillard N. Overweight/obesity revisited as a predictive risk factor in primary IgA nephropathy. Nephrol Dial Transplant 2013;28(suppl 4):iv160–6.
[36] Curran SP, Famure O, Li Y, *et al*. Increased recipient body mass index is associated with acute rejection and other adverse outcomes after kidney transplantation. Transplantation 2014;97:64–70.
[37] Gross ML, Amann K, Ritz E. Nephron number and renal risk in hypertension and diabetes. J Am Soc Nephrol 2005;16(Suppl 1):S27–9.
[38] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.
[39] Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, *et al*. The Role of Adipokines in Health and Disease. Biomedicines 2023;11:1290.
[40] Visser M, Bouter LM, McQuillan GM, *et al*. Elevated C-reactive protein levels in overweight and obese adults. Jama 1999;282:2131–5.
[41] Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol 2012;2:1303–53.
[42] Kinsey GR, McHowat J, Patrick KS, *et al*. Role of Ca2+-independent phospholipase A2gamma in Ca2+-induced mitochondrial permeability transition. J Pharmacol Exp Ther 2007;321:707–15.
[43] Feldkamp T, Park JS, Pasupulati R, *et al*. Regulation of the mitochondrial permeability transition in kidney proximal tubules and its alteration during hypoxia-reoxygenation. Am J Physiol Renal Physiol 2009;297: F1632–46.
[44] Oh SW, Ahn SY, Jianwei X, *et al*. Relationship between changes in body fat and a decline of renal function in the elderly. PLoS One 2014;9: e84052.
[45] Ma C, Avenell A, Bolland M, *et al*. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. Bmj 2017;359:j4849.
[46] Lin M, Wu S, Deng X, *et al*. Visceral fat and its dynamic change are associated with renal damage: Evidence from two cohorts. Clin Exp Hypertens 2023;45:2271187.
[47] Al-Gindan YY, Hankey CR, Govan L, *et al*. Derivation and validation of simple anthropometric equations to predict adipose tissue mass and total fat mass with MRI as the reference method. Br J Nutr 2015;114:1852–67.
[48] Velázquez-Alva MC, Irigoyen-Camacho ME, Zepeda-Zepeda MA, *et al*. Comparison of body fat percentage assessments by bioelectrical impedance analysis, anthropometrical prediction equations, and dual-energy X-ray absorptiometry in older women. Front Nutr 2022;9:978971.