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Patient Frailty Can Increase the Risk of Acute Kidney Injury after Cardiac Surgery: Pilot Study

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Abstract

Background: Acute kidney injury (AKI) is a severe common postoperative complication of cardiac surgery (CS). It increases the risk of mortality by up to 80%. Therefore, it is essential to have preoperative risk evaluation tools. Frailty is a marker of deterioration of physiologic systems and may be associated with AKI. **Purpose:** The study aimed to determine the utility of frailty as a predictor of AKI after CS. **Method:** We enrolled 91 patients undergoing CS with cardiopulmonary bypass to determine if they had frailty before surgery and were associated with postoperative AKI. The diagnosis of postoperative AKI was based on the serum creatinine criteria of the Acute Kidney Injury Network classification up to 7 days following CS. **Results:** The incidence of postoperative AKI was 62% in the frail group and 21% in the non-frail group. Frailty was associated with a higher risk of AKI (relative risk [RR] = 3.00, 95% CI 1.56 - 5.77, p = 0.00). In regression models, there were associations between frailty and postoperative AKI. **Conclusion:** This study demonstrated that frailty could be a predictor for post-CS AKI. Therefore, frailty assessment should become an essential part of the preoperative evaluation to help the anesthesiologist to estimate the surgical risk and develop preoperative and transoperative strategies to preserve the renal function and improve the cardiac surgery outcome.

Keywords

Cardiac Surgery, Heart-Lung Machine, Acute Kidney Injury, Frailty, Cardiopulmonary Bypass

1. Introduction

Acute kidney injury (AKI) is a severe common postoperative complication of cardiac surgery (CS), with an incidence of 20% - 70% [1] [2]. AKI is associated with extended hospital stay, intensive therapy unit stay, and increased mortality risk of up to 80% after CS; these complications significantly increase the surgery's cost, imposing a heavy load on the patients and public health systems [3]. Identifying at-risk patients is the first step in preventing postoperative AKI and its consequences [4]. But the available tools had not fulfilled the task. Despite different prediction models, the CS-AKI incidence remains high [5].

Several studies have outlined diverse risk factors to identify patients at risk for postoperative CS-AKI (post-CS AKI). Currently, there are multiple prediction models [5]. For example, the Cleveland Clinic Scoring System was developed in 2005. It is one of the most popular tools because it has the highest predictive value. It predicts severe AKI, but the prediction is weak for mild AKI; This leaves a significant proportion of patients at risk unidentified when it has been demonstrated that mild forms of AKI also have a substantial impact on morbidity and mortality [6].

The etiology of post-CS AKI is complex and unclear. Therefore, the diagnosis and prediction are complicated and interfere with adequate patient management [7]. Patients undergoing CS may experience multiple insults to the kidneys. Renal blood flow, the primary determinant of renal oxygen delivery, is positively correlated to mean arterial pressure during cardiopulmonary bypass (CPB). This suggests that blood pressure is vital in renal autoregulation, and lower pressures are linked with an imbalance of oxygen supply and demand. The medullary portion of the kidney may be susceptible to ischemic damage caused by low resting PO2 [8]. Following CS, a systemic inflammatory response can be related to postoperative AKI [9]. The physiological changes inherent to aging make the elderly a high-risk population.

The elderly account for 50% of cardiac surgical procedures performed yearly and 78% of total morbidity and mortality [10]. In recent years, the identification of vulnerable elderly patients and frail patients has emerged as an essential indicator for outcomes after CS [10] [11].

Currently, the population is experiencing significant demographic changes; world reports have shown that most people can live beyond 60 years old. Related to this, elderly patients access health services continuously, and therefore the issue of frailty involves not only geriatricians but also surgeons and anesthesiologists [12].

Frailty syndrome has been proposed as a marker of biological age and deterioration of physiologic systems over time [13]. Conceptually, it is defined as the diminished capacity to recover from pathologic stressors due to aging-related impairments and decreased physiological reserves, resulting in increased mortality risk in various health conditions [14].

Kader KA *et al.* demonstrated an association between frailty and AKI in criti-

cally ill patients [15]. Lee *et al.* in 2018 showed that AKI in survivors of critical illness predicted worse frailty status post-discharge, with important implications for clinical decision-making among AKI survivors and the need to understand the drivers of frailty to improve outcomes [16]. There is little information about the impact of frailty on AKI incidence and less data on patients who undergo CS with CPB.

We conducted this prospective cohort pilot study to assess the association of frailty and postoperative AKI in patients undergoing CS with CPB.

2. Materials and Methods

2.1. Cases Data

This pilot study was approved by the ethics committee and institutional review board of the Cardiology Hospital, National Medical Center Siglo XXI (CMN SXXI) of the Instituto Mexicano del Seguro Social (IMSS) in Mexico City. IBR number R-2018-3604-013. The STROBE guidelines were used to ensure correct reporting of this prospective observational study [17].

We included patients who underwent CS with CPB to determine if they had frailty syndrome before surgery and the association with postoperative AKI from August 1, 2018, to January 31, 2019. This sample exceeds the good practice recommendations for pilot studies of Lancaster *et al.* [18].

The inclusion criteria were patients ≥ 60 years old; undergoing CS with CPB; valve, coronary artery bypass graft surgery (CABG), and CABG with valve surgery combined. The exclusion criteria were: urgent and emergent surgeries; CPB time > 120 minutes; Aortic clamp > 90 minutes; sepsis; chronic kidney disease; cardiogenic shock; hypovolemic shock; Intra-aortic balloon pump counter pulsation (IABP); preoperative anemia and hematocrit (hct) levels < 21 mg/dl during CPB as a criterion of elimination.

2.2. Design

We applied the Fried frailty criteria to classify the study cohort. Patients were classified as frail if they met three or more of the following five criteria: [19] [20].

1) Unintentional weight loss of > 10 lbs (>4.5 kg) or >5% of body mass in the last year obtained from patient or caregiver;

2) Poor endurance, exhaustion. Information based on two questions from the Center for Epidemiological Studies Depression (CES-D) scale;

(a) I felt that everything I did was an effort.

(b) I could not get going.

Criterion positive if at least one condition is present for three days or more during the last week.

3) Weakness. Assessment based on the dominant handgrip strength measurement (mean of three sizes); interpretation considers sex and body mass index (BMI). A digital dynamometer was used for grip strength (Table 1);

4) Low physical activity (energy expenditure weekly rate calculated based on

the modified questionnaire Minnesota Leisure Time Activity Questionnaire) the physical activity criterion is positive if physical activity per week is for Male < 383 kcal/week and Female < 270 kcal/week;

5) Slow gait speed. Walking time over a distance of 15 ft. (4.57 m); interpretation of results considers sex and height (m).

The diagnosis of postoperative AKI was based on the serum creatinine (SCr) criteria of the Acute Kidney Injury Network (AKIN) classification. The severity grades were defined based on changes in serum creatinine. Stage 1: increase of ≥0.3 mg/dl or to 1.5 - 1.9 times baseline; stage 2: ≥2 - 2.9 times baseline and stage 3: ≥3 times baseline or ≥0.5 mg/dl increase to at least 4.0 mg/dl or RRT (renal replacement therapy). AKI was diagnosed up to 7 days following the CS with CPB [21].

Table 1. Dominant handgrip strength measurement.

Male		Female	
BMI	Cutoff (kg)	BMI	Cutoff (kg)
≤24	≤29	≤23	≤17
24 - 26	≤30	23-26	≤17.3
26 - 28	≤30	26-29	≤18
>28	≤32	>29	≤21

BMI: Body Mass Index.

2.3. Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges and as percentages for categorical variables. Data were statistically tested using Mann Whitney U or Chi-square tests when appropriate. A logistic regression analysis was used to evaluate the risk of AKI and its association with frailty status. P-values < 0.05 were considered statistically significant. Studies and calculations were conducted using SPSS Statistics V 21.0 (IBM, NY, USA).

3. Results

Ninety-one patients met the inclusion criteria and were included in the pilot study. No patients met the elimination criteria. The baseline data of the cohort are shown in Table 2. Fifty-two of ninety-one (57%) patients were frail. Most frail patients met the Fried frailty criteria of weakness, exhaustion, and weight loss; however, in non-frail patients, the standard of weakness was the most frequent.

AKI occurred in 40 (44%) participants; 62% of frail patients developed AKI; however, in the group of non-frail patients, only 21% did. Stage 1 was the most common type of AKI (93%). One patient had AKI stage II and another stage III; both were frail. Notably, frailty was associated with a higher risk of AKI relative risk RR = 3.00, 95% CI 1.56 - 5.77 p = 0.00 and non-frail patients relative risk RR = 0.48, 95% CI 0.33 - 0.70 p = 0.00 (see Figure 1).

Table 2. Baseline data: comparision between Frail, Non-Frail, and Overall.

Demographic Characteristics	Overall n = 91	Frail n = 52	Non-Frail n = 39	P-Value
Age, yrs	67 ± 5	68 ± 7	66 ± 5	0.18
Male/Female sex	57/34 (63/37%)	31/21 (60/40%)	26/13 (67/33%)	0.49
Body Mass Index, kg/m^2	27.2 ± 4.5	27 ± 4.6	27.4 ± 4.4	0.71
Comorbid conditions				
Diabetes	32 (35%)	18 (20%)	14 (15%)	0.89
Hypertension	76 (84%)	43 (48%)	33 (36%)	0.80
Dyslipidemia	18 (20 %)	11 (12%)	7 (8%)	0.60
LVEF %	58	59	57	0.34
Cardiac surgery risk scores				
STS mortality, %	1.55 ± 0.82	1.70 ± 0.89	1.35 ± 0.67	0.04
EuroSCORE, %	2.15 ± 1.12	2.2 ± 1.09	2.07 ± 1.16	0.58
Laboratory variables				
Hb (mg/dl)	13.93 ± 1.78	13.63 ± 1.77	14.33 ± 1.74	0.65
Hct (%)	41.62 ± 6.63	40.61 ± 7.45	42.97 ± 5.13	0.93
Glucose (mg/dl)	107.1 ± 22.6	107.42 ± 22.9	106.79 ± 22.4	0.89
Cr (mg/dl)	0.92 ± 0.18	0.93 ± 0.19	0.91 ± 0.19	0.59
Urea (mg/dl)	37 ± 11.3	38.19 ± 10.6	35.41 ± 12.1	0.25
Albumin (g/dl)	3.92 ± 0.55	3.84 ± 0.44	4.01 ± 0.66	0.19
CKD-EPI (GFR) (ml/min)	75.43 ± 17.16	74.36 ± 15.6	76.85 ± 19.16	0.49

LVEF = left ventricular ejection fraction; STS = Society of Thoracic Surgeons; EuroSCORE: European system for cardiac operative risk evaluation; CABG: coronary artery bypass graft surgery; CKD-EPI: chronic kidney disease epidemiology collaboration equation; GFR: Glomerular filtration rate; Hb: hemoglobin; Hct: hematocrit; Cr: creatinine.
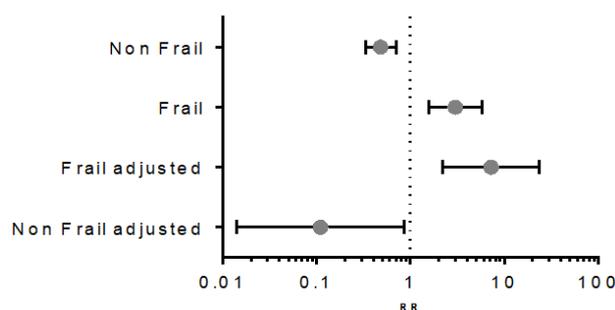
Figure 1. Association between frailty and AKI.

There were no differences in CPB time, ACC time, and lactate during CPB. Blood loss and blood product transfusion were similar (see Table 3).

Table 3. Intraoperative and postoperative data.

Variables during CPB	Overall n = 91	Frail n = 52	Non-Frail n = 39	P-Value
CPB time (min)	91 ± 21	90 ± 21	94 ± 20	0.36
ACC time (min)	70 ± 18	71 ± 31	70 ± 17	0.81
Maximum Lactate	2 ± 0.5	1.9 ± 0.4	2 ± 0.5	0.46
Uresis (ml)	448 ± 193	444 ± 217	452 ± 157	0.89
Minimum Temp (°C)	32 ± 1.5	32 ± 1.1	31.6 ± 1.6	0.19
Minimum MAP (mmHg)	53 ± 5.2	52.38 ± 5.5	52 ± 5.5	0.82
Variables post CPB				
Cr (mg/dl)	1.11 ± 0.3	1.25 ± 0.3	0.9 ± 0.3	0.07
Urea (mg/dl)	46.3 ± 14.5	50 ± 14.3	41 ± 14	0.00
Lactate (mmol/L)	2.1 ± 0.9	2 ± 0.5	2 ± 0.6	0.01
Blood loss (ml)	430 ± 166	417 ± 172	445 ± 162	0.54
Urine volume ml/k/hr	1.9 ± 0.7	2 ± 0.5	2.1 ± 0.8	0.36
RBC (ml)	379 ± 31	375 ± 42	389 ± 84	0.93
FFP (ml)	270 ± 30	275 ± 25	267 ± 28	0.72
Surgery time (min)	250 ± 92	256 ± 46	257 ± 43	0.46
Anesthesia time (min)	332 ± 31	337 ± 40	338 ± 41	0.85
AKI	**40 (44%)**	**32 (62%)**	**8 (21%)**	**0.00**

Temp: temperature; Hb: hemoglobin; Hct: hematocrit; Cr: creatinine; MAP: mean arterial pressure; CBP: cardiopulmonary bypass; ACC: aortic cross-clamp; RBC: red blood cells; FFP: fresh frozen plasma.

Figure 1 shows the relative risk for AKI according to the frailty status; the frailty group had a higher chance of AKI relative risk RR = 3.00, 95% CI 1.56 - 5.77, p = 0.00 and non-frail patients RR = 0.48, 95% CI 0.33 - 0.70, p = 0.00. The bottom of the figure shows the prediction of the frailty variable adjusted with the logistic regression model; there was an association between frailty and postoperative AKI Exp-B = 7.22 CI 95% 2.21 - 23.51 p = 0.001. Our regression model included: weakness, age > 65 years, hypertension, diabetes, dyslipidemia, albumin < 4 g/dl, and GFR < 70 ml/min. We had a value of Nagelkerke R Square of 0.402 and Wald test of 2.068, gl 1, p = 0.01.

The only criterion without difference between AKI and non-AKI patients was slow gait speed, but the weight loss criterion was present in 76% of patients with postoperative AKI (Figure 2).

The incidence of postoperative AKI in patients who had 3 - 5 points in the CCS was 18.7% and 9.9% in those with the lower score RR = 1.84, 95% CI 1.20 - 2.84, p = 0.01.
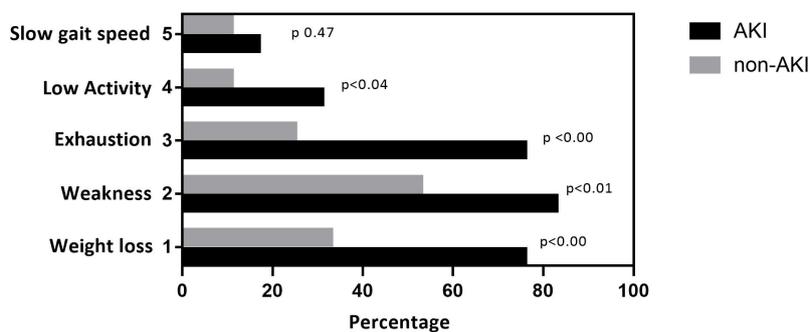
Figure 2. Fried frailty criteria and AKI status of the patients diagnosed as frails before the CS.

4. Discussion

AKI is a common major complication that increases the morbidity and mortality risk after cardiac surgery. Identifying at-risk patients is the first step to implementing preventive actions that may improve patient outcomes. Several tools predict AKI, like the stratification and score systems and some biomarkers. Still, the incidence of CS-AKI remains high and imposes a heavy burden on patients and health care systems. This study demonstrated that frailty could be used as a marker for post-CS AKI.

The complete cohort of the study showed an AKI incidence of 44%, which is between the boundaries reported by other authors; Qinglin Li *et al.*, in 2018, found that the most frequent causes of AKI in geriatric patients are infections 39.6%, hypovolemia 23.8%, cardiovascular events 15.9%, nephrotoxicity 12.0% and surgery 7.1%. Malnutrition is common in elderly patients, and several studies have found that preexisting malnutrition is associated with poor outcomes in AKI patients [22].

Frailty is prevalent with increasing age and confers a high risk for adverse health outcomes, including mortality, institutionalization, falls, and hospitalization. Morton S *et al.* reported that frail patients with AKI had an increased risk of death within one year (RR 2.79 [95% CI 1.66 - 4.71]) [23].

In CS, there are many risk factors for the development of AKI, including female sex, multiple comorbidities, previous cardiac surgery, COPD, DM, hypertension, obesity, hypercholesterolemia, and LVEF of <35%. Also, the intraoperative exposure to aminoglycoside antibiotics, the type of surgical procedure like complex cardiac surgery such as valve and coronary surgery combined and aortic arch surgery, and the CPB [24].

While CPB has been associated with an increased risk of AKI, just one systematic review of 33 randomized controlledtrials comparing on-pump CABG vs. off-pump CABG found an association between on-pump CABG and postoperative AKI. Still, Lamy A in 2009 and Shroyer AL in 2016 reported no reno-protective effects of off-pump surgery, with no significant differences between patients undergoing off-pump and on-pump CABG [25] [26].

In this cohort study, frailty was a predictor for the development of AKI during

the postoperative period of CS (Exp-B = 7.22 CI 95% 2.21 - 23.51), p < 0.001. Frail patients had higher AKI incidence, 62% vs. 21% in non-frail participants. We estimate the Cleveland Clinic Score and find that the patients who had 3-5 points had an increased risk of AKI RR = 1.84, 95% CI 1.20 - 2.84, p = 0.01, but the results show that the risk of AKI was higher in frailty patients RR = 3.00, 95% CI 1.56 - 5.77, p = 0.00.

The following considerations can explain the association between frailty and post-CS AKI. Frailty has been associated with inflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor-α (TNF α). Subsequently, frail patients can be vulnerable and have decreased physiological renal reserve. Finally, as commented previously in the surgical context of CS, frailty is a high-risk factor for adverse outcomes [27]. Ying Yang *et al.* Compared procalcitonin (PCT) to IL-6 and C-reactive protein in their association with frailty among hospitalized patients. IL-6 and PCT were linked with frailty (OR = 5.24; CI 95%, 1.62 - 16.94, p = 0.006) [28]. Renal injury in AKI involves immune cells and cytokines [29].

Given that frailty is associated with worse postsurgical outcomes, including AKI, we need to modify and increase patient fitness before surgery. This concept is known as prehabilitation and is studied mainly in kidney and liver transplants [30]. Prehabilitation, in most studies, means increasing aerobic activity for several weeks before surgery with home and clinic programs. These programs include exercise, nutrition, and mental health interventions [31].

Tze Pin Ng *et al.* in 2015 demonstrated that frailty could be improved. They used moderate physical exercise of 90 minutes and nutritional intervention. The exercise duration was 90 minutes per day, two days per week for 12 weeks, conducted by a qualified trainer, and 12 weeks of home-based exercises; the program was designed to improve strength and balance for older adults. The nutritional intervention considers energy requirements and caloric intake, and the cognitive training in 2-hour weekly sessions where they engaged in mental enhancing activities designed to stimulate short-term memory and to improve attention and information processing skills. Finally, over 12 months, frailty reduction rates in the intervention groups were significantly higher (35.6% - 47.8%) (OR 5.0) [32].

Preoperative renal risk stratification it's essential to develop strategies of early intervention. The present study contributes to all the studies that have addressed this issue and have shown the different risk factors for postoperative AKI in CS.

5. Strengths and Limitations

To our knowledge, this is the first study focused on assessing the association of frailty and postoperative AKI in patients undergoing CS. The results demonstrate that frailty is a novel predictor of AKI after CS, and frailty reduction strategies are essential as well as perioperative renal optimization. The study has limitations. This is a non-randomized study. In consequence, cause and

effect relationship cannot be established. We do not include AKI biomarkers like Cystatin C, Neutrophil gelatinase-associatedlipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and Microalbumin.

6. Conclusion

Acute kidney injury is a common postoperative complication of cardiac surgery with CPB, with an incidence of up to 44%. We found that frail patients have a three times higher risk of developing postoperative AKI after CS with CPB than non-frail patients (RR = 3.00, 95% CI 1.56 - 5.77) and that the preoperative frailty status is comparable with the currently used risk stratifications models and very easy to assess. We demonstrated that frailty syndrome is a predictor for the development of AKI during the postoperative period of CS. The preoperative assessment of frailty may help design preoperative and transoperative strategies to reduce the risk of AKI in frail patients.

Compliance with Ethical Standards

This study was approved by the ethics committee and institutional review board of the Cardiology Hospital, National Medical Center Siglo XXI (CMN SXXI) of the Instituto Mexicano del Seguro Social (IMSS) in Mexico City. IBR number R-2018-3604-013.

Informed Consent

Written informed consents were obtained from all recruited patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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