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Systematic Review

Determinants of acute kidney injury after cardiac surgery: a systematic review

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Acute kidney injury following cardiac surgery (CS-AKI) represents a severe postoperative complication, negatively impacting short-term and long-term mortality. Due to the lack of a specific treatment, effective prevention remains the most powerful tool to overcome the CS-AKI burden. Improving the preventive strategies is possible by establishing appropriate preoperative risk profiles. Various clinical models were proposed as a means to assist physicians in stratifying the risk of CS-AKI. However, these models are used for predicting severe forms of CS-AKI, while their predictive power for mild forms is insufficient. Our paper represents the first systematic approach to review all proposed preoperative risk factors and their predictive power. Our strategy is the starting point for selecting and comparing the predictive elements to be integrated into future risk models. Heart failure, chronic hyperglycemia, anemia, obesity, preoperative exposure to nephrotoxic drugs or contrast media, inflammation, proteinuria, and pre-existing kidney disease were systematically reviewed and were found to be associated with an increased risk of postoperative CS-AKI. As no externally validated and universally accepted risk models currently exist, the clinical judgment and a good knowledge of the preoperative risk factors in the light of new evidence may help personalize preoperative risk profiles as the cornerstone of prevention measures.

Keywords

Acute kidney injury; cardiac surgery; risk factors; risk prediction; risk stratification models

1. Introduction

Acute kidney injury (AKI) following open-heart surgery represents a severe postoperative complication, negatively impacting short-term and long-term mortality. Given the large number of patients undergoing cardiovascular surgery (CS), postoperative AKI incidence is high, ranging from 20% to 70% of cases (Vives et al., 2020). Severe forms of CS-AKI necessitating renal replacement therapy (RRT) have a lower prevalence ($\leq$ 4%) but are subject to high mortality rates ranging from 40% to 70% (Nadim et al., 2018; Vives et al., 2020). However, increased mortality was reported in less severe CS-AKI forms, as an increase of 0.5 mg/dL in serum creatinine is linked to an almost 3-fold higher thirty-day mortality (Duchnowski et al., 2018; Lassnigg, 2004). Furthermore, a small postoperative increase in serum creatinine (0.3 mg/dL) is associated with a significantly higher long-term mortality and a 3-fold higher risk of developing end-stage renal disease (ESRD) (Rydén et al., 2014).

Several important mechanisms are in charge for CS-AKI development: renal hypoperfusion (heart failure, cardiopulmonary bypass, hemorrhage events during surgery), inflammation and oxidative stress (tissue damage, blood passage through cardiopulmonary bypass circuit), use of nephrotoxic drugs and agents (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), exposure to contrast agents), embolic factors and genetic predisposition (Mariscalco et al., 2011; Tecson et al., 2018; Wang and Bellomo, 2017).

Various clinical models were proposed as a means to assist physicians in stratifying the risk of CS-AKI: Cleveland and modified Cleveland scores, Mehta score, and Simplified Renal Index (SRI) score (Huen and Parikh, 2012; O'Neal et al., 2016; Vives et al., 2020). However, these scores are used for predicting severe forms of CS-AKI, while their predictive power for mild forms is poor. There is an imperious need for improved strategies regarding the prevention, diagnosis, and treatment of AKI related to open-heart surgery. Early recognition of AKI plays an important role, since the cornerstone of CS-AKI management is represented by preventive measures, as there is no specific treatment.

The objective of this updated systematic review is to weigh the impact of all reported risk factors in the development of CS-AKI and pave the way to more robust prevention strategies.

2. Materials and methods

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist (Liberati et al., 2009).

3. Data Sources

We performed a systematic search in PubMed, ScienceDirect and Cochrane databases for articles published from January 2005 until October 2020 using the following query terms: "Preoperative risk factors", "Cardiac surgery related acute kidney injury", "Heart failure", "BNP", "NT-proBNP", "hs-cTnT", "cTnI", "CK-MB", "Type 1 diabetes mellitus", "Type 2 diabetes mellitus", "Hemoglobin A_{1c}", "Chronic hyperglycemia", "Anemia", "Obesity", "ACEi", "ARB", "Cardiac catheterization", "Coronary angiography", "High-sensitivity C-reactive protein", "C-reactive protein", "Red blood cell distribution width", "Cystatin C", "Creatinine", "eGFR", "Galectin-3", "Urine albumin to creatinine ratio", "Mild proteinuria", "Heavy proteinuria", "Coronary artery bypass graft surgery". The search was restricted to trials published in English. Disagreements were resolved by consensus.

3.1 Study Selection

Studies involving $\geq$ ten patients over 18 years of age that reported original data regarding the preoperative risk factors for the development of AKI related to specific cardiac surgery types were eligible. Trials were included if adverse renal outcome was defined according to KDIGO, AKIN, or RIFLE criteria (Khwaja, 2012; Lopes and Jorge, 2013). Non-human studies, papers available only in abstract, letters, case reports, and meta-analysis were excluded.

3.2 Data Extraction

Data extracted from each included study were: authors' last name, year of publication, type of study, the preoperative risk factors being evaluated, number of patients, age median/mean, the proportion of patients exposed to a particular risk factor (when available), type of surgical intervention, criteria used to define CS-AKI, number of CS-AKI events. When available, data are presented as percentages, mean/median values, risk ratio (RR), odds ratio (OR), and range of variation. Also, when reported, the ability of a particular preoperative risk factor to improve the prediction power of a clinical model was documented.

3.3 Outcomes

We assessed the risk of developing CS-AKI in relation to the various preoperative risk factors reported in the included trials.

3.4 Quality Assessment

The quality of the non-randomized included trials was assessed using the Newcastle-Ottawa scale for cohort studies concerning three criteria (study group selection, the comparability of the study groups, and the evaluation of the outcome of interest) (Stang, 2010). The risk of bias for randomized trials was appraised using the revised Cochrane Risk of Bias tool (RoB2) (Sterne et al., 2019).

4. Results

Our database search retrieved 841 results. The study selection process is illustrated in Fig. 1. After removing titles and abstracts irrelevant to the topic (n = 756), duplicates (n = 5), meta-analysis (n = 4), and studies that did not meet the inclusion criteria (n = 53), 23 papers were included for the systematic review.

Study design, patients' characteristics, the number of CS-AKI events and the AKI definition for each included study are summarized in Table 1. Twenty non-randomized cohort studies (Barodka et al., 2011; Belley-Côté et al., 2016; Borde et al., 2019; Coca et al., 2013, 2012; De Santo et al., 2009; Duchnowski et al., 2020; Han et al., 2017; Hertzberg et al., 2015, 2019; Huang et al., 2011; Jiang et al., 2018; Karkouti et al., 2011; Kocogulları et al., 2017; O'Sullivan et al., 2015; Oezkur et al., 2015; Özkaynak et al., 2014; Patel et al., 2012; Ranucci et al., 2013; Shlipak et al., 2011; Wyler von Ballmoos et al., 2018; Zou et al., 2019) and one randomized trial (van Diepen et al., 2018) were included. Fourteen studies were single center: Sweden (Hertzberg et al., 2015, 2019), Turkey (Kocogulları et al., 2017; Özkaynak et al., 2014), Germany (Oezkur et al., 2015), Italy (De Santo et al., 2009; Ranucci et al., 2013), Canada (Karkouti et al., 2011; van Diepen et al., 2018), Ireland (O'Sullivan et al., 2015), USA (Barodka et al., 2011), China (Jiang et al., 2018), India (Borde et al., 2019), Taiwan (Huang et al., 2011) and seven studies were multi-centric (Belley-Côté et al., 2016; Coca et al., 2013, 2012; Han et al., 2017; Patel et al., 2012; Shlipak et al., 2011; Wyler von Ballmoos et al., 2018).

The evaluated preoperative risk factors (Fig. 2) and their relation with CS-AKI varied across studies: three studies assessed hemodynamic risk factors (Belley-Côté et al., 2016; Hertzberg et al., 2019; Patel et al., 2012), six papers evaluated metabolic risk factors (De Santo et al., 2009; Hertzberg et al., 2015; Karkouti et al., 2011; Kocogulları et al., 2017; O'Sullivan et al., 2015; Oezkur et al., 2015), seven studies analyzed nephrotoxic drugs and agents (Barodka et al., 2011; Borde et al., 2019; Coca et al., 2013; Jiang et al., 2018; Özkaynak et al., 2014; Ranucci et al., 2013; van Diepen et al., 2018), one paper studied inflammatory risk factors (Han et al., 2017), and four papers examined other comorbidities (Coca et al., 2012; Huang et al., 2011; Shlipak et al., 2011; Wyler von Ballmoos et al., 2018). The AKI definitions differed between studies, KDIGO and AKIN being the most used ones.

Table 2 summarizes the impact (expressed by OR, RR, and confidence intervals - CI) of the different risk factors on the development of CS-AKI as estimated for each study.

Patients with preoperative heart failure or elevated biomarkers of hemodynamic stress (B-type natriuretic peptide - BNP and its precursor, N-terminal pro-B-type natriuretic peptide - NT-proBNP) presented an increased risk of postoperative CS-AKI (Belley-Côté et al., 2016; Hertzberg et al., 2019; Patel et al., 2012). Belley-Côté et al. (2016) showed that other hemodynamic biomarkers (hs-cTnT, cTnI, and CK-MB) were not associated with an increased risk of CS-AKI after multivariate adjustments.

Regarding the metabolic risk factors, Hertzberg et al. (2015) found that both type 1 and type 2 diabetes mellitus were associated with an increased risk of postoperative CS-AKI independently of pre-existing kidney disease. CS-AKI risk was higher in type 1 diabetes mellitus (OR 4.89, 95% CI 3.82-6.25) than type 2 diabetes mellitus (OR 1.27, 95% CI 1.16-1.40). A high preoperative level of hemoglobin $A_{1c}$is associated with a markedly increased risk of AKI after coronary artery bypass grafting (CABG) even in non-diabetic patients. Nonetheless, results have a limited impact due to the small number of patients and the low rate of CS-AKI events

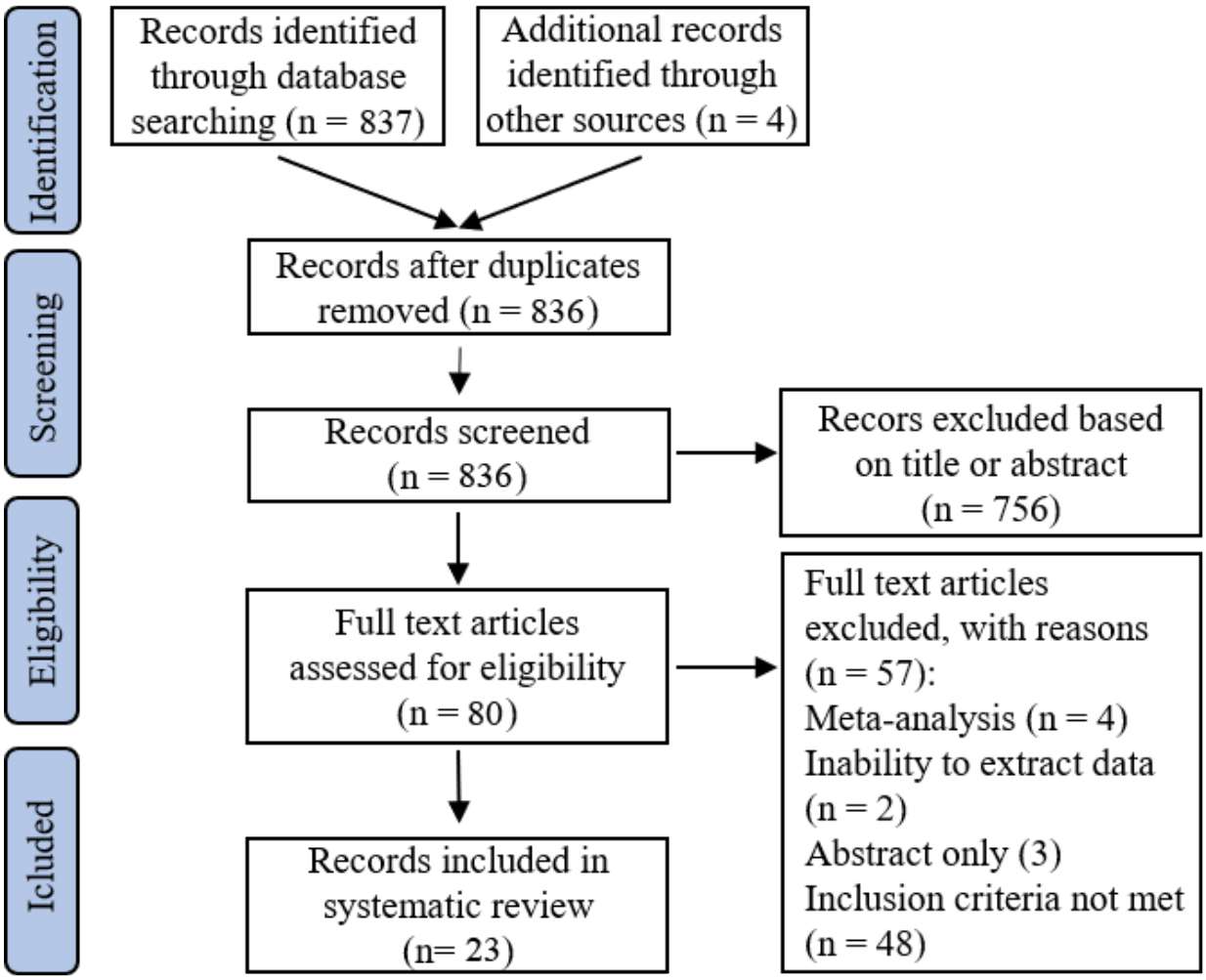

Fig. 1. Flow diagram representing the selection process of papers assessing the risk of developing acute kidney injury following cardiac surgery in relation to the various preoperative risk factors. The database search retrieved 841 papers. After removing titles and abstracts irrelevant to the topic, duplicates, meta-analysis, and studies that did not meet the inclusion criteria, 23 papers were included for the systematic review.

(n = 19, 9.4%). (Kocogulları et al., 2017). Similarly, Oezkur et al. (2015) reported that chronic hyperglycemia (hemoglobin $A_{1c} \geq$ 6.0%) is associated with a higher risk of CS-AKI in patients undergoing CABG regardless of diabetic status. The study is limited by the small size of the patients cohort (n = 307). Obesity (body mass index $\geq$ 30 kg/m^2) was also linked to an increased risk of postoperative CS-AKI after multivariate adjustments (O'Sullivan et al., 2015).

Preoperative anemia is significantly associated with CS-AKI, according to De Santo et al. (2009) and Karkouti et al. (2011). Besides, Karkouti et al. (2011) showed that erythrocyte transfusion on the day of surgery also correlated with higher postoperative AKI rates. Moreover, the correlative effect had a greater magnitude in anemic patients than those without anemia (P-value for trend $<$ 0.0001 vs. 0.1).

Data regarding preoperative treatment with ACEIs or ARBs is discordant. In a randomized trial, van Diepen et al. (2018) reported no difference in CS-AKI incidence between patients who continued the treatment with ACEI/ARB and those in whom treatment was discontinued two days before surgery (P = 0.991). Moreover, continued treatment with ACEI was not associated with higher intensive care unit length of stay (P = 0.420) or increased mechanical ventilation duration (P = 0.680). However, Coca et al. (2013) reported a higher risk of postoperative CS-AKI in patients who continued treatment with ACEI/ARB than those without a history of ACEI/ARB administration. Nonetheless, only patients exhibiting a high CS-AKI risk were enrolled, limiting the study's relevance regarding lower-risk patients. Unexpectedly, Barodka et al. (2011) reported a lower risk of CS-AKI in patients treated with ACEI/ARB. However, the small number of CS-AKI events (n = 19, 5.5%) is an essential limitation of the study.

Two studies (Jiang et al., 2018; Ranucci et al., 2013) assessing the impact of cardiac catheterization within seven days before surgery and coronary angiography on the same day as surgery reported an increased risk of postoperative CS-AKI. Moreover, Jiang et al. (2018) described an increased CS-AKI risk for a dose of contrast media (CM) $>$ 240 mg/kg (OR 2.490, 95% CI 1.392-4.457). Additionally, the incidence of CS-AKI was higher when cardiac surgery was performed within seven days after contrast exposure (with a dose of CM $>$ 240 mg/kg) compared to longer in-

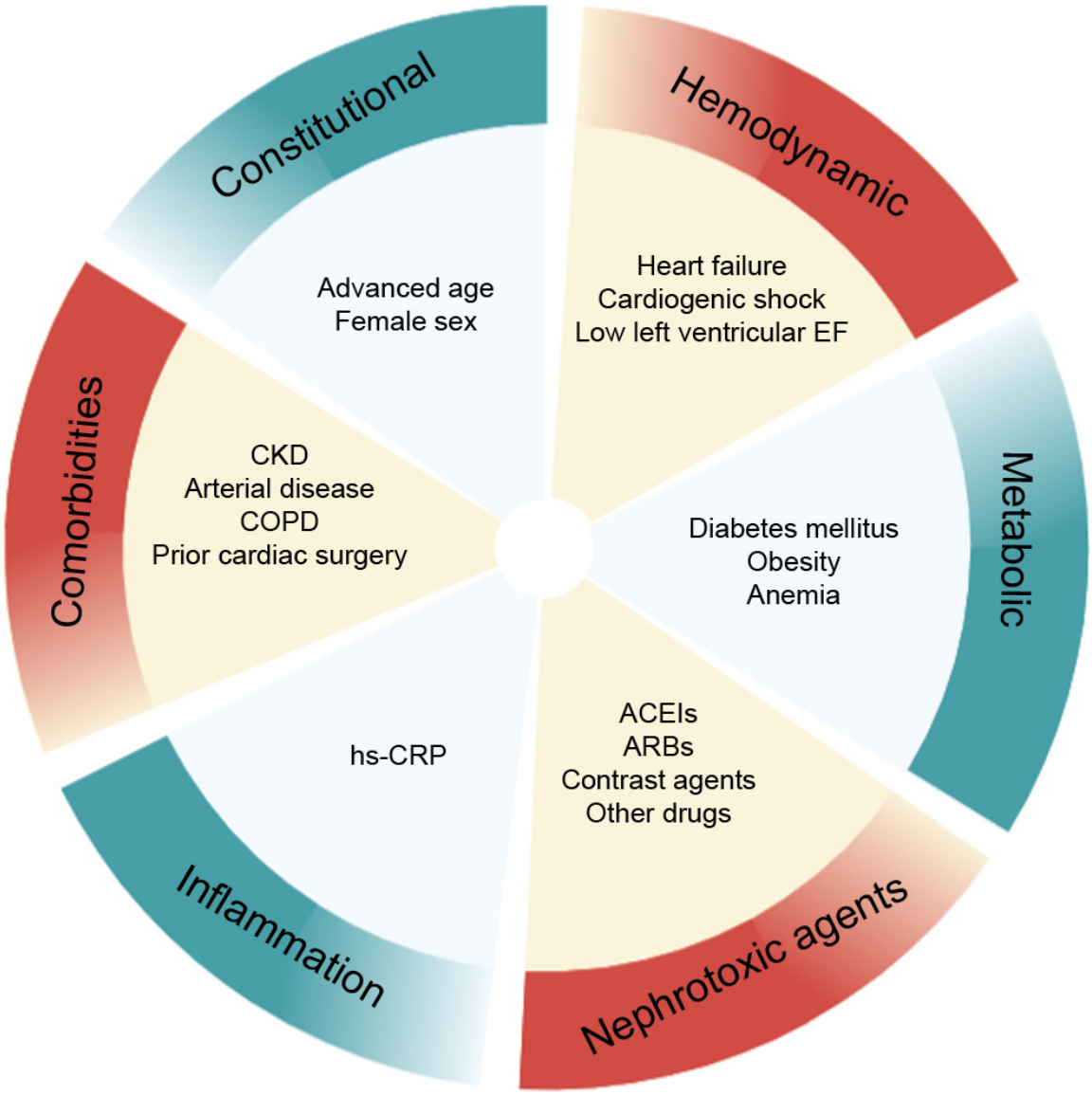

Fig. 2. Known preoperative risk factors for CS-AKI grouped into six categories. (EF - ejection fraction; ACEIs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; hs-CRP - High-sensitivity C-reactive protein; CKD - chronic kidney disease; COPD - chronic obstructive pulmonary disease).

tervals after exposure ($P = 0.025$). Borde et al. (2019) and Özkaynak et al. (2014) did not report a higher incidence of CS-AKI in patients who underwent coronary angiography within seven days before surgery (Borde et al., 2019) or in patients with prior cardiac catheterization (Özkaynak et al., 2014), respectively. However, the former study included only patients who underwent off-pump CABG, making it difficult to extrapolate the data to on-pump surgical techniques.

High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, was associated with CS-AKI. Han et al. (2017) reported that patients with higher hs-CRP levels exhibited a greater risk of CS-AKI after multivariate adjustments.

Pre-existing kidney disease represents an inherent risk factor for postoperative CS-AKI. Shlipak et al. (2011) reported that cystatin C had a stronger correlation with the risk of CS-AKI (OR 4.8, 95% CI 2.9-7.7) compared to creatinine or estimated glomerular filtration rate (eGFR). Besides, only the worst kidney function quintile was independently linked to a greater risk of severe CS-AKI (OR 3.6, 95% CI 1.3-10.1 for cystatin C and OR 2.0, 95% CI 0.9-4.5 for creatinine, respectively). However, no significant correlation between eGFR quintile categories and severe CS-AKI was identified.

Galectin-3 is used as a cardiac biomarker in chronic kidney disease patients. Wyler von Ballmoos et al. (2018) reported that patients with higher levels of Galectin-3 had an approximately three-fold higher risk of stage 2 or 3 CS-AKI and a two-fold more significant risk of stage 1 CS-AKI. Preoperative urine albumin to creatinine ratio (UACR) and dipstick proteinuria was associated with an increased risk of postoperative CS-AKI, as reported by Coca et al. (2012) and Huang et al. (2011). However, most of the patients included in the former study experienced only mild CS-AKI, limiting the ability to assess a relationship between proteinuria and

Table 1. Characteristics of included studies in present systematic review.

Author, year	Type of study	RF evaluated	Patients, No	Patients with RF, No (%)	Type of surgical intervention	Age median/ mean	Acute kidney injury	
							Definition used	Events, No (%)
Hemodynamic risk factors								
(1) (Hertzberg et al., 2019)	Cohort study	Heart failure	36403	3914 (11)	First isolated CABG	67	KDIGO	4432 (14) no RF 1000 (26) with RF
(2) (Patel et al., 2012)	Cohort study	BNP levels	1139	Stratified in quintiles	CABG only, valve only, or both	72	AKIN	465 (41)
(3) (Belley-Côté et al., 2016)	Cohort study	NT-proBNP hs-cTnT cTnI CK-MB	960	Stratified in tertiles	CABG only, valve only, or both	71.53 (no AKI) 70.7 (severe AKI)	Severe AKI - doubling in SCr from baseline, or RRT	37 (3.9) - severe AKI
Metabolic risk factors								
(4) (Hertzberg et al., 2015)	Cohort study	Diabetes mellitus	36106	5581 (15.3)	Primary nonemergent isolated CABG	67.4	AKIN	5199 (14)
(5) (Kocogulları et al., 2017)	Cohort study	Hemoglobin A_{1c}	202	90 (44.5) - with $HbA_{1c} \geq 5.6$ %	Isolated CABG	63.0 ($HbA_{1c} < 5.6$ %) 60.0 ($HbA_{1c} \geq 5.6$ %)	KDIGO	19 (9.4)
(6) (Oezkur et al., 2015)	Cohort study	Chronic hyperglycemia	307	165 (53.7)	Isolated CABG or combination procedures	69	KDIGO	148 (48.2)
(7) (De Santo et al., 2009)	Cohort study	Anemia	1047	320 (28)	Isolated CABG	63.2	RIFLE	42 (4)
(8) (Karkouti et al., 2011)	Cohort study	Anemia	12388	2287 (18.4)	Isolated CABG, valve surgery or other procedures	66 (anemia) 62 (no anemia)	RIFLE	256 (2)
(9) (O'Sullivan et al., 2015)	Cohort study	Obesity	432	128 (29.6)	Isolated CABG, CABG and concomitant procedure, valve surgery, pericardiectomy, Redo procedure, subaortic membrane resection	65.29 (obesity) 66.37 (no obesity)	AKIN and KDIGO	57 (13.2)
Use of nephrotoxic drugs and agents								
(10) (Coca et al., 2013)	Cohort study	ACEi/ARB	1594	231 (14.5) with continued ACEi/ARB	CABG and/or valve surgery	73 (no ACEi/ ARB) 70 (with ACEi/ ARB)	↑SCr $\geq$ 50% or $\geq$ 0.3 mg/dL from baseline	543 (34.7)
(11) (Barodka et al., 2011)	Cohort study	ACEi/ARB	346	122 (35.26)	CABG or valve surgery	74	↑SCr $>$ 2.0 mg/dL or 2x times from baseline, RRT	19 (5.5)
(21) (van Diepen et al., 2018)	Randomized study	ACEi/ARB	126	60 (47.6) with continued ACEi/ARB	CABG and/or valve surgery	67 (with ACEi/ ARB) 64 (no ACEi/ ARB)	↑SCr 2x times baseline or ↓GFR $>$ 50%	2 (1.6)
(12) (Jiang et al., 2018)	Cohort study	Cardiac catheterization	1069	888 (83.1) surgery $\leq$ 7 days 181 (16.9) surgery $>$ 7 days	Isolated CABG, valve surgery or both	61.3 surgery $\leq$ 7 days 63.9 surgery $>$ 7 days	KDIGO	412 (38.5)

Table 1. Continued.

Author, year	Type of study	RF evaluated	Patients, No	Patients with RF, No (%)	Type of surgical intervention	Age median/ mean	Acute kidney injury	
							Definition used	Events, No (%)
(13) (Ranucci et al., 2013)	Cohort study	Coronary angiography	4440	552 (12.4)	Isolated CABG, valve surgery, CABG and other procedures	65.8 (no AKI) 69.8 (with AKI)	AKIN	961 (21.7)
(14) (Borde et al., 2019)	Cohort study	Coronary angiography	900	210 (23.3) surgery $\leq$ 7 days 690 (76, 7) surgery $>$ 7 days	Isolated CABG	60	KDIGO	214 (24)
(15) (Özkaynak et al., 2014)	Cohort study	Cardiac catheterization	573	Stratified in groups	CABG and/or valve surgery or other procedures	59.3	AKIN	233 (41)
Inflammatory risk factors								
(16) (Han et al., 2017)	Cohort study	High-sensitivity C-reactive protein	1656	Stratified in tertiles	Isolated CABG	64.7	KDIGO	549 (33.2)
Other comorbidities								
(17) (Shlipak et al., 2011)	Cohort study	Pre-existing kidney disease (creatinine, eGFR, cystatin C)	1147	Stratified in quintiles	Isolated CABG, valve surgery or both	71	AKIN	407 (36)
(18) (Wyler von Ballmoos et al., 2018)	Cohort study	Galectin-3	1498	Stratified in tertiles	Isolated CABG	64.02 (no AKI) 68.08 (with AKI)	KDIGO	568 (37.9)
(19) (Coca et al., 2012)	Cohort study	Urine albumin to creatinine ratio	1159	Stratified in groups	Isolated CABG, valve surgery or both	Stratified in groups	AKIN	409 (35.2)
(20) (Huang et al., 2011)	Cohort study	Proteinuria (dipstick)	1052	315 (29.9) with mild proteinuria 138 (13.1) with heavy proteinuria	Isolated CABG	65.7	AKIN	183 (17.4)
(21) (Zou et al., 2019)	Cohort study	RDW	13420	10274 (76) unmatched cohort 3146 (24) matched cohort	Isolated CABG	53.3	KDIGO	32.80%
(22) (Duchnowski et al., 2020)	Cohort study	RDW	751	Stratified in groups	Valve surgery	63.5	$\uparrow$SCr $>$ 0.3 mg/dL or urine volume $<$ 0.5	46 (6%)

more severe CS-AKI. Notably, the latter study reported that more severe proteinuria had a higher risk of CS-AKI necessitating RRT (OR 7.29, 95% CI 3.00-17.73, $P = 0.004$).

The quality of non-randomized studies was assessed using the Newcastle-Ottawa scale for cohort studies, and the results are summarized in Supplemental (Table 1). RoB2 assessed the risk of bias of the randomized trial (van Diepen et al., 2018), and the overall risk of bias was estimated as low.

5. Discussions

Our paper represents the first systematic approach to review all proposed preoperative risk factors and their predictive power.

Our strategy is the starting point for selecting and comparing the predictive elements to be integrated into future risk models. Systematically reviewing all risk factors is useful for both physicians and patients as the timely identification and correction (when possible) of preoperative risk profiles may result in safer surgical strategies and better postoperative outcomes.

CS-AKI represents a frequent complication without a specific treatment. Effective prevention, thus, remains the most powerful tool to overcome this problem. Improving the preventive strategies is possible by establishing appropriate preoperative risk profiles. Current clinical models display a low predictive value for milder forms of CS-AKI, although less severe forms are more common and have a negative impact on short and long-term mortality. Therefore, new and integrative models are needed to encompass risk predictions for all severity categories accurately. Before the construction of new models, the first essential step is to comprehensively review all updated original work studying preoperative risk factors for CS-AKI.

Management of pre-existing heart failure is vital as it is associated with a higher incidence of postoperative CS-AKI. Hertzberg et al. (2019) stratified the CS-AKI risk according to the left ventricular ejection fraction (EF). Patients with an EF lower than 30% had a greater risk of CS-AKI than those with a higher EF (OR 1.32, 95% CI 1.06-1.65). In addition, heart failure was associated with increased 30-day mortality. However, an important limitation of this study is that left ventricular filling pressures and relaxation were not considered. Also, patients with high BNP and NT-proBNP levels had a greater incidence of postoperative CS-AKI, as reported by Patel et al. (2012), and Belley-Côté et al. (2016). BNP levels enhanced the clinical model's predictive performance proposed by Patel et al. (2012). In addition, Belley-Côté et al. (2016) reported a higher 1-year mortality in patients with elevated NT-proBNP (OR 1.70, 95% CI 1.35-2.14, $P < 0.0001$), especially for the NT-proBNP highest tertile (OR 27.2, 95% CI 3.46-213.5, $P = 0.002$). However, both studies enrolled patients with a high CS-AKI risk, limiting the study's relevance for patients with a low preoperative risk profile.

A significant number of patients undergoing cardiac surgery have diabetes mellitus, another critical risk factor for CS-AKI. Hertzberg et al. (2015) showed that the therapeutic regimen influences CS-AKI risk in diabetic patients. A greater risk was reported in patients treated with insulin whether combined with oral antidiabetic drugs or not (OR 1.82, 95% CI 1.61-2.06) compared to those treated with oral antidiabetic medication only (OR 1.23, 95% CI 1.08-1.41) or diet only (OR 1.13, 95% CI 0.93-1.38). Moreover, Kocogulları et al. (2017) and Oezkur et al. (2015) reported that chronic hyperglycemia (defined by a high preoperative level of hemoglobin A_{1c}) was associated with postoperative CS-AKI, irrespective of a confirmed diagnosis of diabetes mellitus. This suggests that hemoglobin A_{1c} levels may be useful in the preoperative risk stratification, even for non-diabetic patients. Nonetheless, higher hemoglobin A_{1c} levels were not linked to an increased postoperative mortality or necessity of RRT. Furthermore, obesity represents a potentially modifiable risk factor independently associated with postoperative CS-AKI (O'Sullivan et al., 2015), pointing up the importance of body weight control.

De Santo et al. (2009) and Karkouti et al. (2011) reported that patients with anemia or erythrocyte transfusions had an increased incidence of postoperative CS-AKI. These results indicate that early correction of anemia may play an essential role in reducing the postoperative risk.

International consensus guidelines advocate for preoperative discontinuation of ACEIs and ARBs (Nadim et al., 2018), although data regarding their CS-AKI development risk is discordant. Coca et al. (2013) reported an increased risk of CS-AKI for patients treated with ACEIs or ARBs. Conversely, a randomized trial (van Diepen et al., 2018) revealed similar risks after medication discontinuation. Surprisingly, Barodka et al. (2011) revealed a protective effect of the preoperative treatment with ACEIs or ARBs against CS-AKI development. However, the latter study only included patients over 65 years, limiting the results' interpretation for the younger population.

The international consensus recommends no exposure to contrast agents 24 to 72 h before cardiac surgery (2C level of evidence) (Nadim et al., 2018), although studies are inconsistent. A single-center study from China (Jiang et al., 2018) reported that the dose of the contrast agent is also essential, suggesting that patients receiving a dose higher than 240 mg/kg should postpone the surgery (> 7 days). Ranucci et al. (2013) described an increased risk of postoperative CS-AKI in patients exposed to contrast agents on the surgery day. Conversely, two studies (Borde et al., 2019; Özkaynak et al., 2014) reported no influence of the contrast exposure on CS-AKI incidence. However, a subgroup analysis (Borde et al., 2019) showed that patients with pre-existing kidney disease (eGFR < 50 mL/min) had a greater risk of postoperative CS-AKI (OR 2.70, 95% CI 1.4-5.4, $P = 0.005$) when surgery was performed within seven days after coronary angiography. Thereby, a personalized approach that integrates the time difference between the two interventions, the contrast agents type, and dose, and the preoperative kidney function may prove to be more effective than the time interval strategy alone.

A South Korean observational study (Han et al., 2017) revealed that patients with high hs-CRP levels had an increased risk of postoperative CS-AKI after excluding septic patients (OR 1.88, 95% CI 1.392-2.525, $P < 0.001$). Moreover, a preoperative hs-CRP greater than 1 mg/dL was linked to a higher long-term mortality (HR 1.55, 95% CI 1.261-1.914, $P < 0.001$). High-sensitive CRP represents a cost-effective, routinely available biomarker for CS-AKI risk stratification in preoperative settings.

The preoperative kidney function is crucial as it indicates the baseline functional reserve and may identify the patients with a high risk of CS-AKI. Preoperative serum creatinine, cystatin C,

Table 2. Results reported in studies included in present systematic review.

Author, year	Risk Factor	RR/OR (95% CI)	*P* value
(Hertzberg et al., 2019)	Heart failure	OR 1.12 (1.02-1.23)	–
(Patel et al., 2012)	BNP (highest quintile)	RR 1.87 (1.40-2.49) - at least mild AKI RR 3.17 (1.06-9.48) - severe AKI	< 0.0001 (for trend) 0.049 (for trend)
(Belley-Côté et al., 2016)	NT-proBNP	OR 1.39 (1.03-1.88)	0.03
	hs-cTnT	OR 1.17 (0.84-1.61)	0.4
	cTnI	OR 1.22 (0.92-1.63)	0.2
	CK-MB	OR 1.55 (0.94-2.58)	0.1
(Hertzberg et al., 2015)	Type 1 diabetes mellitus	OR 4.89 (3.82-6.25)	–
	Type 2 diabetes mellitus	OR 1.27 (1.16-1.40)	
(Kocogulları et al., 2017)	Hemoglobin A_{1c}	OR 11.17 (2.21-56.33)	0.003
(Oezkur et al., 2015)	Chronic hyperglycemia ($HbA_{1c} \geq 6.0\%$)	OR 1.65 (1.00-2.71)	0.049
(De Santo et al., 2009)	Anemia	OR 2.06 (1.14-3.70)	0.016
(Karkouti et al., 2011)	Anemia	–	0.0007
(O'Sullivan et al., 2015)	Obesity	OR 2.12 (1.27-3.54)	0.004
(Coca et al., 2013)	ACEi/ARB	RR 1.24 (1.02-1.5)	–
(Barodka et al., 2011)	ACEi/ARB	OR 0.19 (0.04-0.84)	0.029
(van Diepen et al., 2018)	ACEi/ARB	–	0.991
(Jiang et al., 2018)	Cardiac catheterization within 7 days	OR 2.546 (1.548-4.189)	< 0.001
(Ranucci et al., 2013)	Coronary angiography on the same day	OR 1.58 (1.04-2.40)	0.031
(Borde et al., 2019)	Coronary angiography within 7 days	OR 1.32 (0.93-1.9)	0.13
(Özkaynak et al., 2014)	Cardiac catheterization	–	0.09
(Han et al., 2017)	High-sensitivity C-reactive protein	OR 1.86 (1.387-2.489)	< 0.001
(Shlipak et al., 2011)	Cystatin C (highest quintile)	OR 4.8 (2.9-7.7)	–
	Creatinine (highest quintile)	OR 1.8 (1.2-2.6)	–
	eGFR (highest quintile)	OR 1.7 (1.1-2.3)	–
(Wyler von Ballmoos et al., 2018)	Galectin-3 (highest tertile)	OR 2.95 (1.63-5.34) - AKI stage 2 or 3 OR 1.71 (1.24-2.37) - AKI stage 1	< 0.001 0.001
(Coca et al., 2012)	Urine albumin to creatinine ratio 30-299 mg/g	RR 1.64 (1.33-1.97)	–
	Urine albumin to creatinine ratio $\geq$ 300 mg/g	RR 2.21 (1.66-2.73)	–
(Huang et al., 2011)	Mild proteinuria (dipstick)	OR 1.66 (1.09-2.52)	0.018
	Heavy proteinuria (dipstick)	OR 2.30 (1.35-3.90)	0.002
(Zou et al., 2019)	RDW	OR 1.3 (1.21-1.4)	< 0.001
(Duchnowski et al., 2020)	RDW	OR 1.59 (1.21-2.54)	0.003

and eGFR are used for evaluating kidney function. Mainly, cystatin C displays a stronger association with postoperative CS-AKI compared to the others (Shlipak et al., 2011). However, only serum creatinine and eGFR are routinely used due to lower costs.

Galectin-3 is a novel biomarker linked to chronic kidney disease, heart failure, and inflammation. Wyler von Ballmoos et al. (2018) reported that patients with a high concentration of Galectin-3 had a greater incidence of CS-AKI, and the addition of Galectin-3 improved the predictive power of the existing clinical models.

Coca et al. (2012) and Huang et al. (2011) reported that UACR and dipstick proteinuria was associated with a higher risk of CS-AKI. However, there was no association between proteinuria and CS-AKI in patients with eGFR < 45 mL/min/1.73 m^2 (Coca et al., 2012). These results suggest that proteinuria should be incorporated in CS-AKI prediction clinical models. Dipstick proteinuria is an inexpensive alternative to UACR. Its cost-effectiveness may facilitate the integration in clinical risk models.

Regarding preoperative intra-aortic balloon pump (IABP) placement, the international consensus position (Nadim et al., 2018) is that IABP could have a beneficial effect on postoperative CS-AKI incidence. This is based on the results of a meta-analysis of 17 studies (Wang et al., 2016) reporting that the preoperative placement of IABP in patients at high risk was associated with a lower incidence of AKI after CABG (OR 0.54, 95% CI 0.36-0.79, $P = 0.002$).

6. Conclusions

Our study may be regarded as a source of analysis of recent studies on risk factors of AKI after cardiac surgery. AKI following cardiac surgery represents a frequent and severe complication. As there is no specific treatment, prevention measures that identify and minimize preoperative risk factors play a crucial role. Heart failure, chronic hyperglycemia, anemia, obesity, preoperative exposure to nephrotoxic drugs or contrast media, inflammation, proteinuria, and pre-existing kidney disease are associated with an increased risk of postoperative CS-AKI. To date, there are no externally validated or universally accepted clinical models to accurately predict postoperative CS-AKI occurrence, especially in

non-severe clinical forms. For this reason, the clinical judgment and a good knowledge of the preoperative risk factors in the light of new evidence may help to personalize preoperative risk profiles as the cornerstone of prevention measures.

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Authors' contributions

Concept/design: CB, GT;
Data collection: CB, GT;
Data analysis/interpretation: all authors;
Drafting article: all authors;
Critical revision of article: AB, IVP;
Approval of article: all authors.

Conflict of Interest

The authors declare no conflict of interest.

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