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Kidney Injury after Cardiac Surgery: Prevention-Associated Cost Reduction

Lesão Renal no Pós-Operatório de Cirurgia Cardíaca: Redução de Custos Associada à Prevenção

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ABSTRACT

Introduction: Cardiac surgery may induce acute kidney injury and the need for renal replacement therapy. It is also associated with higher hospital costs, morbidity and mortality. The aims of this study were to investigate predictors of cardiac surgery associated acute kidney injury in our population and to determine the burden of acute kidney injury in elective cardiac surgery, evaluating the potential cost effectiveness of preventing it through the application of the Kidney Disease: Improving Global Outcomes bundle of care to high-risk patient groups identified by the [TIMP-2]x[IGFBP7] used as a screening test.
Methods: In a University Hospital single-center retrospective cohort study we analyzed a consecutive sample of adults who underwent elective cardiac surgery between January and March 2015. A total of 276 patients were admitted during the study period. Data from all patients was analyzed until hospital discharge or the patient's death. The economic analysis was performed from the hospital costs' perspective.
Results: Cardiac surgery associated acute kidney injury occurred in 86 patients (31%). After adjustment, higher preoperative serum creatinine (mg/L, OR_{adj} = 1.09; 95% CI: 1.01 – 1.17), lower preoperative hemoglobin (g/dL, OR_{adj} = 0.79; 95% CI: 0.67 – 0.94), chronic systemic hypertension (OR_{adj} = 5.00; 95% CI: 1.67 – 15.02), an increase in cardiopulmonary bypass time (min, OR_{adj} = 1.01; 95% CI: 1.00 – 1.01) and perioperative use of sodium nitroprusside (OR_{adj} = 6.33; 95% CI: 1.80 – 22.28) remained significantly associated with cardiac surgery related acute kidney injury. The expected cumulative surplus cost for the hospital linked with cardiac surgery associated acute kidney injury (86 patients) was €120 695.84. Based on a median absolute risk reduction of 16.6%, by dosing kidney damage biomarkers in every patient and using preventive measures in high-risk patients, we would expect a break-even point upon screening 78 patients, which would translate, in our patient cohort, into an overall cost benefit of €7145.
Conclusion: Preoperative hemoglobin, serum creatinine, systemic hypertension, cardiopulmonary bypass time and perioperative use of sodium nitroprusside were independent predictors of cardiac surgery associated acute kidney injury. Our cost-effectiveness modelling suggests that the use of kidney structural damage biomarkers combined with an early prevention strategy could be associated with potential cost savings.
Keywords: Acute Kidney Injury/economics; Acute Kidney Injury/etiology; Biomarkers; Cardiac Surgical Procedures/adverse effects; Hospital Costs; Risk Factors

RESUMO

Introdução: A cirurgia cardíaca pode induzir lesão renal aguda e levar à necessidade de terapêutica de substituição renal. A esta cirurgia associam-se também maiores custos hospitalares, morbilidade e mortalidade. Os objetivos deste estudo foram investigar os preditores de lesão renal aguda associada a cirurgia cardíaca na nossa população e determinar o impacto da lesão renal aguda na cirurgia cardíaca eletiva. Avaliou-se também o potencial custo-efetividade da sua prevenção através da aplicação do *Kidney Disease: Improving Global Outcomes bundle of care* a grupos de doentes de alto risco identificados pelo [TIMP-2]x[IGFBP7] como teste de rastreio.
Métodos: Foi realizado um estudo retrospetivo num centro hospitalar universitário, onde foi analisada uma amostra consecutiva de adultos que foram submetidos a cirurgia cardíaca eletiva entre janeiro e março de 2015. Durante o período do estudo, foram admitidos no total 276 doentes. Os dados de todos os doentes foram analisados até à alta hospitalar ou morte do doente. Foi realizada uma análise económica da perspetiva de custos para o hospital.
Resultados: Oitenta e seis doentes (31%) desenvolveram lesão renal aguda no pós-operatório de cirurgia cardíaca. Após ajuste, os valores elevados de creatinina sérica pré-operatória (mg/L, OR_{adj} = 1,09; IC 95%: 1,01 – 1,17), hemoglobina pré-operatória baixa (g/dL, OR_{adj} = 0,79; IC 95%: 0,67 – 0,94), hipertensão arterial sistémica crónica (OR_{adj} = 5,00; IC 95%: 1,67 – 15,02), tempo prolongado de circulação extra-corporal (min, OR_{adj} = 1,01; IC 95%: 1,00 – 1,01) e o uso perioperatório de nitroprussiato de sódio (OR_{adj} = 6,33; IC 95%: 1,80 – 22,28) mantiveram-se significativamente associados a lesão renal aguda no pós-operatório de cirurgia cardíaca. O custo cumulativo foi de €120 695,84. Baseando-nos numa redução de risco absoluta de 16,6%, ao dosear os biomarcadores de lesão renal estrutural em todos os doentes juntamente com medidas preventivas de lesão renal aguda nos doentes de alto risco, esperaríamos um ponto de equilíbrio ao tratar 78 doentes, que se traduziria, na nossa coorte, num benefício total de custos de €7145.
Conclusão: A hemoglobina pré-operatória, creatinina sérica, hipertensão sistémica, tempo de *bypass* cardiopulmonar e o uso perioperatório de nitroprussiato de sódio foram preditores independentes de lesão renal aguda associada a cirurgia cardíaca. O nosso modelo de custo-efetividade sugere que o uso de biomarcadores renais em combinação com estratégias preventivas precoces poderá estar relacionado com uma potencial poupança de custos.
Palavras-chave: Biomarcadores; Custos Hospitalares; Fatores de Risco; Lesão Renal Aguda/económica; Lesão Renal Aguda/etiologia; Procedimentos Cirúrgicos Cardíacos/efeitos adversos

INTRODUCTION

Acute kidney injury (AKI) complicates 22% to 36% of cardiac surgery (CS) procedures, which ultimately increases hospital costs, morbidity and mortality.[1-3] In the United States, incremental costs go further than one billion

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United States dollars (USD).[4] Cardiac surgery associated acute kidney injury (CS-AKI) requiring dialysis raises risk of progression to end-stage kidney disease and mortality rate up to 60%.[3,5]

Rapidly worsening renal function in CS-AKI is the net result of perioperative insults and its chances of reversibility are poor.[6] Therefore, most efforts have been directed towards the development of prevention strategies in high-risk patient groups.[7,8] The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline includes various recommendations to prevent AKI in high-risk patients (KDIGO bundle of care).[7]

There are many known risk factors associated with CS-AKI, reported in Table 1.[9-11] Derived from these, several risk scoring systems have shown high negative predictive value, but lower reliability in high-risk group discrimination.[12] Improved performance of these scoring systems can be achieved by combining clinical risk factors with kidney structural damage and functional biological markers (biomarkers).[13] Biomarkers are indicators of normal biological processes, pathogenic processes, or response to an intervention.[14] The traditional biomarkers of CS-AKI are serum creatinine and urine output, reflecting a decrease in glomerular filtration rate (GFR). These two markers are robust late markers of AKI employed in the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) and KDIGO scores. However, they fail to translate early nephron stress or injury and can be influenced by non-renal conditions.[15]

Recent advances in biology have yielded finer grained biomarkers (damage biomarkers) that may enable earlier and more specific identification of kidney injury with potential impact in risk prediction.[16] These new molecules, biological substances, and cellular and molecular patterns have been discovered in urine and serum and correlate with different types, phases, and pathways of AKI. Tubular injury can be detected by damage biomarkers, whereas the degree of organ failure is estimated through the use of functional biomarkers such as serum creatinine or urine output, complementing each other.[16]

Point-of-care tests to assess damage biomarkers are available mostly as research tools for neutrophil gelatinase associated lipocalin (NGAL) and combined tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein7 {[TIMP-2]x[IGFBP7]}. TIMP-2 and IGFBP7 are metalloproteinases that induce G1 cell cycle arrest and can be found in urine to predict, diagnose and assess the severity of AKI.[13,16,17] The use of these tests in clinical practice requires considerable investment and its cost-effectiveness is yet to be clarified.[17,18]

The aim of this study was to investigate predictors of CS-AKI in our population and to determine the burden of AKI in elective cardiac surgery. We also modelled the potential cost effectiveness of preventing it through the application of the KDIGO bundle of care to high-risk patient groups identified by the [TIMP-2]x[IGFBP7] used as a screening test.

METHODS

Ethics statement

The study was approved by the local Hospital Ethics Committee. Patient consent was waived due to the retrospective and observational nature of the research.

Study design

A consecutive retrospective cohort of 276 adult patients who underwent elective cardiac surgery of all types between January 2nd and March 31st of 2015 at the Department of Cardiothoracic Surgery of a tertiary university hospital.

Data collection

Data was collected from available electronic health records and physician notes, from the period of 24 hours

Table 1 – Risk Factors for cardiac surgery associated acute kidney injury described in the literature[8-12]

Risk Factors/Predictors				
Anthropometric	**Comorbidities**	**Surgery**	**Nephrotoxic**	**Analytical**
Age	BMI	Urgency	RASI	Preoperative anemia
Female sex	Diabetes	Type of surgery (valvular)	Aminoglycosides	Baseline GFR
	COPD	Reintervention	Non-steroidal anti-inflammatory agents	Preoperative serum creatinine
	Chronic kidney disease	CPB time	Contrast	
	Reduced left ventricular ejection fraction	Clamping time		
	Heart failure (NYHA class)	Nadir HTC		
	HTN	RBC transfusion		
	PAD			

before surgery to hospital discharge or death. Variables were: (i) preoperative data (at admission): age, gender, body mass index (BMI); diagnostic tests: hemoglobin, serum creatinine, serum urea, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF); comorbidities: chronic systemic hypertension (HTN) (defined as persistent systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg according to the 2020 International Society of Hypertension and the 2014 Eighth Joint National Committee and/or report of anti-hypertensive therapy), diabetes mellitus [defined as glycated hemoglobin (HbA_1c) ≥ 6.5% and discriminating insulin therapy], active smoking status (self-reported), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) (defined as an eGFR < 60 mL/min/1.73 m^2 calculated according to Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) 2021), peripheral arterial disease (PAD), heart failure [graded according to the New York Heart Association (NYHA) classification]; previous cardiac surgery; European System for Cardiac Operative Risk Evaluation (EuroSCORE) II; ongoing medication and preoperative exposure to renin-angiotensin system inhibitors (RASI, including angiotensin converting enzyme inhibitors and angiotensin receptor blockers), diuretics or aminoglycosides; (ii) intraoperative data: type of surgery, on-pump/off-pump, extracorporeal and aortic cross-clamp times (considering zero minutes for off-pump surgeries), need for blood transfusion during the procedure, lowest (nadir) hematocrit (HTC) during the procedure, perioperative exposure to furosemide, sodium nitroprusside or vancomycin.

The primary outcome was the development of postoperative AKI according to the KDIGO criteria: an abrupt increase in serum creatinine (≥ 0.3 mg/dL within 48 hours or ≥ 50% within seven days) or a reduction in urine output (< 0.5 mL/kg/hr for more than six consecutive hours),[7] calculated from hourly nursing intensive care unit (ICU) records.

Secondary outcomes included: 30-day mortality, hospital and intensive care length of stay (LOS).

Statistical analysis

Continuous and ordinal variables were described as median and interquartile ranges (IQR) and absolute and relative frequencies were reported for categorical variables. Comparison between CS-AKI and non-CS-AKI patients were made using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

A *post-hoc* sub-group analysis of patients with HTN was conducted to evaluate the effect of preoperative RASI on the development of CS-AKI.

Missing data is presented for each variable and bias analysis was performed by CS-AKI status.

A backward stepwise-selection logistic regression was built from predictors with marginal association with AKI development in univariate analysis ($p < 0.2$) upon excluding variables with either evident collinearity (e.g., preoperative serum creatinine and eGFR) or multicollinearity assessment with variance inflation factors (VIF), with a cut-off of 10. A likelihood ratio with a p value > 0.1 was used as cut-off for variable removal. The accuracy of the model was assessed by the area under receiver operating characteristic (AU-ROC) curve and calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The results of the multivariate model are expressed as β coefficient and adjusted odds ratio (OR_{adj}) with 95% confidence interval (CI) and p-values. The significance level for all tests was defined as two-tailed $\alpha = 0.05$. The multivariate model was reassessed for the effect of RASI-HTN. Data were analyzed using IBM® SPSS Statistics for Windows®, version 28 (IBM® Corp., Armonk, N.Y., USA) and JASP (Version 0.16.1).

Economic analysis

Economic analysis was restricted to hospital costs. Mean daily CS patient costs were retrieved from the institution's financial department, without discrimination between ICU and ward. Cost-center charges included supplies, personnel, laboratory, and other diagnostics, as well as costs related to any treatment (Table 2). Incremental costs of CS-AKI development were obtained with Hedges' g estimate.

Costs associated with the potential introduction of [TIMP-2]x[IGFBP7] (Nephrocheck®) as a screening test were estimated according to Vijayan *et al*[19]: cost of laboratory test machine (€2923.95) and cost of one cartridge per patient (€49.71). Cost adjustment from USD to euros (€) was performed using Campbell and Cochrane Economics Methods Group (CCEMG) – EPPI-Centre Cost Converter as of 2019.[20]

Cost-effectiveness was modeled through break-even analysis (Python 3.9 script with numpy library) assuming absolute risk reduction (ARR) of 16.6% (CI 95% = 5.5% – 27.9%) reported by Meersch *et al* while applying the KDIGO bundle of care[7] to high-risk patients as identified by Nephrocheck® {[TIMP-2]x[IGFBP7] > 0.3}.[21] From our rate of CS-AKI we estimated the number of patients that would have been deemed at high-risk by Nephrocheck® and thus undergo the KDIGO intervention assuming a true positive rate/recall of 0.9 recently summarized in a systematic review and meta-analysis.[22,23]

Table 2 – Estimation of direct hospital costs

Considered costs	Average costs (€)
Average hospitalization daily costs	705.72
[TIMP-2]x[IGFBP7] cartridge costs	49.71

Direct hospital costs estimated considering cost-center charges. Hospitalization daily costs include ward and intensive care unit room, supplies, personnel, laboratory and other diagnostics, as well as costs related to any treatment.

The following formulas were applied:

- Equation 1
  - Costs related to screening = analyzer machine + cartridge x number of patients.
- Equation 2
  - Potential cost benefit of the intervention = difference in postoperative costs (POC) between CS-AKI and non-CS-AKI (median) x expected number of CS-AKI cases prevented (as integer after rounding).
- Equation 3
  - Expected number of CS-AKI cases prevented = number of patients x incidence of AKI in our cohort x high-risk patients/CS-AKI cases (control group in Meersch *et al*)[21] x recall (reported for Nephrocheck®)[22,23] x ARR (and 95%CI).[21]

Break-even points were estimated as patient number needed for the potential cost benefit of the intervention to outweigh the costs related to screening.

RESULTS

Study sample

Two-hundred and seventy-six patients were included in our cohort, of which 86 (31%) developed CS-AKI. All admitted patients were white.

AKI incidence and predictors

In univariate analysis (Table 3), preoperative variables including older age, HTN, CKD, diabetes and insulin-therapy, lower preoperative hemoglobin, higher serum creatinine, higher serum urea, lower eGFR and higher EuroSCORE II were significantly associated with CS-AKI incidence. Need for intraoperative blood transfusion, lower nadir HTC during the procedure and perioperative use of sodium nitroprusside were also significantly associated with CS-AKI. Active smoking, male gender, on-pump surgery, longer cardiopulmonary bypass (CPB), aortic cross-clamp time and perioperative use of furosemide were marginally associated (p > 0.05, but < 0.15) with CS-AKI.

A sub-group analysis of patients with HTN was conducted to evaluate the effect of preoperative RASI on the development of CS-AKI. In the subgroup of patients taking RASI, HTN was not significantly associated with CS-AKI (p = 0.749) but, in those not previously treated with RASI, HTN was significantly associated with CS-AKI (p = 0.005).

The final multivariate model is presented in Table 4. The model's AU-ROC curve was 0.645 (95% CI: 0.567 – 0.732). The Hosmer and Lemeshow test did not show evidence for lack of fit (p = 0.729). After adjustment, higher preoperative serum creatinine, lower preoperative hemoglobin and HTN remained significantly associated with CS-AKI. An increase in CPB time and perioperative use of sodium nitroprusside were also significantly associated with the risk of CS-AKI. Male gender was marginally associated with CS-AKI.

Regarding the subgroup analysis, the final model was re-calculated considering the effect of RASI treatment on patients with HTN (Table 4). Preoperative serum creatinine, preoperative hemoglobin, HTN and perioperative use of sodium nitroprusside remained significantly associated with the risk of CS-AKI. Gender was also significantly associated with CS-AKI.

CS-AKI and other outcomes

Other outcomes were also analyzed in our population and are discriminated in Table 3. Length of stay was significantly higher in patients with CS-AKI.

The postoperative mortality was 2.5%, with one patient dying in the first 24-postoperative hours and six in the first 30-days. The cause of death was cardiogenic shock in all patients but one, who died due to septic shock. Postoperative mortality was not related to CS-AKI: the mortality rate was 3.5% in patients who developed CS-AKI and 2.1% in those who did not (p = 0.623).

Overall, LOS was of 7 (IQR 6 – 10) days, 7 (IQR 6 – 9) days for those without CS-AKI *versus* 9 (IQR 7 – 14) days for those with CS-AKI (p < 0.001). Patients who developed CS-AKI also had longer ICU stays: 4 (IQR 2 – 6) *versus* 3 (IQR 2 – 4) days, with p = 0.0015. Overall ICU stay was three days (IQR 2 – 5).

Missing data - sensitivity analysis

Missing data sensitivity analysis was computed for each variable, by CS-AKI status. Significant bias was found for lowest HTC during the procedure (with data missing for eight patients that developed CS-AKI *versus* six patients without CS-AKI) (Table 5). For the evaluation of the impact of this missing bias, the 75th percentile value for controls (27%) was imputed for all 14 patients with missing data (to decrease the association between lowest HTC during the procedure and CS-AKI). The univariate association between lowest HTC during the procedure and CS-AKI remained significant (p = 0.004 after imputation).

Cost-analysis and modelling

Cost analysis is presented in Table 6. The incremental median cost for CS-AKI was thus €1403.44 (95% CI: 701.72 – 2105.16), p value < 0.001 and Hedges' g = 0.304 (small to medium effect size). Cumulative incremental cost estimation was calculated by multiplying incremental average cost by the number of patients developing CS-AKI. The expected cumulative surplus cost for the hospital, associated with CS-AKI (86 patients), was €120 695.84 (Table 6).

The break-even analysis for cost-effectiveness according to the specified model is depicted in Fig. 1. For a median

Table 3 – Univariate analysis

	Total n = 276		AKI n = 86		Without AKI n = 190		*p*-value
Demographics							
Age (y)	69	(60 – 76)	73	(67 – 77)	67	(58 – 75)	< 0.001*
Male, n (%)	169	(61)	59	(69)	111	(58)	0.110
BMI, kg/m²	26	(24 – 30)	26	(24 – 30)	27	(24 – 30)	0.934
BSA, m²	1.77	(1.64 – 1.89)	1.78	(1.65 – 1.92)	1.77	(1.63 – 1.89)	0.344
Preoperative analytical data							
Hemoglobin, g/dL	8.19	(7.26 – 9.06)	7.7	(6.70 – 8.69)	8.38	(7.51 – 9.06)	0.004*
Serum creatinine, mg/dL	73.39	(61.89 – 91.07)	81.35	(69.85 – 112.29)	71.62	(59.24 – 84.00)	< 0.001*
Serum urea, mg/dL	43	(35 – 53)	47	(38 – 59)	43	(34 – 51)	0.014*
eGFR, ml/min/1.73m²	90	(73 – 99)	79	(57 – 92)	92	(78 – 102)	< 0.001*
LVEF - Good, n (%) **Moderate**, n (%) **Poor**, n (%) **Very poor**, n (%)	201 11 2 -	(76) (4) (1)	60 3 1 -	(75) (4) (1)	138 8 1 -	(77) (4) (1) -	0.892
Comorbidities							
Obesity, n (%)	61	(22)	19	(22)	42	(22)	0.999
HTN, n (%)	217	(79)	77	(90)	140	(74)	0.003*
DM, n (%) **- insulin-therapy**, n (%)	93 28	(34) (10)	38 14	(44) (16)	55 14	(29) (7)	0.019* 0.031*
Active smoker, n (%)	50	(18)	10	(12)	40	(21)	0.065
CKD, n (%)	44	(16)	12	(14)	32	(17)	< 0.001*
PAD, n (%)	31	(11)	11	(13)	20	(10)	0.681
Heart failure (NYHA class)	II	(II – III)	III	(III – IV)	II	(II – III)	0.591
Previous cardiac surgery, n (%)	14	(5)	5	(6)	9	(5)	0.560
EuroSCORE II (%)	3.1	(1.7 – 5.4)	3.7	(2.2 – 6.8)	2.9	(1.6 – 4.8)	0.003*
Preoperative exposure							
ACEi, n (%)	116	(42)	41	(48)	75	(40)	0.236
ARB, n (%)	44	(16)	15	(17)	29	(15)	0.723
Diuretics, n (%)	117	(42)	42	(49)	75	(40)	0.151
Aminoglycosides, n (%)	3	(1)	2	(2)	1	1 (1)	0.380
Surgery details							
Type of surgery **- isolated CABG**, n (%) **- single non-CABG**, n (%) **- 2 procedures**, n (%) **- 3 or more procedures**, n (%)	 95 126 54 1	 (34) (46) (20)	 27 39 19 -	 (31) (45) (22)	 66 90 34 1	 (35) (47) (18) (1)	0.415
On-pump surgery, n (%)	254	(92)	83	(97)	171	(90)	0.091
CPB time, min	103	(79 – 134)	110	(84 – 140)	100	(77 – 132)	0.088
Clamping time, min	67	(50 – 94)	73	(56 – 98)	66	(49 – 94)	0.071
Nadir HTC, %	24	(21 – 27)	22	(21 – 25)	24	(21 – 27)	0.002*
Perioperative exposure							
Intraoperative blood (RBC) transfusion, n (%)	113	(41)	47	(55)	66	(35)	0.002*
Sodium nitroprusside, n (%)	15	(5)	10	(12)	5	(3)	0.007*
Vancomycin, n (%)	8	(3)	3	(4)	5	(3)	0.706
Furosemide, n (%)	229	(83)	66	(79)	164	(88)	0.066
Other outcomes							
Postoperative mortality, n (%)	7	(2.5)	3	(3.5)	4	(2.1)	0.623
LOS (days)	7	(6 – 10)	9	(7 – 14)	7	(6 – 9)	< 0.001*
ICU stay (days)	3	(2 – 5)	4	(2 – 6)	3	(2 – 4)	0.0015*

*: $p < 0.05$

BSA: body surface area; DM: diabetes mellitus; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 4 – Multivariate analysis including RASI-HTN interaction

	Multivariate analysis (final original model)			Multivariate analysis (with RASI-HTN interaction)		
	β	*p*-value	OR_{adj} (95% CI)	β	*p*-value	OR_{adj} (95% CI)
Male	0.702	0.053	2.02 (0.99 – 4.11)	0.726	0.039*	2.07 (1.04 – 4.12)
Hemoglobin	-0.225	0.012*	0.80 (0.70 – 0.98)	- 0.233	0.006*	0.79 (0.67 – 0.94)
Serum creatinine	0.096	0.022*	1.10 (1.01 – 1.19)	0.085	0.030*	1.09 (1.01 – 1.17)
HTN	1.068	0.014*	2.91 (1.24 – 6.84)	1.610	0.004*	5.00 (1.67 – 15.02)
RASI-HTN interaction	-	-	-	-1.373	0.146	0.25 (0.04 – 1.61)
RASI	-	-	-	1.152	0.188	3.17 (0.57 – 17.62)
CPB time	0.008	< 0.001*	1.01 (1.00 – 1.01)#	0.007	0.001*	1.01 (1.00 – 1.01)#
Sodium nitroprusside	1.670	0.009*	5.31 (1.51 – 18.72)	1.845	0.004*	6.33 (1.80 – 22.28)

*: $p < 0.05$; #: 1.008 (1.003 – 1.013)

ARR of 16.6% as reported by Meersch *et al*[21] we would expect a break-even point upon screening 78 patients, which would translate, in our 276 patients' cohort, in an overall cost benefit of €7145, but the 95% CI are wide and for an ARR of 27.9% these would be 37 patients and €25 410, respectively. On the other hand, for the worst expectation of only 5.5% ARR there would be no expected economic benefit at all, even in the long run.

DISCUSSION

CS-AKI was associated with higher morbidity, mortality, and increased hospital costs.[1-3] Several studies were developed regarding the development of predictive scores,[24-26] and identification of tools that, adequately and in a timely fashion, allow to recognize and manage CS-AKI[12,21] in order to minimize its impact.

We have conducted an analysis to investigate the predictors of CS-AKI in our population which, according to the tendency demonstrated in literature, showed some conflicting results, although the incidence of CS-AKI in our population (31%) is comparable to previous reports in the literature.[27,28]

The male gender in our population was associated with an increased risk of CS-AKI development, contradicting many previous reports[29,30] but is in agreement with a more recent systematic review and meta-analysis by Neugarten *et al.*[31]

Preoperative creatinine plasma levels, low preoperative hemoglobin and HTN were identified as predictors of CS-AKI in our study. Preoperative creatinine, mirroring the patient's renal reserve, has been consistently identified as an independent risk factor[2,32] and therefore included in several predictive scoring systems for CS-AKI.[24-26,33,34] In our population, an increase of 1 mg/dL was associated with a 9% (95% CI: 1% – 17%) increase in the risk of developing CS-AKI. Low preoperative hemoglobin has been reported as an independent risk factor for the development of CS-AKI, with an attributed 2.6-fold increased risk[35,36]: AKI in anemic patients is associated with inflammation, renal hypoxia and oxidative stress, explaining why these patients have an increased susceptibility to concomitant renal insults, such as hypoperfusion, increasing their vulnerability to CS-AKI when on CPB.[2,37] In our study, a reduction of 1 g/dL in preoperative hemoglobin was associated with a 21% (95% CI: 6% – 33%) increase in the odds of CS-AKI. Red blood cell (RBC) transfusion also exacerbates the risk of CS-AKI in anemic patients, representing, by itself, an independent risk factor.[35,36] Moreover, in an observational study performed in 2014, Kahn *et al* concluded that the risk of AKI was highest in patients receiving more than two units of RBCs.[38] Although several studies[35,37,39] demonstrated that, regardless

Table 5 – Missing data

n (%)	**Missing data**	***p*-value**
Preoperative analytical values		
Hemoglobin	5 (1.8)	0.648
Serum creatinine	5 (1.8)	0.648
Serum urea	5 (1.8)	0.648
eGFR	5 (1.8)	0.648
LVEF	16 (5.8)	0.585
Comorbidities		
NYHA class	63 (22.8)	0.428
EuroSCORE II (%)	5 (1.8)	0.648
Surgery details		
CBP time	6 (2.2)	0.078
Clamping time	6 (2.2)	0.078
Nadir HTC	14 (5.1)	0.04
Perioperative exposure		
Vancomycin	5 (1.8)	0.648
Furosemide	5 (1.8)	0.648

Table 6 – Comparison of patient costs

	AKI (n = 86)	Without AKI (n = 190)	*p*-value
Median POC *per* patient (€)	6 315.48 (4912.04 – 9122.36)	4 912.04 (4210.32 – 6315.48)	< 0.001*
Total POC estimation (n = 276)	= Median POC *per* patient x n = 1476,418.88		
Median POC difference *per* patient (€)	= POC (AKI) – POC (without AKI) = 1403.44 (701.72 – 2,105.16)		
Expected cumulative surplus cost (n = 86) (€)	= Median POC difference per patient x n = 120695.84		

*: $p < 0.05$

of the existence of anemia, transfusion of RBC entails an important risk for AKI, our study was not able to corroborate it, since intraoperative RBC transfusion was significantly associated with CS-AKI only in univariate analysis.

Regarding HTN, in a prospective study of 157 patients, Kenji *et al* found that a drop in mean arterial pressure (MAP) of more than 26 mmHg between preoperative and intraoperative values was associated with the development of CS-AKI, explaining why HTN is considered a risk factor and why this could be the focus of an intervention.[40] In this study, the presence of HTN represented a 5-fold increase in the odds of CS-AKI.

We could not find a significant impact of RASI in the incidence of CS-AKI in our population. Preoperative use of RASI has been associated with an increase in preoperative CS-AKI not mediated by an effect in blood pressure. This association possibly reflects the effects in glomerular capillary pressure caused by renal efferent arteriolar vasodilation and impairment of autoregulation.[41] Nevertheless, some publications showed opposite results, suggesting a treatment benefit in these patients.[2,42-45] On the other hand, in a sub-group analysis of patients with HTN, patients treated with RASI had no increased incidence of CS-AKI, unlike patients not treated with RASI, thus suggesting a protective

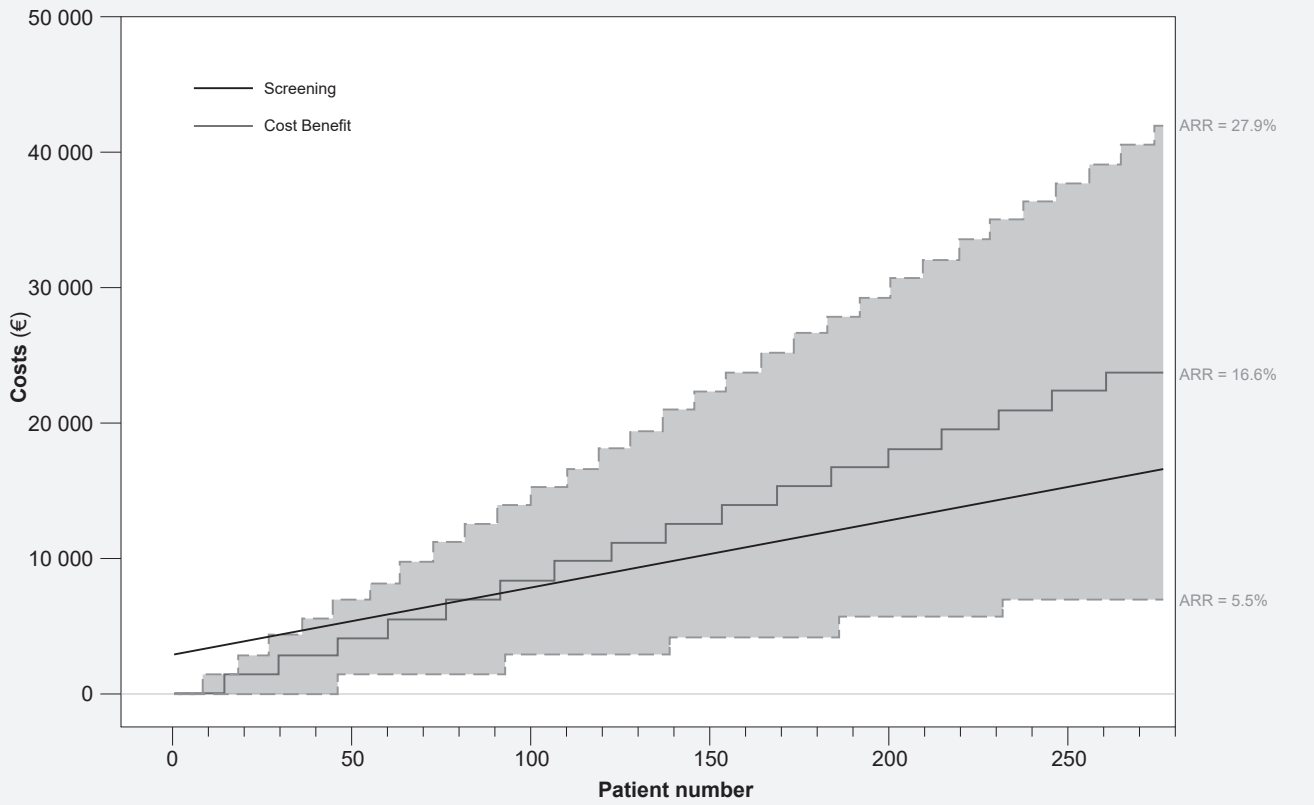

Figure 1 – Modelling of break-even analysis for the introduction of the KDIGO bundle of care in high-risk patients after Nephrocheck® screening. The costs related to Nephrocheck® screening, including the test machine and consumables, are plotted as a black solid line. The potential cost-reduction related to the intervention is plotted as a grey solid line, and the shaded area corresponds to the 95% CI, according to the ARR reported by Meersch *et al*.[21]

role of RASI in hypertensive patients. Our study didn't include both the analysis of preoperative treatment with other anti-hypertensive agents, and of the efficacy of preoperative blood pressure control; however, considering the sub-group analysis, a better control of preoperative HTN might be associated with a lower incidence of CS-AKI.

Amongst intraoperative factors, the duration of CPB was significantly associated with CS-AKI in which a 60-minute increase of extracorporeal circulation represents a 60% increase in CS-AKI (OR_{adj} = 1.61), reflecting the influence in renal outcomes of the contact activated inflammatory response and significant hemodynamic changes associated with CPB.[5] Also, the institution of CPB in coronary artery bypass graft (CABG) surgery is associated with a systemic inflammatory response, coagulopathy, embolism and CS-AKI.[5] It has been proposed that the avoidance of CPB by the implementation of an off-pump CABG (OPCAB) technique would reduce the incidence and severity of CS-AKI. Several systematic reviews and meta-analysis of randomized control trials (RCT)[2,46,47] and one multicenter RCT[48] point to a lower risk of CS-AKI in OPCAB surgery patients, whereas this has not been confirmed by Reents *et al* in his post hoc analysis of 1612 patients.[49] In the present study, on-pump surgery was marginally associated with CS-AKI incidence only in univariate analysis. On the other hand, prolonged aortic cross-clamp time, according to historical reports, increases the risk of low cardiac output state (LCOS) and renal ischemia.[50,51] Our findings did not support the association between longer aortic cross-clamp time and CS-AKI, but the occurrence of LCOS was not determined in our population. Regarding the type of surgery, we did not find an association with CS-AKI, although the literature strongly suggests that patients presenting for CABG develop less CS-AKI in comparison to other types of cardiac surgery,[52-54] probably due to less CPB time.[55] Conversely, a meta-analysis published by Yi Q. *et al* demonstrated otherwise, not establishing an absolute association between these factors.[10]

Still within intraoperative factors, the use of sodium nitroprusside was significantly associated with the development of CS-AKI, determining a 533% increase in the risk of CS-AKI. In most experimental models, renal autoregulation capability was impaired following ischemic injury, suggesting a residual ability to vasodilate and a greater fraction of fixed total resistance, originating a substantial increase (50%) in renal vascular resistance, a 40% decrease in renal blood flow and severe impairment in renal oxygenation in CS-AKI patients, compared with post-cardiac surgery patients with no AKI.[56] The use of vasodilators can further reduce the renal blood flow.[57] Finally, in what concerns nadir HTC, an association with CS-AKI was not demonstrated in our results contrarily to what was to be expected. Ranucci *et al* studied the role of nadir oxygen delivery (DO_2), nadir HTC and pump flow during CPB, and risk of CS-AKI[58,59] and found that a nadir DO_2 of less than 262 mL/min/m^2 during CPB was associated with AKI stage 2 (according to AKIN classification), and nadir DO_2 level was significantly associated with prolonged ICU and postoperative LOS.[58]

As mentioned above, if treatment bundles are to be effective, they need to be applied before the condition of interest develops; in order to achieve this, the right tools are required. Since we were aiming to estimate the potential cost reduction by identifying, in a timely manner, the risk of developing CS-AKI, we decided to use data related to TIMP-2 and IGFBP7 (Nephrocheck®) for our economic analysis, given its very high specificity and very good predictive value.[22,23] In our population, the overall LOS was significantly increased for patients with CS-AKI.

Following the implementation of Nephrocheck® screening alongside with the application of the KDIGO bundle of care to high-risk patients, a cost reduction associated with the estimated decrease of CS-AKI incidence could be achieved.[21]

Limitations

The main limitation of our study is its retrospective nature, regarding data routinely assessed within the hospital stay, and the fact that it was conducted in a single center.

During the period considered, evaluation of HbA_1C was not standardized in the preoperative assessment of diabetic patients, which did not allow us to assess the preoperative metabolic control of our patients. Regarding the remaining variables described as possible risk predictors, we had a low number of missing values in the clinical records consulted and only nadir HTC presented missing bias. Despite this, after missing imputation, this variable remained significantly associated with CS-AKI in univariate analysis.

Our multivariate analysis model had sufficient power to include up to eight variables.[60] Still, due to a sample of just 276 patients, lack of power may not have allowed the analysis of other predictors. A larger sample would also allow a discrimination of CS-AKI stages.

In the estimation of costs, cost-center charges did not discriminate average ICU daily costs per patient, which would enable a more precise calculation of CS-AKI associated cost increase. Our economic analysis was based on average hospitalization costs; not having individualized patient costs could limit our accuracy of value determination. Cost-analysis modelling is based on studies from other groups and data collected was from 2015, which has consequences regarding this study's external validity; consequently, our conclusions may not be completely generalizable to our current population. Data regarding sensibility/recall are predominantly based on studies performed in

critical patients; however, there is a low sample study on the post-operative period after cardiac surgery with similar values/outcomes to our study (0.92).[22] Additionally, further studies are needed to precisely calculate the direct savings of applying [TIMP-2]x[IGFBP7] only to high-risk patients estimated by risk prediction scores[9-12] *versus* all patients, and to evaluate the economic benefit of applying the KDIGO bundle of care for all patients.

CONCLUSION

Our work reinforces the existing evidence that increased preoperative creatinine, HTN, low preoperative hemoglobin, long CPB time and intraoperative sodium nitroprusside were independent risk factors for CS-AKI. Moreover, our cost-effectiveness modelling suggests that the use of kidney structural damage biomarkers combined with an early prevention strategy could be cost saving.

AUTHOR CONTRIBUTIONS

JM, AFR, CA: Study design, data collection and analysis, writing of the manuscript.

ALD: Study design, statistical analysis, data interpretation, writing of the manuscript.

BA, AL: Study design, data collection.

ALM: Study design, data interpretation.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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