

## ORIGINAL RESEARCH OPEN ACCESS

# The Incidence, Associated Factors and in-Hospital Outcomes of Cardiac-Surgery-Associated Acute Kidney Injury Among Children Undergoing Cardiac Surgery at Jakaya Kikwete Cardiac Institute. A Hospital-Based Prospective Cohort Study

Joyce Gimonge<sup>1</sup> | David Muhunzi<sup>2</sup>  | Zawadi Edward<sup>3</sup> | Rodrick Kisenge<sup>1</sup>

<sup>1</sup>Department of Pediatrics and Child Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania | <sup>2</sup>School of Clinical Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania | <sup>3</sup>Department of Pediatrics, Jakaya Kikwete Cardiac Institute, Dar es Salaam, Tanzania

**Correspondence:** Joyce Gimonge ([joy.gimonge@gmail.com](mailto:joy.gimonge@gmail.com))

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## ABSTRACT

**Background and Aims:** Cardiac surgery-associated acute kidney injury (CSA-AKI) is one of the serious complications that can potentially increase the risk of morbidity, long-term adverse effects and mortality. Despite the advances in the care and increased survival of children post-cardiac surgery, CSA-AKI is still a big problem with considerable morbidity and mortality in high-risk children. Prevention of CSA-AKI is important for survival and minimization of long-term adverse outcomes of children after cardiac surgery. This study aimed to determine the proportion of acute kidney injury, associated risk factors and in-hospital outcomes among children undergoing cardiac surgery at the Jakaya Kikwete Cardiac Institute (JKCI).

**Methodology:** A prospective cohort study was conducted to determine the proportion, risk factors, and in-hospital outcomes among children who developed cardiac surgery-associated acute kidney injury (CSA-AKI) at JKCI. Data collection was done using a structured questionnaire, Intensive care unit (ICU) chart review, and hospital records. Diagnosis of CSA-AKI was done based on KDIGO criteria. Serum creatinine was measured pre-operatively and subsequently, daily up to day seven post-operatively to determine the presence of CSA-AKI.

**Results:** A total of 210 children were recruited into the study, of which 120 (57.1%) were males. The median age of the study participants was 36 months. Of the recruited children, 23 (11.0%) developed cardiac surgery-associated acute kidney injury (CSA-AKI). Intraoperative hypotension [ARR = 2.7; 95% CI 1.37-5.26; *p*-value = 0.004], intraoperative platelet transfusion [ARR = 2.7; 95% CI 1.37-5.22; *p*-value = 0.004] and two or more days on mechanical ventilation [ARR = 2.3; 95% CI 1.1-4.71; *p*-value = 0.019] were found to be significantly associated with CSA-AKI. There were 8 (3.8%) deaths, of these, 7 (87.5%) were from children who developed CSA-AKI. Children who developed CSA-AKI had, on average, a longer ICU stay, with a mean difference of 1.959 days.

**Abbreviations:** CPB, cardiopulmonary bypass; CSA-AKI, cardiac surgery associated acute kidney injury; ICU, intensive care unit; KDIGO, kidney disease improving global outcome; MUHAS, Muhimbili University of Health and Allied Sciences; sCR, serum creatinine; VILI, ventilator-induced lung injury.

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**Conclusion:** This study's findings highlighted the prevalence and severity of cardiac surgery associated with acute kidney injury in pediatric patients. The identified risk factors, such as intraoperative hypotension, platelet transfusion, and prolonged mechanical ventilation, provide crucial insights for improving patient outcomes. The study's results also emphasize the need for interventions targeting these modifiable factors to reduce mortality among children undergoing cardiac surgery.

## 1 | Introduction

Cardiac-surgery-associated acute kidney injury (CSA-AKI) is a common complication following cardiac surgery, and it is associated with increased morbidity and mortality [1]. The incidence of CSA-AKI in children in developed countries ranges from 41% to 53%, while in developing countries, it is from 9.3% to 37.3% [1–3]. Factors associated with CSA-AKI following cardiac surgery among pediatric patients include young age, cardiac defect complexity, prolonged CPB time and circulatory arrest, and low preoperative haemoglobin level [3]. Other possible risk factors include thrombocytopenia, preoperative renal insufficiency, peri-operative use of nephrotoxic medications, and low serum albumin levels [4, 5]. CSA-AKI is associated with an increased length of ICU and hospital stay, as well as mortality [5–10]. Despite an increase in cardiac surgeries done in Tanzania, there is limited information on the incidence of CSA-AKI, its associated factors and in-hospital outcomes among pediatric patients. This study, therefore, aimed at determining the incidence, associated factors and in-hospital outcomes among children with CSA-AKI at the Jakaya Kikwete Cardiac Institute in.

## 2 | Methodology

This was a facility-based prospective cohort study involving pediatric patients undergoing cardiac surgery from July 2022 to March 2023. A consecutive sampling method was used to enrol study participants. The study was conducted in the paediatrics department at Jakaya Kikwete Cardiac Institute (JKCI) in Dar es Salaam, Tanzania. JKCI is a government-owned and the largest super-specialized cardiovascular centre in Tanzania. The institute has a 103-bed capacity, and it attends an average of 700 outpatients and 100 inpatients per week. About 250 children with cardiac defects undergo cardiac surgery per year in this institution.

The study population included children aged 1 month to 15 years undergoing cardiac surgeries at JKCI during the study period. Children were followed up until discharge. Children with incomplete results, who died within 12 h post-surgery, and those whose caregivers did not consent to participate in the study were excluded from the study. The primary outcome of the study was the development of CSA-AKI, while the length of ICU stays, the need for renal replacement therapy and mortality were the secondary outcomes.

In this study, CSA-AKI was defined using the KDIGO criteria based on an increase in serum creatinine by  $\geq 0.3$  mg/dL ( $\geq 26.5$   $\mu$ mol/L within 48 h post-cardiac surgery or an increase in serum creatinine to  $\geq 1.5$ – $1.9$  times baseline levels, which occurred within 7 days post-cardiac surgery [11].

A structured questionnaire was used to collect data on the socio-demographic and clinical characteristics of the study participants.

Clinical data such as preoperative medications, preoperative kidney function, surgical details, intraoperative parameters and postoperative investigations were retrieved from chart reviews and hospital records. preoperative variables were collected within 24 h before surgery. Similarly, intra-operative variables were documented within 24 h after the operation. Postoperative variables were collected for 7 days post-surgery. Serum creatinine results on day seven were collected to determine CSA-AKI resolution for those who developed CSA-AKI.

Data were entered and analyzed using SPSS version 23. Continuous variables were expressed as median and interquartile range, or mean and standard deviation where appropriate, while categorical variables were summarized as percentages. The chi-square and Fisher's exact test were used to determine the association between categorical variables. Multivariate regression analysis was used to determine independent factors associated with CSA-AKI. A *p-value* of less than 0.05 was considered statistically significant for association.

Ethical clearance was sought from the Research and Ethics Committee at the Muhimbili University of Health and Allied Sciences (MUHAS). The permission to conduct the study was obtained from the Directorate of Research, Training, and Consultancy at JKCI. A written informed consent was obtained from the caregivers of the respective participants. For caregivers who couldn't read or write a thumbprint was taken in the presence of an unbiased witness. Each participant was assigned a study identification number, and information recorded from the participants remained confidential.

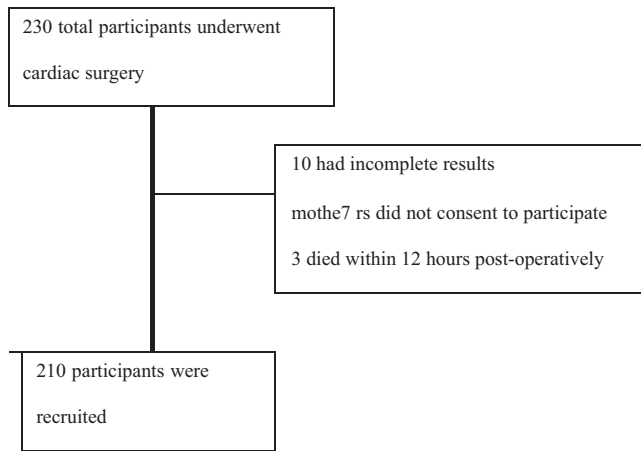
All participants of the study received appropriate and standard monitoring and management as per the hospital treatment guidelines.

## 3 | Results

A total of 230 children underwent cardiac surgery during the study period; of these, 210 met the inclusion criteria (Figure 1), and 120 (57.1%) were male. The median age was 36 months (IQ range 1–171) (Table 1).

Among the pediatric patients who were recruited into the study, 23 (11.0%) developed CSA-AKI (Figure 2). Of these, 10 (43.5%) cases occurred within the first 24 h post-surgery. Regarding severity classification based on the KDIGO AKI serum creatinine criteria, 13 (56.5%) children were diagnosed with CSA-AKI Stage 3, requiring initiation of hemodialysis. Additionally, six patients (26.1%) had CSA-AKI Stage 2, while four patients (17.4%) were classified as CSA-AKI Stage 1.

The socio-demographic characteristics of children with CSA-AKI are shown in Table 2 below.



**FIGURE 1** | Flow chart showing the recruitment of study participants.

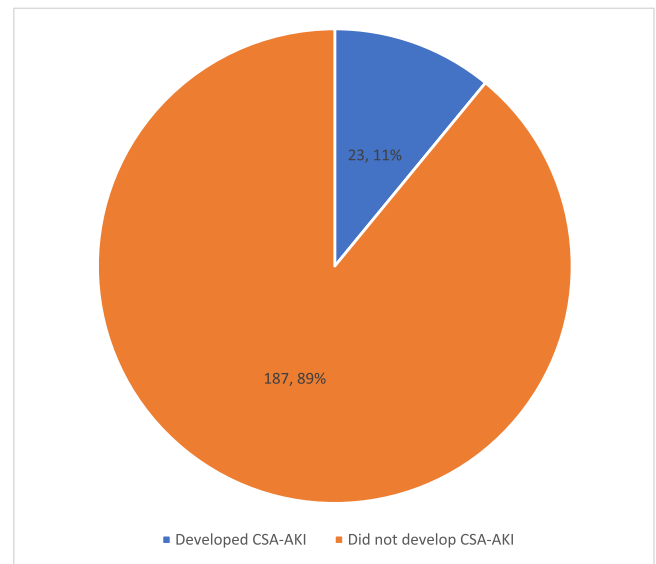
**TABLE 1** | Socio-demographic characteristics of the study participants.

Variable	No. of children (N)	Percentage
Age group in months		
< 24	84	40
≥ 24	126	60
Sex of the child		
Male	120	57.1
Female		
Nutritional status		
Normal	52	24.8
Underweight	129	61.4
Overweight	29	13.8
Type of heart disease		
Congenital acyanotic	107	50.9
Congenital cyanotic	93	44.3
Acquired heart disease	10	4.8
Preoperative anaemia		
Yes	80	38.1
No	130	61.9
Preoperative inflammatory markers*		
Raised	108	51.4
Normal	102	48.6

\*These include C-C-reactive protein (CRP) and white blood cell count.

### 3.1 | Factors Associated With Cardiac-Surgery-Associated Acute Kidney Injury

On multivariate analysis, intraoperative hypotension [ARR = 2.7; 95% CI 1.37–5.26;  $p$ -value = 0.004], intraoperatively platelet transfusion [ARR = 2.7; 95% CI 1.37–5.22;  $p$ -value = 0.004] and greater than or equal 2 days on mechanical ventilation [ARR = 2.3; 95% CI 1.1–4.71;  $p$ -value = 0.019] were found to be



**FIGURE 2** | Proportion of CSA-AKI among study participants.

significantly associated with CSA-AKI among participants. Aorta cross-clamping time greater than or equal to 60 min [CRR = 3.1; 95% CI 1.12–8.55;  $p$ -value = 0.03] was associated with CSA-AKI in univariate but not multivariate analysis (Table 3).

### 3.2 | Outcomes of CSA-AKI Among Study Participants

#### 3.2.1 | Number of Days in ICU

The overall mean length of ICU stay was  $4.84 \pm 1.036$  days. The mean ICU stay for the children who developed CSA-AKI was  $6.54 \pm 5.24$  days, while for those who did not, it was  $4.48 \pm 4.13$  days. The mean difference in length of ICU stay between the two groups was 1.959 days ( $p$ -value = 0.28).

#### 3.2.2 | Mortality Among Children With CSA-AKI

Of the 210 children recruited into the study, 8 (3.8%) died, and 7 (87.5%) of them had CSA-AKI;  $p$ -value = 0.001 (Figure 3).

## 4 | Discussion

This was a facility-based prospective cohort study to determine the incidence, associated factors, and in-hospital outcomes of cardiac surgery-associated acute kidney injury among pediatric patients undergoing cardiac surgery at the Jakaya Kikwete Cardiac Institute in Tanzania.

The proportion of CSA-AKI in this study is comparable to that of a study done in India by Ekure EN et al. [10]. The similarity in findings could partly be explained by the fact that both studies were done in developing countries and therefore may have a similar rate of cardiac surgeries, a well-known risk factor of CSA-AKI. However, Bilal Aon et al. reported a lower proportion of CSA-AKI [12].

**TABLE 2** | Socio-demographic and clinical characteristics between CSA-AKI and non-CSA-AKI groups.

Variable	No CSA-AKI, N (%)	CSA-AKI, N (%)
Age group in months		
< 24	73 (37.9)	11 (47.8)
≥ 24	114 (62.1)	12 (52.2)
Sex of the child		
Male	105 (56.1)	15 (65.2)
Female	82 (43.9)	8 (34.8)
Nutritional status		
Normal	48 (25.7)	4 (17.4)
Underweight	112 (59.9)	17 (73.9)
Overweight	27 (14.4)	2 (8.7)
Type of heart disease		
Congenital acyanotic	104 (55.6)	13 (56.5)
Congenital cyanotic	83 (44.4)	10 (43.5)
Preoperative anaemia		
Yes	70 (37.4)	10 (43.5)
No	117 (62.6)	13 (56.5)
Preoperative inflammatory markers**		
Raised	102 (54.5)	6 (26.1)
Normal	85 (45.5)	17 (73.9)
Use of nephrotic drugs		
Yes	185 (58.2)	23 (100)
No	2 (41.8)	0 (0.0)
Aorta cross-clamping time in minutes		
< 60	69 (36.9)	2 (8.7)
60 -< 120	103 (55.1)	15 (65.2)
≥ 120	15 (8.0)	6 (26.1)
CPB time in minutes		
< 120 min	115 (61.5)	10 (43.5)
≥ 120	72 (38.5)	13 (56.5)
Intraoperative hypotension		
Yes	35 (18.7)	9 (39.1)
No	152 (81.3)	14 (60.9)
Intraoperative platelet transfusion		
Yes	35 (18.7)	10 (43.5)
No	152 (81.3)	13 (56.5)
Number of days on a mechanical ventilator		
< 2	117 (62.6)	9 (39.1)
≥ 2	70 (37.4)	14 (60.9)

Note: The \*\* was supposed to indicate the inflammatory markers in question below the table, which were leukocytosis and elevated CRP.

Contrary to our findings, a study done in Korea reported a higher proportion (36.6%) of CSA-AKI [13]. This was a single-centred retrospective study involving 505 pediatric patients who underwent congenital heart surgery, where recruitment of their

large sample size could have led to a true representation of the general population [14]. The management of complex congenital heart conditions, such as left heart syndrome, may have contributed to a higher prevalence despite Korea being a resource-rich country.

Several studies that looked at risk factors for developing AKI post-cardiac surgery found that age less than 12 months was associated with an increased risk of CSA-AKI [1, 6, 8, 15]. This could be explained by the inability to adapt to post-CPB inflammation and ischemia-reperfusion injury of the kidney in younger patients, leading to inflammatory and ischemic events that affect kidney function [1, 16]. In our study, 40% of the participants were younger than 2 years; among them, 17.9% developed CSA-AKI post-cardiac surgery, but this was not statistically significant. This is consistent with the findings from the study done by Bilal Amon et al., which found no correlation between the occurrence of CSA-AKI and age [12].

Existing literature has reported that intraoperative hypotension is among the main causes of postoperative renal failure [17]. In our study, intraoperative hypotension was independently associated with CSA-AKI, which is consistent with findings from another similar study in developing countries [10]. Perioperative hypotension results in a reduction of renal perfusion pressure, hence inducing glomerular ischemia and stimulating the release of renin and angiotensin II, which further decreases the renal blood flow.

This study also found that platelet transfusion is significantly associated with CSA-AKI. This could be explained by several mechanisms, such as hemodynamic instability. Transfusion reactions or fluid overload can also exaggerate the hemodynamic instability, further compromising kidney function [18]. Platelet transfusion may also trigger an inflammatory response, leading to increased levels of circulating pro-inflammatory markers and damage to renal parenchymal cells [19].

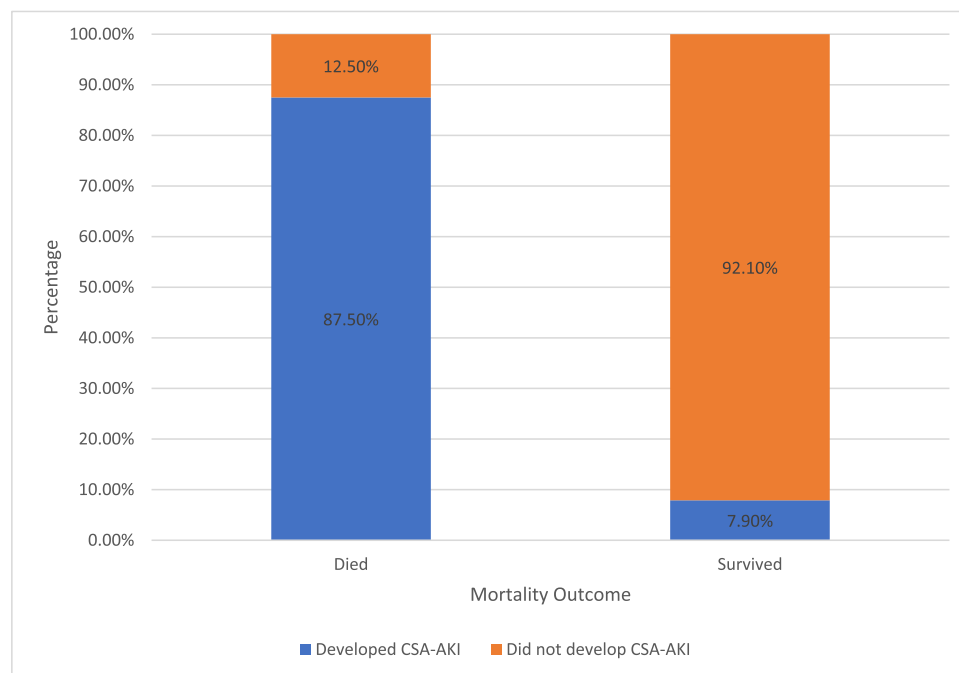
Moreover, our study found that the use of a mechanical ventilator for two or more days is an independent risk factor for CSA-AKI. This can be explained by several mechanisms, one of which is increased intra-thoracic pressure due to positive pressure ventilation [5]. The increased intra-thoracic pressure results in the reduction of venous return and, therefore, cardiac output, eventually renal hypoperfusion and damage. In addition to hemodynamic changes, mechanical ventilation can also result in ventilator-induced lung injury, which can further contribute to CSA-AKI [5]. Studies have shown that higher tidal volumes and peak inspiratory pressures during mechanical ventilation are associated with an increased risk of CSA-AKI in children undergoing cardiac surgery [20].

This study found that children who developed CSA-AKI after cardiac surgery had a longer mean length of ICU stay. Furthermore, the majority of deaths after surgery were attributed to children who developed CSA-AKI. A different finding was, however, observed in a meta-analysis series that involved subgroup analysis, which reported a lower mortality associated with CSA-AKI in Belgium and the Netherlands [15]. The higher rate of mortality in our study can be explained by the nature of our study setting, being in resource-limited settings and

**TABLE 3** | Univariate and multivariate analysis for factors associated with CSA-AKI among study participants.

Variable	Univariate analysis			Multivariate analysis		
	CRR	95% CI	<i>p</i> value	ARR	95% CI	<i>p</i> value
Age group in months						
< 24	1.7	0.87–3.46	0.12	1.6	0.83–3.16	0.16
≥ 24	Ref					
Sex						
Male	1.88	0.87–4.06	0.11	1.7	0.82–3.68	0.15
Female	Ref					
Aorta cross-clamping time						
<60 min	Ref					
≥ 60 min	3.1	1.12–8.55	0.03	2.4	0.72–7.68	0.16
CPB time (minutes)						
< 120	Ref					
≥ 120	1.6	0.81–3.19	0.175	0.9	0.41–1.93	0.77
Hypotension						
Yes	2.9	1.48–5.65	0.002	2.7	1.37–5.26	0.004
No	Ref					
Platelet transfusion (Intraoperatively)						
Yes	2.8	1.4–5.39	0.003	2.7	1.37–5.22	<b>0.004</b>
No	Ref					
Number of days on mechanical ventilation						
< 2	Ref					
≥ 2	2.8	1.43–5.57	0.003	2.3	1.1–4.71	<b>0.019</b>

Note: Bold values are statistically significant.



**FIGURE 3** | Mortality outcome among study participants.

therefore more likely to have post-cardiac surgery complications such as CSA-AKI.

## 5 | Limitations of the Study

This study was not able to identify other factors, apart from CSA-AKI, that contributed to mortality and prolonged hospital stays.

## 6 | Conclusion and Recommendations

This study found that there is a significant burden of acute kidney injury following cardiac surgery among pediatric patients. The factors associated with CSA-AKI include intraoperative hypotension, intraoperative platelet transfusion and the use of mechanical ventilation for two or more days. The study also revealed that CSA-AKI is associated with significant mortality and longer ICU stays. Interventions to reduce the burden of CSA-AKI should target early identification and intervention for intraoperative hypotension, judicious use of mechanical ventilation and platelet transfusion.

## 7 | Definition of Terms

**Acute kidney injury (AKI)** is defined as the sudden loss of kidney function, which leads to a decline in glomerular filtration rate with the accumulation of nitrogenous waste products and impairment of the regulation of extracellular volume and electrolytes. In this study, due to the availability of resources and the environment, CSA-AKI was defined as any increase in serum creatinine by 26.5  $\mu\text{mol/litre}$  within 48 h post-cardiac surgery.

**Anemia**, according to WHO, is a decrease in red blood cell mass or blood haemoglobin concentration lower than normal for age and sex.

**Cardiopulmonary Bypass** – This is a form of extracorporeal circulation whose function is circulatory and respiratory support along with temperature management to facilitate surgery of the heart and great vessels.

**Cyanotic heart disease** is a form of congenital heart disease with low oxygen tension in the blood due to the mixing of the oxygenated and deoxygenated blood in systemic circulation.

**Intraoperative hypotension** is defined as an intraoperative mean arterial pressure of  $< 40 \text{ mmHg}$ .

**Moderate Acute Malnutrition** – is defined as MUAC of 115–124 mm or weight for length Z score of  $-2$  to  $-3$ .

**Severe acute malnutrition** is defined as a mid-upper arm circumference (MUAC) of less than 115 mm or a Weight for Length z score of less than  $-3$  with or without bilateral pitting oedema.

**Underweight** – is defined as body mass index (calculated as weight in kilograms divided by height in meters squared) z score  $< -2$  standard deviation.

**Stunting** (indicates chronic malnutrition), which is defined as height or length Z score below  $-2$ .

## Responsibility Statement

All authors have read and approved the final version of the manuscript. The corresponding author has full access to all of the data in this study and takes complete responsibility for the integrity of the data and accuracy of the data analysis.

### Author Contributions

**Joyce Gimonge:** conceptualization, funding acquisition, methodology, data curation, formal analysis, project administration, writing – original draft. **David Muhunzi:** writing – original draft, writing – review and editing, data curation, formal analysis, visualization, software. **Zawadi Edward:** conceptualization, writing – review and editing, supervision. **Rodrick Kisenge:** supervision, writing – review and editing, methodology.

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### Consent

Written informed consent was obtained from the guardians of all study participants.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Transparency Statement

The lead author, Joyce Gimonge, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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