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The role of the neutrophil–lymphocyte ratio for pre-operative risk stratification of acute kidney injury after tetralogy of Fallot repair

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Abstract

Introduction: Acute kidney injury is a risk factor for chronic kidney disease and mortality after congenital heart surgery under cardiopulmonary bypass. The neutrophil–lymphocyte ratio is an inexpensive and easy to measure biomarker for predicting outcomes in children with congenital heart disease undergoing surgical correction. *Objective:* To identify children at high risk of acute kidney injury after tetralogy of Fallot repair using the neutrophil–lymphocyte ratio. *Methods:* This single-centre retrospective analysis included consecutive patients aged < 18 years who underwent tetralogy of Fallot repair between January 2014 and December 2018. The pre-operative neutrophil–lymphocyte ratio was measured using the last pre-operative complete blood count test. We used the Acute Kidney Injury Network definition. *Results:* A total of 116 patients were included, of whom 39 (33.6%) presented with acute kidney injury: 20 (51.3%) had grade I acute kidney injury, nine had grade II acute kidney injury (23.1%), and 10 (25.6%) had grade III acute kidney injury. A high pre-operative neutrophil–lymphocyte ratio was associated with grade III acute kidney injury in the post-operative period ($p = 0.04$). Patients with acute kidney injury had longer mechanical ventilation time ($p = 0.023$), intensive care unit stay ($p < 0.001$), and hospital length of stay ($p = 0.002$). *Conclusion:* Our results suggest that the pre-operative neutrophil–lymphocyte ratio can be used to identify patients at risk of developing grade III acute kidney injury after tetralogy of Fallot repair.

Acute kidney injury is a serious and well-known complication of cardiac surgery under cardiopulmonary bypass, particularly in children. Acute kidney injury is associated with mortality, longer mechanical ventilation time, extended intensive care unit stay, and prolonged hospital admission.[1] Identifying children who are at high risk of acute kidney injury using low cost, readily available biomarkers could guide clinical care to prevent acute kidney injury.

Certain biomarkers, such as *N*-terminal pro-B-type natriuretic peptide, Galectin-3, ST2, interleukins, and tumour necrosis factor-α, have been used to stratify acute kidney injury after congenital heart surgery under cardiopulmonary bypass.[2–6] However, the test kits to measure them are not readily available, and some are expensive to measure.

The neutrophil–lymphocyte ratio, defined as the ratio of the absolute neutrophil–lymphocyte count, was identified as a widely available low-cost biomarker to predict outcomes such as acute kidney injury, low cardiac output syndrome, mortality, longer mechanical ventilation time, intensive care unit stay, and hospital admission for children with congenital heart disease after surgical correction under cardiopulmonary bypass.[7–13] This biomarker has been widely studied in adult patients, demonstrating its ability to predict outcomes in the post-operative period, even in apparently healthy individuals.[14–16] In children, it has only recently become a research focus.[7–11]

The aim of this retrospective analysis was to investigate the association between the pre-operative neutrophil–lymphocyte ratio and the risk of post-operative acute kidney injury in children undergoing tetralogy of Fallot repair under cardiopulmonary bypass.

Patients and methods

Patients who underwent tetralogy of Fallot repair between January 2014 and December 2018 were retrospectively enrolled from an existing database of 116 patients of a previous study.[10] The study was conducted at the Heart Institute (InCor) of the Hospital das Clínicas of Universidade de São Paulo, Brazil, whose institutional review board and ethics committee approved the study.

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Table 1. Baseline characteristics of 116 patients who underwent surgical correction of tetralogy of Fallot between January 2014 and December 2018

Variable	Non-acute kidney injury (77 patients)	Acute kidney injury (39 patients)
Gender (male:female)	(45:32)	(23:16)
Age (months)	8.7 (interquartile range: 6.5–15.7)	8.6 (interquartile range: 6.4–13.6)
Weight (kg)	7.7 (interquartile range: 6.5–9.5)	7.6 (interquartile range: 6.2–8.8)
Pre-operative ventricular dysfunction	0	0
Associated diagnosis	25 (21.6%)	17 (14.6%)
Pre-operative mechanic ventilation	4 (3.4%)	2 (1.7%)
Genetic syndrome	8 (6.9%)	6 (5.2%)
Down syndrome	5 (4.3%)	4 (3.4%)
Di George	0	1 (0.9%)
Other	3 (2.6%)	1 (0.9%)
Pre-operative serum creatinine (mg/dL)	0.35 (interquartile range: 0.28–0.39)	0.22 (interquartile range: 0.19–0.31)
Total neutrophil	3565 (interquartile range: 2498–4717)	3719 (interquartile range: 2649–5341)
Total lymphocyte	5751 (interquartile range: 3451–7890)	4435 (interquartile range: 3823–5907)
Neutrophil–lymphocyte ratio	0.61 (interquartile range: 0.34–1.18)	0.71 (interquartile range: 0.50–1.36)

We included all patients less than 18 years of age who underwent tetralogy of Fallot repair and for whom pre-operative complete white blood cell counts were available.

The exclusion criteria were reoperation, partial or total atrioventricular septal defect, pulmonary atresia with intact ventricular septum, pulmonary valve agenesis, coronary artery anomaly, severe pulmonary artery stenosis, or any other hemodynamically significant congenital heart disease, pre-operative hemodynamic instability, surgical complications leading to increased cardiopulmonary bypass and cross-clamp times, suspected or evidenced infection (leukocytosis), prior antibiotic administration during the same hospital admission, primary hematological or other immunological disease, or a positive viral screening.

Pre-operative demographic data included patient age, sex, and weight at the time of the surgery, oxygen saturation, pre-operative ventricular function, history of other associated congenital heart disease, presence of chromosomal or structural anomalies, need for pre-operative mechanical ventilation, most recent serum creatinine level, most recent pre-operative total neutrophil count, and total lymphocyte count obtained from the peripheral blood samples at 48 hours pre-operatively. All patients with phenotypic characteristics suggestive of genetic syndromes were tested at our institution.

Intra-operative variables included cardiopulmonary bypass and cross-clamp times, need for a transannular patch, and associated procedures.

Post-operative variables studied included post-operative (48 hours) and pre-discharge serum creatinine levels, acute dialysis, mechanical ventilation time, intensive care unit length of stay, total length of stay, in-hospital mortality, and re-admission within 30 days. All patients received corticosteroids in the operating room.

Definition of variables

The pre-operative neutrophil–lymphocyte ratio was defined as the ratio of the absolute neutrophil–lymphocyte count.

Post-operative acute kidney injury was defined according to the Acute Kidney Injury Network definition.[1] An increase in serum creatinine level from baseline can be used to classify acute kidney injury as grade I (≥150–200%), grade II (≥200–300%), or grade III (>300%).[1] Higher grades of acute kidney injury are associated with worse clinical outcomes.

The sample was divided into non-acute kidney injury (for all those who did not meet any of the Acute Kidney Injury Network criteria) and acute kidney injury (for all those who met any of the acute kidney injury criteria regardless of the degree of injury) groups.

Statistical analysis

Standard descriptive statistics were calculated. Continuous numerical variables are presented as median and interquartile range (25th–75th percentiles). Categorical variables are expressed as numbers and percentages of patients and were compared using the chi-square test. The Mann–Whitney U-test was used to compare two groups, whereas the Kruskal–Wallis test was used to compare more than two groups. A sub-analysis was performed to compare the non-acute kidney injury group with each group who developed acute kidney injury (grades I, II, and III). Receiver-operating characteristic curve analysis was used to determine the optimal cutoff levels of the pre-operative neutrophil–lymphocyte ratio that predicted acute kidney injury. The level of statistical significance was set at $p < 0.05$. The data were analysed using IBM SPSS (version 23.0; IBM Corp., Armonk, NY, USA) and MedCalc statistical software version 19.1.3.

Results

Pre-operative data are summarised in Table 1. A total of 116 patients were assigned to two groups according to the Acute Kidney Injury Network classification: non-acute kidney injury (77 patients) and acute kidney injury (39 patients) groups. The median age was 8.7 (interquartile range: 6.5–15.7) months for the non-acute kidney injury group and 8.6 (interquartile range: 6.4–13.6) months for the acute kidney injury group. The median weight was 7.7 (interquartile range: 6.5–9.5) kg in the non-acute kidney injury group versus 7.6 (interquartile range: 6.2–8.8) kg in the acute kidney injury group.

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Table 2. Intra-operative data complications and mortality of 116 patients who underwent surgical correction of tetralogy of Fallot between January 2014 and December 2018

Variables	Non-acute kidney injury (77 patients)	Acute kidney injury (39 patients)
Cardiopulmonary bypass (minutes)	125 (interquartile range: 110–145)	136 (interquartile range: 115–154)
Cross-clamp (minutes)	98 (interquartile range: 82–113)	105 (interquartile range: 93–117)
Transannular patch	39 (33.6%)	25 (21.6%)
Right ventricular dysfunction	2 (1.7%)	6 (5.2%)
Associated procedures	22 (19%)	20 (17.2%)
Atrial septal defect closure	7 (6.0%)	13 (11.2%)
Persistent ductus arteriosus occlusion	5 (4.3%)	2 (1.7%)
Persistent foramen oval occlusion	2 (1.7%)	1 (0.9%)
Pulmonary arteries repair	6 (5.2%)	3 (2.6%)
Atrial septal defect and pulmonary repair	2 (1.7%)	1 (0.9%)
Complications	10 (8.6%)	8 (6.9%)
Neurologic	3 (2.6%)	2 (1.7%)
Respiratory	1 (0.9%)	1 (0.9%)
Infection	1 (0.9%)	3 (2.6%)
Cardiogenic shock	1 (0.9%)	2 (1.7%)
Others	4 (3.4%)	0
Post-operative serum creatinine (mg/dL)	0.34 (interquartile range: 0.28–0.42)	0.53 (interquartile range: 0.40–0.74)
Acute kidney injury grade I	–	0.46 (interquartile range: 0.35–0.54)
Acute kidney injury grade II	–	0.68 (interquartile range: 0.45–0.74)
Acute kidney injury grade III	–	0.95 (interquartile range: 0.56–1.06)
Mechanical ventilation time (hours)	24 (interquartile range: 16–72)	48 (interquartile range: 18–201)
Intensive care unit length of stay (days)	6 (interquartile range: 4–9.5)	10 (interquartile range: 6–17)
Hospital length of stay (days)	12 (interquartile range: 9–16.5)	15 (interquartile range: 12–32)
Serum creatinine at discharge (mg/dL)	0.34 (interquartile range: 0.26–0.43)	0.35 (interquartile range: 0.27–0.42)
Re-admission in 30 days	6 (5.2%)	1 (0.9%)
In-hospital mortality	2 (1.7%)	3 (2.6%)

The median of saturation was the same between the two groups, 91% (interquartile range: 85–95%), but it varied within the acute kidney injury group; the more severe the acute kidney injury grade, the lower the saturation, grade I 92% (interquartile range: 81–95%), grade II 91% (interquartile range: 86–95%), and grade III 90% (interquartile range: 84–93%).

In the acute kidney injury group, the median serum creatinine level was 0.22 (interquartile range: 0.19–0.31) mg/dL and the median neutrophil–lymphocyte ratio was 0.71 (interquartile range: 0.50–1.36). In contrast, in the non-acute kidney injury group, the median serum creatinine level and the neutrophil–lymphocyte ratio were 0.35 (interquartile range: 0.28–0.39) mg/dL and 0.61 (interquartile range: 0.34–1.18), respectively.

The intra- and post-operative data are shown in Table 2. The median cardiopulmonary bypass time was 125 (interquartile range: 110–145) minutes in the non-acute kidney injury group versus 136 (interquartile range: 115–154) minutes in the acute kidney injury group. The median cross-clamp time was 98 (interquartile range: 82–113) minutes for the non-acute kidney injury group and 105 (interquartile range: 93–117) minutes for the acute kidney injury group (Table 2). Seventy-seven patients had no acute kidney injury, and 39 patients presented with acute kidney injury: grade I (21/39; 53.8%), grade II (8/39; 20.5%), and grade III (10/39; 25.6%). Minor additional procedures were performed in 36.2% of cases for atrial septal defect closure, patent ductus arteriosus occlusion, patent foramen ovale occlusion, and pulmonary artery repair.

Outcomes

A high pre-operative neutrophil–lymphocyte ratio was not associated with acute kidney injury in the present study ($p = 0.086$) (Fig 1a). When we analysed the non-acute kidney injury and grade III acute kidney injury groups, we observed an association between the neutrophil–lymphocyte ratio and grade III acute kidney injury ($p = 0.040$) (Fig 1b). In the receiver-operating characteristic analysis, the cutoff value of the pre-operative neutrophil–lymphocyte ratio as a predictor of grade III acute kidney injury was > 0.93, with a sensitivity of 70% and specificity of 71.7%. The area under the curve was 0.697 (95% confidence interval = 0.60–0.77; $p = 0.033$) (Fig 2). The Kruskal–Wallis test showed statistical significance between grades II and III acute kidney injury ($p = 0.029$), but this difference was not observed otherwise, possibly due to the small sample size.

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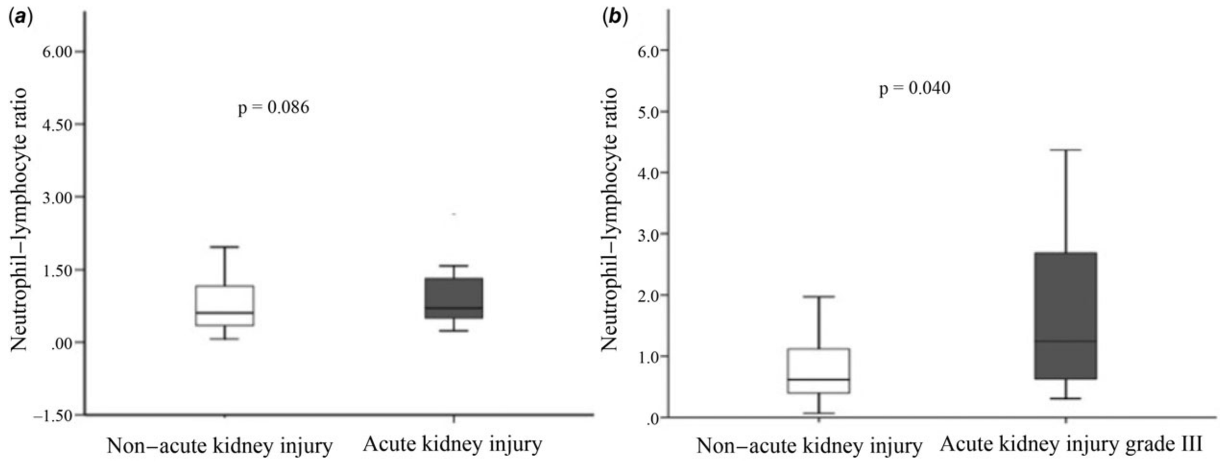

Figure 1. (***a***) No statistically significant differences were seen between patients in the non-acute kidney injury and acute kidney injury groups. (***b***) The association between neutrophil–lymphocyte ratio and grade III acute kidney injury.

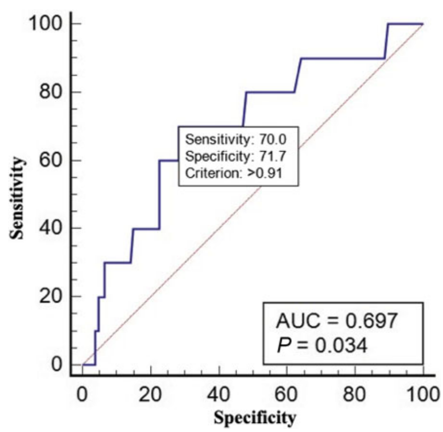

Figure 2. Receiver-operating characteristic analysis showing the pre-operative neutrophil–lymphocyte ratio as a predictor of acute kidney injury grade III with a cutoff value of > 0.93, a sensitivity of 70%, and specificity of 71.7%. The area under the curve was 0.697 (95% confidence interval = 0.60–0.77; p = 0.033).

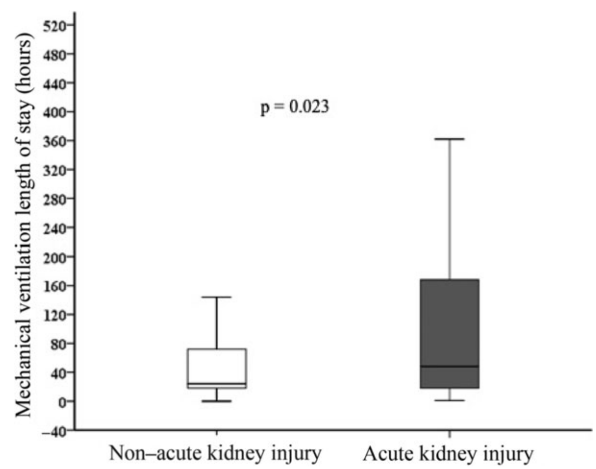

Figure 3. A demonstration of the association between a high neutrophil–lymphocyte ratio and prolonged mechanical ventilation time.

Patients in the acute kidney injury group had longer mechanical ventilation ($p = 0.023$), intensive care unit length of stay ($p < 0.001$), and hospital length of stay ($p = 0.002$) (Figs 3–5).

Thirty-day mortality occurred in 4.3% (five patients) of cases. Three of these patients were in the acute kidney injury group, including two patients with grade III acute kidney injury. Causes of death were cardiogenic shock in three patients and sepsis in two patients.

Discussion

In this retrospective study, we found that an elevated pre-operative neutrophil–lymphocyte ratio was associated with an increased incidence of grade III acute kidney injury during the first 48 hours after tetralogy of Fallot repair, although the difference between the non-acute kidney injury and acute kidney injury groups was not statistically significant. Acute kidney injury is a complex disease characterised by a decrease in renal excretory function lasting for a period of hours to days. The accumulation of waste products of nitrogen metabolism, such as creatinine and urea, occurs in a variety of clinical settings.[17] An increase in creatinine levels is associated with increased mortality. Acute kidney injury is most common in critically ill patients, with an incidence of approximately 5000 non-dialysis-requiring patients and 295 dialysis-requiring patients per million people per year, accounting for 30–50% of intensive care unit admissions.[1,17–19]

Cardiac surgery under cardiopulmonary bypass is the primary risk factor for acute kidney injury in intensive care unit admissions in developed countries.[1,18] Although a marked increase in serum creatinine level is associated with poor outcomes, even minor changes in serum creatinine level are associated with high mortality.[20]

In the pediatric population, acute kidney injury is also common, occurring in 5–45% of patients after congenital heart surgery.[19,21,22] Mortality in these patients can exceed 70% in the most severe forms of acute kidney injury.[22] This was not evident in our study, possibly due to the small sample size, although 60% of the patients died from acute kidney injury.

There is a need to identify patients who are likely to develop acute kidney injury during the post-operative period. In this study, 33.6% (39) of patients presented with acute kidney injury, which is similar to other studies.[19,21,22]

Significant progress has been made in identifying these patients pre-operatively using biomarkers. Some biomarkers, such as neutrophil gelatinase-associated lipocalin, *N*-terminal pro-B-type natriuretic

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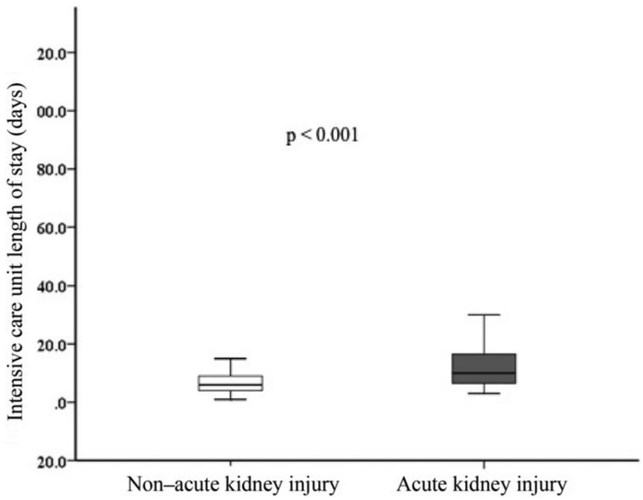

Figure 4. A demonstration of the association between a high neutrophil–lymphocyte ratio and intensive care unit length of stay.

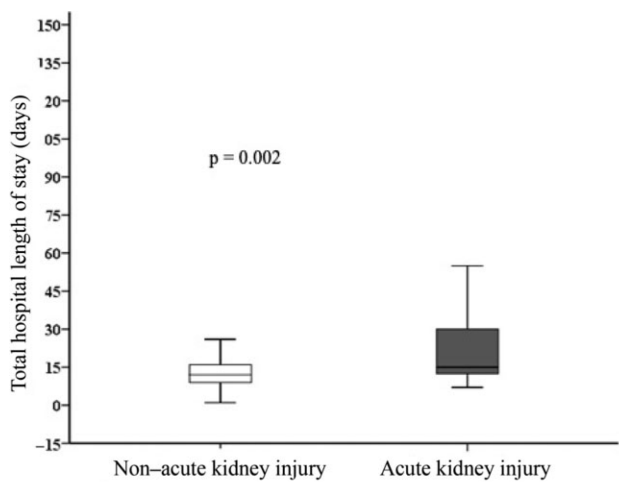

Figure 5. A demonstration of the association between a high neutrophil–lymphocyte ratio and total hospital length of stay.

peptide, Galectin-3, ST2, interleukins, and tumour necrosis factor-α, have been used to stratify acute kidney injury after congenital heart surgery under cardiopulmonary bypass.[2–6,23] These specific biomarkers are not readily available, and some are expensive.

A widely available and inexpensive pre-operative biomarker with the potential to predict acute kidney injury after congenital heart surgery would be of great clinical importance in the care of these patients.

The neutrophil–lymphocyte ratio was recently presented as an inexpensive and widely available predictor of outcomes such as acute kidney injury, low cardiac output syndrome, mechanical ventilation time, intensive care unit length of stay, and hospital length of stay, mortality, and 48-month survival for children with congenital heart disease after surgical correction under cardiopulmonary bypass.[7–13]

A study that analysed the role of pre-operative neutrophil–lymphocyte ratio in 53 patients with hypoplastic left heart syndrome who underwent the Norwood procedure showed that the pre-operative neutrophil–lymphocyte ratio was associated with a high post-operative serum creatinine level ($p = 0.001$).[8] In the present study, a sub-analysis demonstrated that a high pre-operative neutrophil–lymphocyte ratio was also associated with a high serum creatinine level ($p = 0.04$).

The reason why the neutrophil–lymphocyte ratio is higher in some patients is still unclear. However, possible hypotheses for both cyanotic and acyanotic patients have been proposed. Neutrophils are the first line of the innate immune system that responds to inflammation or injury, increasing the number of cytokines. Many cytokines reduce the number of lymphocytes that play a key role in the regulation of the inflammatory response. Thus, immunosuppression may impact the neutrophil–lymphocyte ratio.

For cyanotic patients, we believe that the response of the myocardium to stress caused by hypoxia is similar to that of bacterial infection and can be clinically relevant.[8,9] Cyanotic patients are continuously exposed to this condition, and consequently, an imbalance between the total number of neutrophils and lymphocytes is reflected in the pre-operative neutrophil–lymphocyte ratio.

For acyanotic patients, increased blood flow to the lungs causes vascular wall stress, leading to an inflammatory response. This causes chronic sub-clinical inflammation in the pre-operative period, even before fixed pulmonary artery hypertension occurs, which is reflected in the pre-operative neutrophil–lymphocyte ratio.[23] In conclusion, these patients may have a baseline inflammatory state in the immediate pre-operative period. The level of inflammation varies from patient to patient, and the cause is not yet known. We believe that the severity of cyanosis and the degree of pulmonary hypertension in cyanotic and acyanotic patients are possible contributing factors.

Ischemia caused by the non-endothelialised surface and continuous blood flow of cardiopulmonary bypass (vasoconstriction) is associated with severe surgical trauma and uncontrolled activation of the innate immune system in patients with a high pre-operative neutrophil–lymphocyte ratio, which can lead to tissue damage.[22,24] A high pre-operative neutrophil–lymphocyte ratio reflects the severity of the systemic inflammation.

As for saturation, it was the same between groups, with and without acute kidney injury, but it varied between different degrees of acute kidney injury; the more cyanotic, the greater the degree of injury. We believe that the same is due to the sample size of patients with acute kidney injury grade I and because they presented saturation similar to non-acute kidney injury when compared with acute kidney injury II or III. It is known that saturation less than or equal to 90% is associated with a higher concentration of pro-inflammatory cytokines in the myocardium of patients with congenital heart disease.[25]

Acute kidney injury is a multi-factorial disorder, but inflammation plays an important role in its pathogenesis. To the best of our knowledge, there is no evidence to explain the pathophysiology of the neutrophil–lymphocyte ratio in acute kidney injury in children undergoing congenital heart surgery under cardiopulmonary bypass.

Children with a high pre-operative neutrophil–lymphocyte ratio develop an exacerbated inflammatory response to surgical trauma and cardiopulmonary bypass, which can cause tissue damage to different organs, including the kidney.[5–7]

Why is the neutrophil–lymphocyte ratio not used as a prognostic biomarker in patients undergoing surgery to correct or palliate congenital heart disease?

The major advantages of the neutrophil–lymphocyte ratio over the prognostic biomarkers previously studied are that it is easy and

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inexpensive to measure. The neutrophil–lymphocyte ratio has been widely studied in adult patients with acquired heart disease, with promising results, but with little clinical application.[24,26]

The fundamental principle of preventing acute kidney injury is to treat the underlying cause or trigger. No established pharmacotherapy currently exists to prevent acute kidney injury.[11] Despite these efforts, current prevention strategies are ineffective.[20,21] The early identification of these patients using a low-cost biomarker will be important for the future development of more targeted therapies to prevent acute kidney injury, or to indicate that the placement of a peritoneal dialysis catheter should be performed prophylactically at the time of cardiac surgery.

It is possible that pre-operative inflammatory modulation can contribute significantly to these observations. To date, it seems that the decrease in the non-endothelialised surface of the cardiopulmonary bypass circuit, short cardiopulmonary bypass time, monitoring tissue oxygenation using near-infrared spectroscopy, and decreased hemolysis may decrease the incidence of acute kidney injury in the post-operative period.

Conclusion

Our study findings suggest that there was no statistically significant difference in the pre-operative neutrophil–lymphocyte ratio between the non-acute kidney injury and acute kidney injury groups. The pre-operative neutrophil–lymphocyte ratio can be used to identify patients at risk of developing grade III acute kidney injury after tetralogy of Fallot repair. It is an inexpensive and universally available test that may be an alternative biomarker for identifying patients at high risk of developing acute kidney injury. A preventive strategy can be applied for the placement of a peritoneal dialysis catheter at the time of cardiac surgery in patients with a high neutrophil–lymphocyte ratio.

Limitations. The main limitations of this study are its retrospective nature and single-centre design. Another limitation was the small sample size. Our sample was limited for homogeneity to eliminate potential bias.

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Conflicts of interest. None.

Ethical standards. This work complies with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008.

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