General Thoracic and Cardiovascular Surgery (2019) 67:669–676
https://doi.org/10.1007/s11748-019-01081-y

ORIGINAL ARTICLE

Neutrophil–lymphocyte ratio as a mortality predictor for Norwood stage I operations

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Received: 21 August 2018 / Accepted: 3 February 2019 / Published online: 21 February 2019

Abstract

Background Hypoplastic left heart syndrome is a lethal congenital heart malformation when untreated resulting in a 95% mortality in the first month of life. In this study, we aimed to investigate the newly introduced inflammatory biomarker, neutrophil–lymphocyte ratio, as a mortality predictor in postoperative hypoplastic left heart syndrome patients.

Methods Patients were divided into two groups; Group 1 consisted of 33 patients who were discharged and Group 2 including 20 patients who were deceased following surgery. Patients' preoperative demographic characteristics, total white blood cell counts, neutrophil counts, lymphocyte counts, neutrophil–lymphocyte ratio, C-reactive proteins, alanine aminotransferase, aspartate transaminase, urea, and creatinine levels were recorded. Studys' primary endpoint was all-cause patient mortality following surgery.

Results The preoperative neutrophil–lymphocyte ratio was found to be significantly different between the groups ($p=0.001$). High neutrophil–lymphocyte ratio was found to be associated with an increased risk of death. The ROC curves of neutrophil–lymphocyte ratio were found to be associated with mortality. The area under curve for the preoperative neutrophil–lymphocyte ratio was 0.74. Neutrophil–lymphocyte ratio predicted mortality with a sensitivity of 78% and a specificity of 65%.

Conclusion Neutrophil–lymphocyte ratio can contribute to the early identification of patients at high risk for complications. In addition, through the use of NLR, clinicians could implement measures for the optimal therapeutic approach of cardiac surgery patients and the elimination of adverse patient outcomes.

Keywords Hypoplastic left heart syndrome · Mortality · Congenital heart · Neutrophil–lymphocyte ratio · Biomarker

Introduction

Hypoplastic left heart syndrome is a lethal congenital heart malformation when untreated, resulting in a 95% mortality in the first month of life and accounting for 22% of the deaths caused by congenital heart disease in the first year of life [1]. In addition, It is high-risk congenital heart disease in spite of advances in surgical techniques, perioperative and postoperative management [2].

The inflammatory response is potentially initiated and maintained by complement activation via the alternate pathway, neutrophil activation and adhesion to endothelium and release of pro- and anti-inflammatory [3, 4]. The resulting endothelial dysfunction increases the microvascular permeability, tissue injury, and multiorgan dysfunction. Systemic manifestations of the inflammatory response include fever, reduced level of consciousness, hemodynamic instability, capillary leakage, pulmonary dysfunction and myocardial depression [3, 5].

The systemic inflammation is reflected by an increased number of neutrophil granulocytes in the circulation [6]. Neutrophils ensure rapid neutralization and clearance of pathogens during the onset of inflammation, and neutrophils contribute to tissue damage by secreting a number of proteolytic enzymes [7]. Higher neutrophil percent or lower lymphocyte percent can be considered to signify an increased inflammatory response. In adult studies, neutrophils, lymphocyte, and neutrophil–lymphocyte ratio have been used as markers for inflammation [8]. The neutrophil–lymphocyte ratio (NLR) is such a measurement instrument and it has been determined to be a potentially

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useful biopredictor of inflammation in cardiovascular disease [9]. Inflammation is a normal and expected process following surgery and the intensive care process. Therefore, increased and prolonged inflammation increases the risk of mortality and morbidity [10].

In our study, we aimed to determine the short-term mortality of elevated neutrophil–lymphocyte ratio in hypoplastic left heart syndrome patients undergoing Norwood stage I procedure.

Materials and methods

Following our institutional ethics committee (K 2016.3/1–6) approval, families read and signed an informed consent form. This is a retrospective study including 53 consecutive patients with single-ventricle physiology who underwent stage 1 procedure between May 2011 and August 2015 at our clinic.

For purposes of inclusion in this study, we selected patients with a diagnosis of hypoplastic left ventricle defined as aortic atresia/mitral atresia, aortic stenosis/mitral stenosis, aortic atresia/mitral stenosis, and aortic stenosis/mitral atresia. Patients with single left ventricle, unbalanced atrioventricular canal, double-outlet right ventricle, tricuspit atresia and patients who underwent hybrid procedure were excluded. Patients were divided into two groups; Group 1 consisted of 33 patients who were discharged, and Group 2 including 20 patients who were deceased following surgery; Sano shunt was applied in 16 patients and modified BT shunt was applied in 37 patients. Nine patients were entubated preoperatively.

Data collection

Demographic data were recorded, including gender, weight, gestational age and age at first surgery, and size of ascending aorta. Preoperative events such as endotracheal intubation, need for cardiopulmonary resuscitation were recorded. Renal function was evaluated with urea and creatinine, and hepatic function was evaluated with alanine aminotransferase and aspartate transaminase.

Intraoperative data included that operation time, cardiopulmonary bypass time, cross-clamp time, antegrade cerebral perfusion time, fluid volume perfused, unit of blood used, and inotrop score. Preoperative white blood cell counts, neutrophil counts, lymphocyte counts, neutrophil–lymphocyte ratio, and C-reactive proteins values of patients were recorded. Studys' primary endpoint was all-cause patient short-term mortality following surgery.

Surgical procedure

Our anesthesia protocol was standard in all the patients. Standard monitoring started with ECG and pulse oximetry followed by Fentanyl 5 µg/kg, rocuronium 1 mg/kg and midazolam 0.1 mg/kg for anesthesia induction. Orotracheal intubation, right radial artery, and right jugulary vein cannulation was performed subsequently, for continuous arterial and central venous pressure monitoring. After inhalation induction with sevoflurane, bolus doses of fentanyl, rocuronium and midazolam were repeated as needed. Norwood stage 1 procedure was performed using standard surgical techniques. Cardiopulmonary bypass was established via cannulation of double arterial (right innominate artery and descending aorta above the diaphragmatic segment) and bicaval venous cannulation. Operation was performed at moderate hypothermia. Cardioplegia was administered via innominate artery cannula (custodiol solution was used). After division of ductus arteriosus coarctated segment was excised and descending aorta was anastomosed to the arcus aorta at the posterior (dorsal) face and porcin pericardial patch was used to augment minor curvature of the arcus aorta. Proximal main pulmonary artery was anastomosed to the proximal aorta side to side with prolen sutures. Then, same pericardial patch is anastomosed to the anastomosed common ostium. 5-mm or 6-mm gore-tex graft was anastomosed to the autologus gluteraldehyde fixed pericardial patch. Then, patch is anastomosed to the pulmonary bifurcation. Atrial septectomy was performed via right atriotomy during rewarming. Then, gore-tex graft was anastomosed to the right ventricle anterior wall for completing Sano-type shunt. In cases where Sano shunt was not preferred, gore-tex graft was anastomosed to the innominate artery and right pulmonary artery. Completing the cardiopulmonary bypass was performed as usual techniques. We routinely prefer not to close sternum for the first day.

Early postoperative care of Norwood 1 procedures focused on ventilatory manipulation, of pulmonary vascular resistance, inotropic support for limit pulmonary blood flow. Systemic oxygen delivery was evaluated regularly with monitoring mixed oxygen saturation. Sedation and muscle paralysis continued until the sternum is closed and according to hemodynamic status.

Statistical analysis

Statistic analysis was performed with SPSS version 16.0 (SPSSInc., Chicago, IL, USA). Normally distributed continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed

as number and percentages. Demographic characteristics, perioperative variables, and calculated values were compared using an independent sample *t* test while Chi square test, Fisher's exact test were used for categorical variables. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cutoff levels of the preoperative neutrophil–lymphocyte ratio to predict mortality. Potential prognostic factors were entered into univariate models of mortality. Effects of different variables on mortality were calculated using univariate analysis. Multivariate analysis was completed for parameters with a threshold of $p < 0.15$ computed by univariate analysis. $p < 0.05$ was considered statistically significant.

Results

Fifty-three children with hypoplastic left heart syndrome who underwent Norwood stage 1 procedure were enrolled in the study. Thirty-eight patients (71.7%) were male and 15 patients (28.3%) were female. Four children were diagnosed premature upon admission to the pediatric intensive care unit. Four patients in Group 1 and, five patients in Group 2 were intubated preoperatively (Table 1).

In Group 1, median length of ventilation was 14 (8–25) days, the median length of stay in intensive care unit was 24 (15–53) days and length of stay in hospital was 46 (30–65) days and in this group, 5 (15.1%) patients underwent postoperative CPR.

9 of 53 patients were intubated, and in intubated patients, NLR was statistically higher than non-intubated patients ($p = 0.026$). Correlation between preoperative NLR and urea, creatinine, AST, ALT, CRP was evaluated. In addition, correlation between creatinine and NLR and between AST and NLR was statistically significant (respectively, $p = 0.03$, $p = 0.001$) but CRP, urea and ALT were not (respectively, $p = 0.9$, $p = 0.8$, $p = 0.6$).

Operative characteristics were evaluated for both groups. The amount of intravenous fluid used perioperatively and unit of blood products transfused during this period were similar between the groups ($p = 0.35$, $p = 0.27$) (Table 1).

The preoperative white blood cell, neutrophil counts, and neutrophil–lymphocyte ratio were found to be significantly different between groups (respectively, $p = 0.001$, $p = 0.001$, $p = 0.001$). Increased neutrophil–lymphocyte ratio was found to be associated with an increased risk of death but total white blood cell, neutrophil and lymphocyte counts, C-reactive proteins, alanine aminotransferase, aspartate transaminase, urea and creatinine levels were not different between the two groups (Table 2). The postoperative neutrophil count and NLR were significantly different between the groups (respectively, $p = 0.01$, 0.02) (Table 3).

The ROC curves of neutrophil–lymphocyte ratio were found to be associated with mortality following Norwood stage 1 operation. The area under curve (AUC) for the

Table 1 Preoperative and operative characteristics of patients versus overall mortality

Patients characteristics	Group 1 ($n = 33$)	Group 2 ($n = 20$)	p
Age at first surgery (day)	16.5 ± 1.4	16.1 ± 1.8	0.44
Gestational age			0.89
< 37 weeks	6 (18.2%)	4 (20%)	
≥ 37 weeks	27 (81.8%)	16 (80%)	
Sex (male), %	23 (69.7%)	15 (65%)	0.4
Weight (kg)	3.3 ± 0.6	3.2 ± 0.5	0.71
Preop. entubated patients	4 (17.4%)	5 (33.3%)	
Ascending aorta diameter (mm)	3.4 ± 1.8	3.0 ± 1.6	0.36
Cardiopulmonary resuscitation	7 (35%)	6 (18.2%)	0.17
HLHS type (%)			
AA/MA	11 (33.3%)	7 (35%)	
AA/MS	8 (24.2%)	6 (30%)	
AS/MA	4 (12.1%)	3 (15%)	
AS/MS	8 (24.2%)	4 (20%)	
Type of shunt (%)			
Sano shunt	10 (30.3%)	6 (30%)	0.41
Modified BT shunt	23 (69.7%)	14 (70%)	0.28
Operative data			
Intraoperative fluids (cc)	53.7 ± 4.0	55.1 ± 5.5	0.35
Intraoperative blood (cc)	72.5 ± 13.7	75.2 ± 8.5	0.27
Operative time (min)	205.3 ± 38.5	210.9 ± 42.8	0.18
CPB duration (min)	165.6 ± 46.7	168.2 ± 38.5	0.45
Cross-clamp time (min)	43.1 ± 12.6	44.8 ± 17.9	0.51

Table 2 Preoperative hematologic parameters of patients

	Group 1	Group 2	p	95% CI
Hematological parameters				
White blood cell (10^9/L)	10.4 ± 2.3	15.4 ± 3.8	**0.001**	**11–13.4**
Neutrophil count (10^9/L)	6.6 ± 1.7	12 ± 2.9	**0.001**	**7.6–9.9**
Lymphocyte count (10^9/L)	3.6 ± 0.9	3.1 ± 1.6	0.19	3–3.8
NLR	1.9 ± 0.6	5.3 ± 2.7	**0.001**	**2.47–4.08**
CRP (mg/dL)	0.8 ± 0.4	0.7 ± 0.3	0.11	0.7–0.9
Renal function				
Creatinine (mg/dL)	0.6 ± 0.2	0.7 ± 0.1	0.32	0.6–0.7
Urea (mg/dL)	56 ± 21	59 ± 19	0.72	50–64
Liver function				
AST (U/L)	35.8 ± 11.6	38.3 ± 10.2	0.5	33–40
ALT (U/L)	42 ± 17.8	47.3 ± 17.1	0.38	38–50

Statistically significant values are in bold (P < 0.05)

Table 3 Postoperative hematologic parameters of patients

	Group 1	Group 2	*p*	95% CI
Hematological parameters				
Neutrophil count (10^9/L)	7.5 ± 2.8	13.6 ± 4.8	**0.01**	**0.79** to **6.2**
Lymphocyte count (10^9/L)	3.4 ± 1.6	2.8 ± 0.4	0.38	− 1.7 to 0.7
CRP (mg/dL)	1.2 ± 0.7	1.58 ± 1.8	0.43	− 0.6 to 1.4
NLR	2.79 ± 1.75	4.84 ± 2.8	**0.02**	**0.27 to 3.8**
Renal function				
Creatinine (mg/dL)	0.5 ± 0.24	1.09 ± 0.5	**0.001**	**0.29 to 0.9**
Urea (mg/dL)	30.9 ± 16.5	35.1 ± 14.9	0.46	− 7.1 to 15.5
Liver function				
AST (U/L)	84.4 ± 82.6	297.7 ± 437.2	**0.02**	**4.3 to 422.3**
ALT (U/L)	52.8 ± 16.6	72.5 ± 104.6	0.06	− 12.3 to 107.7

Statistically significant values are in bold (P < 0.05)

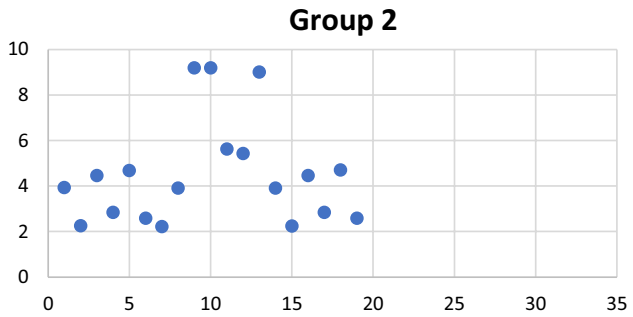

Fig. 1 Distribution of nonsurvival groups' NLR

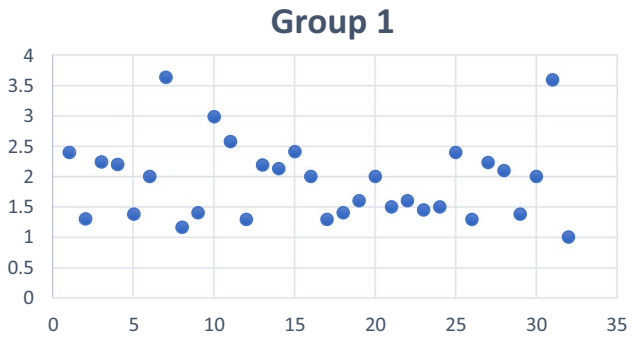

Fig. 2 Distribution of survival groups' NLR

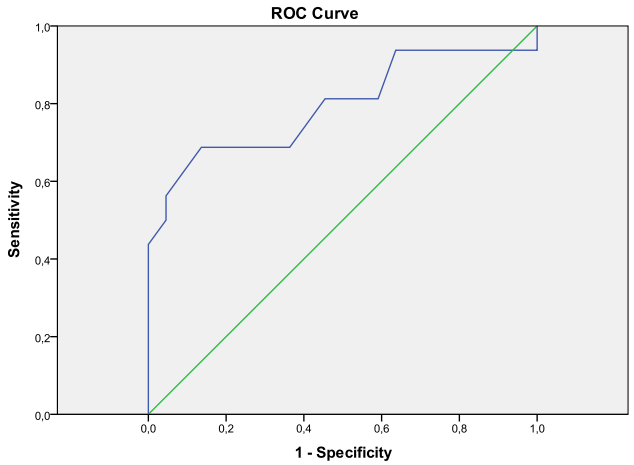

Fig. 3 The receiver-operating characteristic (ROC) curve analysis of neutrophil to lymphocyte ratio for mortality prediction

Table 4 Causes of death

	No. of patients	%
Right ventricular failure	7	35
Infection	5	25
Sudden death or arrhythmia	2	10
Necrotizing enterocolitis	2	10
Failure of tricuspid valve	4	20

preoperative neutrophil–lymphocyte ratio was 0.74 (95% CI 0.63–0.95; $p = 0.001$). Using a cutoff value of 2.57, the preoperative neutrophil–lymphocyte ratio predicted mortality with a sensitivity of 78% and specificity of 65%. When the study population was divided into 2 groups using a cutoff value of 2.57, the odds ratio (OR) of patients with a neutrophil–lymphocyte ratio greater than 2.57 was calculated as 13 (95% CI 2.7–62.9; $p = 0.001$). The distribution of groups were shown (Figs. 1, 2, 3).

Causes of death were added (Table 4) and the preoperative neutrophil–lymphocyte ratio cutoff value of 2.57 remained as a univariate independent predictor of mortality (OR 1.06; 95% CI 0.86–1.26; $p = 0.001$) together with age at first surgery, total WBC count, neutrophil count, CRP and ALT (Table 5). In the multivariate model which included neutrophil–lymphocyte ratio, age at first surgery, total white blood cell count, neutrophil count, C-reactive proteins, alanine aminotransferase and neutrophil–lymphocyte ratio

Table 5 Univariate analysis of mortality predictors

	Odds ratio	95% CI	*p*
Age at first surgery	1.03	−0.99 to 1.07	0.07
Prematurity	0.89	0.22 to 3.63	0.87
White blood cell (10^9/L)	**1.62**	**1.17 to 2.07**	**0.001**
Neutrophil count (10^9/L)	**1.55**	**1.26 to 1.84**	**0.001**
Lymphocyte count (10^9/L)	0.31	−0.16 to 0.78	0.19
NLR	**1.06**	**0.86 to 1.26**	**0.001**
CRP (mg/dL)	0.32	−0.06 to 0.7	0.11
Creatinine (mg/dL)	0.88	−1.22 to 1.47	0.32
Urea (mg/dL)	0.69	−0.01 to 1.19	0.72
AST (U/L)	0.79	−0.02 to 1.37	0.51
ALT (U/L)	0.79	−0.01 to 1.23	0.11
CPB duration (min)	1.2	−0.7 to 1.7	0.43
Cross-clamp time (min)	0.97	−0.87 to 1.07	0.38
Antegrade cerebral perfusion (min)	1.25	−0.91 to 1.81	0.16
Entubated patients	0.65	−0.21 to 2.15	0.19
Vasoactive-inotrop score	**1.58**	**0.73 to 2.11**	**0.02**
Cardiopulmonary resuscitation	2.42	0.68 to 8.67	0.17

Statistically significant values are in bold (P < 0.05)

Table 6 Multivariate analysis of mortality predictors

	Odd ratio	95% CI	*p*
NLR	**5.36**	**4.42 to 6.29**	**0.001**
White blood cell (10^9/L)	**4.63**	**2.65 to 6.61**	**0.001**
Neutrophil count (10^9/L)	**5.41**	**3.86 to 6.94**	**0.001**
Age at first surgery	1.01	−0.95 to 1.15	0.21
CRP	0.66	−0.04 to 0.8	0.11
ALT	5.2	−6.6 to 17	0.38

Statistically significant values are in bold (P < 0.05)

(NLR > 2.57; OR 5.36; 95% CI 4.42–6.29; $p = 0.001$) were found to be independent predictors of mortality. In addition to high vasoactive-inotrop score found to be associated with mortality (OR 4.16; 95% CI 2.68–6.73; $p = 0.02$) but postoperative cardiopulmonary resuscitation did not affect survival after successful Norwood operations for hypoplastic left ventricle patients ($p = 0.17$) (Table 6).

Discussion

In our retrospective study results of 53 infants with hypoplastic left ventricle syndrome, we found that elevated NLR on admission was associated with short-term mortality.

Early death is associated with change in the pulmonary-to-systemic flow ratio and low cardiac output, but understanding of the reasons of the high post-procedural mortality is still incomplete. Many risk factors for early mortality after Norwood procedure have been reported, but its controversy still exists [11].

We lost 20 patients after Norwood stage 1 procedure. Postoperative right ventricle failure with low cardiac output occurred in 7 patients (35%), infection caused death in 5 patients (25%), failure of tricuspid valve was the cause of death in 4 patients (20%), in 2 patients (10%) sudden death as a result of arrhythmia occurred, and necrotizing enterocolitis was the cause of death in 2 patients (10%) (Table 5).

Reported risk factors for early mortality after the Norwood procedure differ among centers and include patient-related factors such as prematurity, genetic or noncardiac abnormalities [12], anatomic factor such as smaller ascending aorta, operative factors such as older age at surgery, DHCA time [13], shunt type [14], and CPB time [15]. Differences in reported risk factors between centers can reflect variation among centers, variation in patients or small number of patients.

The risk factors such as cardiopulmonary bypass time, cross-klemp time, small ascending aortic diameter were not associated with mortality in our study similar to reports by Kern et al. [16]. A smaller ascending aorta does not change the hemodynamic conditions after operation.

Some studies have shown that renal or hepatic injury are risk factors for operative mortality in hypoplastic left ventricle [17] but in our study operative survival was not found to be associated with preoperative renal or hepatic organ damage. Preoperative serum level of aminotransferases, urea, and creatinine was not found to be predictors of mortality.

Prematurity is a risk factor for operative mortality as reported by Daebritz et al. [18]. This observation may be associated with age (maturity of the child), but there is no consensus of opinion that this factor can affect short-term survival [19, 20]. In our study, prematurity was not associated with operative mortality. This is similar to the reports by Sano et al. [21].

The inflammatory response is potentially initiated and maintained by complement activation via the alternate pathway, neutrophil activation and adhesion to endothelium, and release of pro- and anti-inflammatory cytokines. The resulting endothelial dysfunction increases the microvascular permeability, tissue injury, and multiorgan dysfunction. Systemic manifestations of the inflammatory response include fever, reduced level of consciousness, hemodynamic instability, capillary leakage, pulmonary dysfunction, and myocardial depression [22].

Previous studies demonstrated an association between morbidity and mortality of patients with cardiovascular disease and systemic changes in leucocyte subtypes such as neutrophilia, lymphopenia, and increased neutrophil–lymphocyte ratio [23]. In the postoperative period, increased neutrophil–lymphocyte ratio not only assesses the immune

condition of the patient but also provides valuable clues regarding morbidity and mortality. Elevated neutrophil–lymphocyte ratio has been shown to be associated with increased tumor necrosis factor (TNF) alpha and various interleukins levels (IL-6, IL-7, IL-8, IL-12, IL-17) [24]. These markers are known to be associated with poor outcome in critically ill patients, as well as with increased incidence of recurrent ischemic events in cardiac patients [24].

Multiple markers of inflammation such as C-reactive protein, fibrinogen, and various interleukin levels have been used to predict cardiovascular morbidity and mortality in the adult population, but these values are not routinely obtained in the pediatric populations [25]. The immunological mechanisms and anatomical characteristics are relatively different in children compared to adult [26].

Nevertheless, white blood cell counts with differentials are routinely obtained in the pediatric cardiac patients undergoing cardiac surgery. Inflammatory cytokines are useful biomarkers, although their increased cost, and limited availability. White blood cell count is a widely used and low-cost inflammatory marker, and neutrophils and leukocytes are known to play a significant role in the course of inflammatory disease. Cabrera et al. [27] showed that preoperative lymphopenia had an increased likelihood of postoperative mortality, longer hospital stay, longer length of mechanical ventilation, and in another study, Jones et al. [28] found that lymphopenia was a predictor of increased likelihood of postoperative mortality and longer postoperative stay. On the contrary, in our study, we did not find a difference between preoperative lymphocyte counts in two groups, although lymphopenia in both groups. Patients undergoing cardiac surgery with cardiopulmonary bypass have been shown to have a characteristic postoperative lymphopenia and even preoperative cell count is normal [29]. It may possible that lower lymphocyte counts were in a more stressed state preoperatively.

Neutrophils play an important role in the acute inflammatory response to tissue injury and reperfusion injury [30]. Cooper et al. [31] and Gurm et al. [32] showed a significant association between elevated neutrophil count as well as reduced lymphocyte count and cardiac death. Another study by Bocsi et al. [33] found that preoperative neutrophilia and lymphopenia were associated with postoperative effusions and edema. Thus, activated immune system preoperatively may result in an in a more pronounced systemic inflammatory response to the stress of tissue injury, cardiac operations, especially in patients undergoing cardiopulmonary bypass and it could contribute to worsened outcomes. In our study, we found neutrophilia in all the patients. Nonetheless, neutrophil count was higher in Group 2 than Group 1 and neutrophil count was a predictor of mortality. More recent studies found the NLR to be more sensitive predictor of adverse outcomes in cardiac patients [34].

The NLR is a low cost, routinely used, derived from the white blood cell count and has been shown to be a marker of systemic inflammatory response. Neutrophils induce the secretion of several inflammatory cytokines, and the inflammation thus triggered by these molecules can lead to further inflammation due to cell dysfunction in various organs.

Appachi et al. showed that the inflammatory response was significantly higher in hypoplastic left ventricle patients preoperatively as well as postoperatively. There was a correlation between the degree of inflammatory response and postoperative outcome in all neonates and mortality in the hypoplastic left ventricle patients. The study showed that the HLHS group of infants was at risk for significant activation of the inflammatory cascade before CPB. The hemodynamic instability and stress that these neonates were exposed to preoperatively may explain this finding [35].

Mitchell et al. showed that there was a significantly higher NLR the first day after hybrid procedure in patients that subsequently required an arch intervention. In addition, they evaluated that anatomical issues may place these patients at increased risk for arch intervention if one starts with a narrow orifice, but the underlying cause of ongoing stenosis is likely secondary to inflammation and fibrosis due to the PDA stent. In adult, the development of coronary stent restenosis is complex and multifactorial, but inflammation probably plays a major role [36].

Recent studies have shown that complete blood count parameters may reflect inflammation. In this regard, NLR has been widely studied in various disease and in particular cardiovascular pathologies [37, 38]. Silberman et al. [39] found that elevated NLR is associated with a higher incidence of adverse outcomes after cardiac surgery. Increased lymphocyte number is an indicator of an incompetent active inflammatory process. Correlation between lymphopenia, progression of atherosclerosis and major cardiac complications has been demonstrated [40]. As activated neutrophils have a crucial role in a majority of inflammatory processes, local pulmonary vascular inflammation may affect neutrophils and also platelets [41].

Gursoy et al. evaluated the correlation of NLR and CRP values with pulmonary artery pressure in 201 pediatric cardiac surgery cases. In this series with positive correlation between NLR and CRP with pulmonary artery pressure, the NLR was significantly higher in patients in whom postoperative pulmonary hypertensive crisis developed [42].

Total white blood cell count was the first biopredictor associated with mortality. Bagger et al. determined white blood cell as a predictor of post-coronary artery bypass graft 30-day mortality in their study on 2058 patients [43]. Newal et al. also demonstrated a correlation between preoperative white blood cell count and perioperative myocardial injury and 1-year mortality [44]. As white blood cell count is a nonspecific marker that can increase due

to various conditions, it is accepted to be a non-reliable marker by itself, thus studies to obtain specific markers has gained popularity.

Demir et al. showed that higher NLR has a positive correlation with pressure and is elevated in non-dippers compared with dippers. It is very well known that inflammation plays an important role in myocardial ischemia [45]. Suliman et al. suggest that neutrophil–lymphocyte ratio provides a simple and inexpensive method for the assessment of inflammatory status in patients with acute coronary syndrome [46].

Nunez et al. showed that a decreased relative percentage of lymphocytes correlate with morbidity and mortality in acute heart failure patients [47]. Uthamalingam et al. demonstrated that patients with acute decompensated heart failure in the highest tertile for neutrophil–lymphocyte ratio, experienced increased mortality and 30-day readmission rate [48]. In our study, increased NLR (cutoff value 2.57) predicted mortality. This is a simple clue that makes NLR worth to be evaluated as a mortality predictor.

In summary, we found that the NLR is an easily calculated parameter from the blood count test and is an inflammatory biomarker in the determination of the inflammatory condition. However, increased and prolonged inflammation increases the risk of mortality and morbidity. It may contribute to the early diagnosis of patients with a high risk of mortality. In addition, they can contribute to our planning of the interventions and treatments for these patients, the optimal therapeutic approach and measures to eliminate negative patient outcomes.

Limitation

The study was single centered, retrospective and consisted small number of patients. Further studies are needed to explain the mechanism and evaluate the therapeutic applications of these findings. The use of morbidity and mortality as a primary endpoint provides an objective measure of the outcome. On the other hand, no data were obtained about other important factors of morbidities and mortalities such as prenatal diagnosis, surgical technique and neonatal management of children with hypoplastic left ventricle. Data are also lacking about pre- and postoperative medications, and the effect of general improvement in surgical technique and perioperative care could not be analyzed in the study. Another limitation of our study is the lack of measurement for known inflammatory markers such as interleukins, procalcitonin, and erythrocyte sedimentation rate. However, the topic merits further investigations among a large-scale sample with various congenital cardiac pathologies.

Funding No financial support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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