Journal of the American Heart Association

ORIGINAL RESEARCH

Prognostic Value of Preoperative Absolute Lymphocyte Count in Children With Tetralogy of Fallot

Xie Wu, MD; Qipeng Luo, MD; Zhanhao Su, MD; Yinan Li, MD; Hongbai Wang, MD; Su Yuan, MD; Fuxia Yan, MD

BACKGROUND: Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. Absolute lymphocyte count (ALC) is a low-cost and easy-to-obtain inflammatory indicator; however, its association with the prognosis of patients with TOF remains unknown. This study aimed to determine the prognostic value of preoperative ALC in children with TOF.

METHODS AND RESULTS: This retrospective study included 707 patients aged <6 years who underwent corrective operations for TOF between January 2016 and December 2018 in Fuwai Hospital, China. The end points were mortality, extracorporeal membrane oxygenation placement, postoperative hospital stay >30 days, and severe postoperative complications; patients were grouped on the basis of prognosis: poor prognosis (n=76) and good prognosis (n=631). Univariable and multivariable logistic regression analyses were performed to identify the independent risk factors for poor prognosis, on which a risk scoring system was based. The receiver operating characteristic curve was used to assess model performance. Using another model without ALC, the effect of the addition of ALC was assessed. Results suggested that ALC was an independent factor with a cutoff point of 4.36×10^9/L. The addition of ALC improved the area under the curve from 0.771 to 0.781 (P<0.001). To avoid reverse causality and further control for confounding factors, the patients were further divided on the basis of ALC level, and a propensity score matching was performed; 117 paired patients were identified for further analysis. Low ALC levels had an odds ratio of 3.500 (95% CI, 1.413–8.672).

CONCLUSIONS: Low preoperative ALC represents an independent predictor of poor prognosis in children with TOF.

Key Words: lymphocyte ■ prediction ■ prognosis ■ tetralogy of fallot

Tetralogy of Fallot (TOF) is a common congenital heart defect characterized by ventricular septal defect, pulmonary artery stenosis, overriding aortic root, and right ventricular hypertrophy. Although its birth prevalence is low, with an incidence of 3.6 per 10 000 live births globally[1] and 2.1 in China,[2] it is still one of the most common congenital heart defects. Because of the advancements in surgical techniques, more children can survive, and have excellent long-term outcomes through TOF repair.[3] The prognosis after TOF repair is related to many factors, such as age, weight, surgical eras, concurrent genetic syndrome, previous palliative procedure, and cardiopulmonary bypass (CPB) time[3–8]; however, few studies have considered the impact of absolute lymphocyte count (ALC).

As one of the most common, easily acquired, and low-cost preoperative indexes, ALC is closely related to the general health status and chronic inflammatory state. Previous studies of other types of cardiac surgery in adults[9–11] and children[12–16] showed that patients with a decreased ALC preoperatively tended to have adverse outcomes. However, the detailed effect of ALC on the prognosis of children with TOF remains unknown. Therefore, this retrospective study aimed to

Correspondence to: Fuxia Yan, MD, Department of Anesthesiology, Fuwai Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College, 167 Beilishi Rd, Xicheng District, Beijing, 100037, China. E-mail: yanfuxia@sina.com

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Children with tetralogy of Fallot and a lower preoperative absolute lymphocyte count level are associated with poor prognosis after surgery.
- Younger age, longer cardiopulmonary bypass time, lower body surface area, and preoperative blood oxygen saturation are independent risk factors for poor prognosis.

What Are the Clinical Implications?

- Absolute lymphocyte count is a common, cheap, and readily available parameter that is an excellent prognosticator for children with tetralogy of Fallot.
- We constructed a scoring system using 5 factors: age, body surface area, cardiopulmonary bypass time, preoperative blood oxygen saturation, and absolute lymphocyte count, as these factors have shown good predictive ability for prognosis after corrective operations for tetralogy of Fallot.

Nonstandard Abbreviations and Acronyms

ALC	absolute lymphocyte count
CPB	cardiopulmonary bypass
PSM	propensity score matching
SpO_2	blood oxygen saturation
TOF	tetralogy of Fallot

determine the prognostic value of preoperative ALC in children with TOF.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because other related projects are in progress.

Study Design and Participants

This observational retrospective study was conducted at Fuwai Hospital, Beijing, China. The study was approved by the institutional review committee with a waiver of informed consent. We collected the clinical data of 782 patients who had undergone corrective operations for TOF (from January 2016 to December 2018). The exclusion criteria were as follows: (1) patients aged >6 years; (2) patients with known risk factors for poor prognosis, including previous palliative operations,[3,4,6] complex malformations[5,17](double-outlet right ventricle, complete endocardial cushion defect, right ventricular outflow tract stenosis, and severe pulmonary hypertension), and concurrent genetic syndrome,[3,12] such as Di George and trisomy 21; (3) patients with abnormal mechanical ventilation, such as those chronically mechanically ventilated or those who underwent surgery with a laryngeal mask; (4) emergency surgery; and (5) death within the first 48 hours after surgery. After applying the exclusion criteria, 707 patients were finally included in the analyses, of which 76 had a poor prognosis (Figure 1). On the basis of the rule of 5 to 10 events per variable in logistic regression,[18,19] there was a sufficient number of events allowing for the multivariable model.

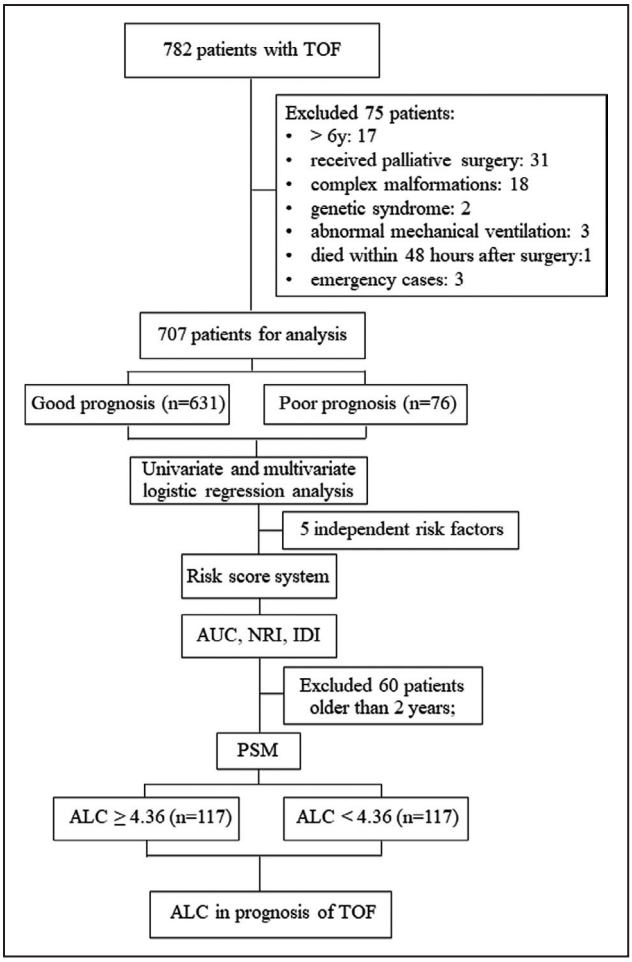


Figure 1. Flowchart of this study.
ALC indicates absolute lymphocyte count; AUC, area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement; PSM, propensity score matching; and TOF, tetralogy of Fallot.

Variables and Definitions

Patient data related to the procedure and anesthetic were obtained from the medical records and were checked by 2 independent medical researchers. No informed consent was required for this study. Demographic data included gestational age, age, sex, weight, and height. Body surface area (BSA) was calculated through height and weight (BSA=0.0061×height [cm]+0.0128×weight [kg]−0.1529). Preoperative data included diagnosis, blood oxygen saturation (SpO_2), American Society of Anesthesiologists Physical Status Classification, left ventricular ejection fraction, and routine blood test results, including white blood cell count, ALC, absolute neutrophil count, absolute monocyte count, hemoglobin levels, and platelet counts. Operative data included CPB time, aortic cross-clamp time, minimum temperature during CPB, intraoperative blood loss, red blood cell transfusion, and infusion volume. Postoperative data included postoperative complications, duration of mechanical ventilation, length of intensive care unit stay, length of hospital stay, length of postoperative hospital stay, and total cost of hospitalization. One of the authors had full access to all the data in this study and takes responsibility for their integrity and analyses.

Outcomes

Our study outcomes were as follows: in-hospital mortality, extracorporeal membrane oxygenation placement, postoperative hospital stay > 30 days, or any untoward severe postoperative complications that were life threatening or resulted in mortality,[20] such as respiratory failure or extubation failure, thromboembolic events, significant cardiac disorders, severe cerebrovascular accident, and severe renal failure. Extubation failure was defined as a failure to extubate within the first 120 hours after the operation or the need for reintubation and ventilation within 24 hours after tube removal. The outcomes of patients were independently assessed by 2 experienced physicians. Poor prognosis was defined as the adverse outcomes listed above.

Statistical Analysis

The workflow of the analysis is depicted in Figure 1. Statistical analysis was performed using SPSS software version 26 (IBM Corp, Armonk, NY), and $P<0.05$ was considered statistically significant. Continuous variables were presented as medians with interquartile ranges, and categorical variables were presented as frequencies and percentages. The participants were first stratified into the poor and good prognosis groups. The differences in baseline and perioperative characteristics between the 2 groups were compared using the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Univariable and multivariable logistic regression analyses were performed to evaluate the association between preoperative ALC and prognosis. Preoperative and intraoperative variables with $P<0.1$ in Mann-Whitney *U* test and χ^2 test or clinically relevant variables were included in a forward selection multivariable logistic regression model.

On the basis of the above-mentioned multivariable logistic regression model, we further constructed a risk score model by transforming continuous variables into categorical variables. Age was categorized according to clinically meaningful cutoff values; the other variables were categorized on the basis of the cutoff points calculated by receiver-operating characteristic curves, and the best threshold was the one that minimized the distance to the ideal point (sensitivity=specificity=1) on the receiver-operating characteristic curve. The subscores of each factor were the b-coefficients of the logistic regression model divided by the model's minimum coefficient and rounded to the nearest integers.[21] Receiver-operating characteristic curves were also used to evaluate the discriminative performance of the scoring system and compared using the DeLong method.[22] Moreover, to assess whether the incorporation of ALC can provide greater information to the clinical setting, we established another model without ALC, and compared the 2 models by calculating the area under the curve (AUC), net reclassification improvement, and integrated discrimination improvement.

Although the above logistic regression model showed that preoperative ALC of $<4.36\times10^9$/L was an independent risk factor for prognosis, we could not avoid reverse causality. Reverse causality means the

Table 1. Patients With Adverse Outcomes

Adverse Outcomes	No. (%) of Patients
Death	3 (0.42)
ECMO placement	2 (0.28)
LOPS >30d Severe complications	10 (1.41)
Respiratory failure or extubation failure	47 (6.65)
Thromboembolic events	7 (0.99)
Significant cardiac disorders	13 (1.84)
Severe cerebrovascular accident	3 (0.42)
Severe renal failure	20 (2.83)
Total	76 (10.75)

Values are presented as number (percentage) of patients. Total number exceeds 76 as patients may have had >1 major adverse outcome. ECMO indicates extracorporeal membrane oxygenation; and LOPS, length of postoperative hospital stay.

outcome preceded and led to the exposure instead of conversely, which can influence findings in cardiovascular research.[23] To avoid reverse causality and further control for confounding factors, we limited the age to <2 years, and redivided the patients into low (<4.36×10^9/L) and high (≥4.36×10^9/L) groups based on ALC level. Then, propensity score–matching (PSM) analysis was performed to minimize the influence of confounding factors (age, BSA, SpO_2, and CPB time). Through nearest neighbor matching, each patient in the low ALC group was matched with one patient in the high ALC group, and a caliper of width equal to 0.02 of the SD of the logit of the propensity score. The conditional logistic regression was used to compare variables between the 2 groups after PSM.

RESULTS

A total of 707 patients were enrolled in this study: 76 patients with poor prognosis and 631 patients with good prognosis. Table 1 presents a summary of poor prognoses, with an incidence of 10.75%; there were 3 in-hospital deaths (mortality rate, 0.42%).

Demographic data and preoperative and intraoperative variables of the patients in both groups are shown in Table 2. In the overall 707 patients, the median (interquartile range) age was 9 (6–14) months, median weight was 8.5 (7.4–9.8) kg, and median SpO_2 was 89% (82%–95%). There was a significant male predominance (61.0% versus 39.0%), and the American Society of Anesthesiologists Physical Status Classification was mainly III (635 [89.82%]) or IV (72 [10.18%]). All operations were performed on CPB, with a median CPB time of 98 (82–120) minutes, aortic cross-clamp time of 68 (55–85) minutes, and the minimum temperature of 30°C (28°C–30). Compared with the patients with a good prognosis, the patients with poor prognosis were younger, were shorter, weighed less, and had a lower preoperative SpO_2, white blood cell count, ALC, and platelet count. During the procedures, the patients with a poor prognosis had longer CPB and aortic cross-clamp times and lower minimum temperature.

According to the results in Table 2, we selected 10 potential risk factors and calculated their odds ratios and 95% CIs through a univariable logistic analysis. The results are shown in Table 3. Then, a multivariable logistic regression analysis was performed, and 5 variables (age, BSA, SpO_2, CPB time, and preoperative ALC) were included in the final model. The results showed that after adjusting for the 10 potential risk factors, a longer CPB time was significantly associated with poor prognosis, and higher age, BSA, preoperative SpO_2, and ALC were significantly associated with a good prognosis.

Table 2. Demographic and Perioperative Data in Patients With Good and Poor Prognosis

Variables	Good Prognosis (n=631)	Poor Prognosis (n=76)	*P* Value
Demographics			
Gestational age, mo	39 (38–40)	39 (38–40)	0.322
Age at operation, mo	9 (6–14)	7 (6–10)	0.006
Sex (men/women)	(380/251)	(51/25)	0.245
Weight, kg	8.6 (7.5–10.0)	8.0 (6.8–9.0)	0.001
Height, cm	70 (66–76)	67 (63–72)	<0.001
BSA, m^2	0.39 (0.35–0.43)	0.36 (0.32–0.40)	<0.001
Preoperative data			
SpO_2, %	89 (81–95)	82 (72–88)	<0.001
ASA class (III/IV)	(570/61)	(65/11)	0.191
LVEF, %	66 (64–71)	65 (62–70)	0.160
Concomitant cardiac malformations, n (%)			
ASD	63 (9.98)	8 (10.53)	0.882
PDA	58 (9.19)	10 (13.16)	0.268
PFO	176 (27.89)	17 (22.37)	0.307
PLSVC	23 (3.65)	6 (7.89)	0.145
Blood: routine parameter			
WCC, ×10^9/L	9.72 (8.08–11.90)	9.13 (7.43–11.37)	0.055
ANC, ×10^9/L	2.33 (1.67–3.45)	2.56 (1.69–3.50)	0.472
ALC, ×10^9/L	6.18 (4.72–7.88)	5.43 (3.74–6.82)	0.004
AMC, ×10^9/L	0.57 (0.44–0.73)	0.56 (0.45–0.79)	0.805
Hb, g/L	128 (113–146)	128 (108–151)	0.994
PLT, ×10^9/L	315 (250–389)	293 (191–386)	0.017
NLR	0.41 (0.26–0.58)	0.44 (0.33–0.64)	0.031
PLR	51.39 (38.40–68.16)	49.67 (35.15–75.17)	0.943
Intraoperative data			
CPB time, min	96 (81–117)	110 (89–134)	<0.001
ACC time, min	66 (54–84)	78 (61–98)	0.001
T_{min}, °C	30 (28–30)	29 (28–30)	0.003
Blood loss, mL	30 (20–40)	30 (20–40)	0.575
Transfusion of RBCs, mL	30 (20–40)	30 (20–50)	0.384
Infusion volume, mL	60 (45–80)	60 (49–80)	0.939

Data expressed as number (percentage) of patients or median (interquartile range).

ACC indicates aortic cross-clamp; ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ASA class, American Society of Anesthesiologists Physical Status Classification; ASD, atrial septal defect; BSA, body surface area; CPB, cardiopulmonary bypass; Hb, hemoglobin level; LVEF, left ventricular ejection fraction; NLR, neutrophil-lymphocyte ratio; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PLR, platelet-lymphocyte ratio; PLSVC, persistent left superior vena cava; PLT, platelet count; RBC, red blood cell; SpO_2, blood oxygen saturation; T_{min}, minimum temperature; and WCC, white blood cell count.

Table 3. Univariable and Multivariable Logistic Regression Analyses of Potential Risk Factors in the Study Population

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, mo	0.943 (0.903–0.984)	0.007	0.930 (0.891–0.970)	0.001
BSA, m^2	0.002 (0.000–0.074)	0.001	0.002 (0.000–0.069)	0.001
SpO_2, %	0.943 (0.924–0.964)	<0.001	0.947 (0.927–0.968)	<0.001
CPB time, min	1.012 (1.006–1.019)	<0.001	1.012 (1.005–1.019)	<0.001
ACC time, min	1.014 (1.006–1.023)	0.001		
T_{min}, °C	0.820 (0.720–0.933)	<0.001		
WCC, $\times 10^9$/L	0.912 (0.829–1.003)	0.047		
ALC, $\times 10^9$/L	0.844 (0.752–0.946)	0.004	0.860 (0.763–0.968)	0.013
PLT, $\times 10^9$/L	0.997 (0.995–0.999)	0.015		
NLR	1.520 (1.174–1.968)	0.002		

ACC indicates aortic cross-clamp; ALC, absolute lymphocyte count; BSA, body surface area; CPB, cardiopulmonary bypass; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; PLT, platelet count; SpO_2, blood oxygen saturation; T_{min}, minimum temperature; and WCC, white blood cell count.

After transforming continuous variables into categorical variables, the risk score for prognosis is displayed in Table 4. The incidences of poor prognosis were 1.8%, 7.2%, and 24.9% for risk scores −3 to 0 (n=166), 1 to 2 (n=348), and 3 to 5 (n=193), respectively. The prevalence of poor prognosis in patients with a score of 5 (n=13) was as high as 69.2%. The receiver-operating characteristic curve was used to analyze the performance of the scoring system, with an AUC of 0.78 (95% CI, 0.72–0.83; *P*<0.001). In the new model without ALC, the scores of other variables remain unchanged, except that ALC was deleted. By comparing the 2 models with and without ALC, we found that the addition of ALC significantly improved the AUC from 0.771 to 0.781 (DeLong: *P*<0.001), and the net reclassification improvement and integrated discrimination improvement were 31.88% (*P*<0.001) and 1.95% (*P*<0.001), respectively (Figure 2).

To avoid reverse causality, we redivided the patients on the basis of ALC levels. As shown in Table 5, the baseline and perioperative data were similar in the 2 independent groups after PSM (standardized mean difference <0.01). The adjusted cohort was then used to compare the prognosis and the postoperative variables (Table 6). Patients with preoperative ALC of <4.36×10^9/L had a significantly poorer prognosis, and the hospital days, postoperative days, and total cost of this group were also significantly higher than those with ALC of >4.36×10^9/L. Mechanical ventilation time and intensive care unit residence time were not statistically significant but were nominally longer in the group with lower preoperative ALC.

DISCUSSION

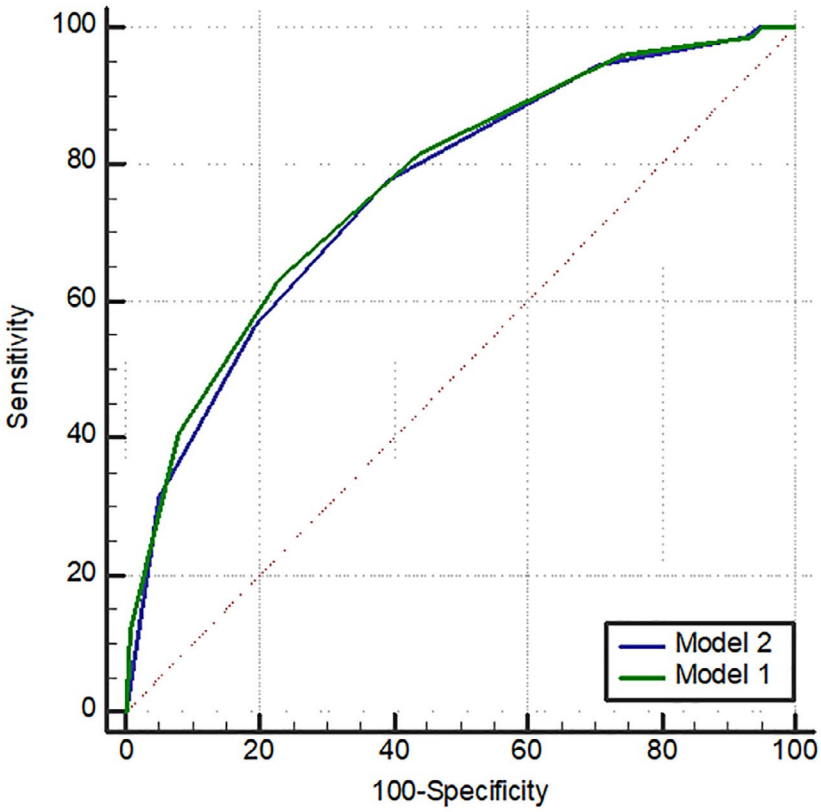
Although many studies have explored the prognostic value of ALC for outcomes in other types of cardiac surgery, as far as we know, this is the first study in children with TOF. In this study, we retrospectively compared the preoperative and intraoperative data that may influence the outcome of the patients with TOF, minimized the effect of the confounding factors through various methods, and finally clarified the prognostic value of ALC in children with TOF. The main finding of the current data is that the children with TOF with a lower ALC level preoperatively tend to have a poor prognosis after surgery, and the cutoff point is 4.36×10^9/L. In addition, younger age, longer CPB time, lower BSA, and preoperative SpO_2 are also independent risk factors for poor prognosis. We also established a practical risk score for prognosis, hoping to identify high-risk patients as early as possible to improve the patients' prognosis.

In-hospital mortality in our study (0.42%) was significantly lower than that in other similar studies[3,5,6,24,25] (ranging from 1.99% to 4.13%), but similar to the results from a previous study in Fuwai hospital[4] (0.24%). This might be mainly because some patients with a poor prognosis forewent treatment and died at home because of economic reasons and the national culture.[20] In addition, it is closely related to the patients' inclusion

Table 4. Adjusted OR and the Score for Each Parameter After Transforming Continuous Into Categorical Variables

Variables	OR (95% CI)	*P* Value	Score
Age, mo			
6–24			0
<6	0.773 (0.334–1.789)	0.548	0
>24	0.127 (0.017–0.974)	0.047	−3
BSA<0.38, m^2	2.005 (1.165–3.451)	0.012	1
SpO_2<85, %	4.538 (2.705–7.616)	<0.001	2
CPB time>96, min	2.586 (1.492–4.481)	0.001	1
ALC<4.36, $\times 10^9$/L	2.401(1.425–4.045)	0.003	1

The risk score model was constructed from the multivariable regression model (Table 3). ALC indicates absolute lymphocyte count; BSA, body surface area; CPB, cardiopulmonary bypass; OR, odds ratio; and SpO_2, blood oxygen saturation.



	Model 1	Model 2	*P*
AUC	0.781	0.771	< 0.001
	Model 1 vs. Model 2		
NRI	31.88%		< 0.001
IDI	1.95%		< 0.001

Figure 2. Receiver-operating characteristic curves for the scoring models with and without absolute lymphocyte count (ALC).
Model 1, body surface area+blood oxygen saturation+cardiopulmonary bypass time+ALC. Model 2, body surface area+blood oxygen saturation+cardiopulmonary bypass time. AUC indicates area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

criteria and the advances in surgical techniques. Our results suggest a male predominance, which was also reported in other studies.[2,3,24] The specific mechanism remains unclear and warrants further investigation. Some studies suggest that this may be because the Y chromosome is more susceptible than the X chromosome.[26] Furthermore, the sex variations in this study were more prominent than in other studies, which may be related to sex discrimination and the preference for male children in China.

Similar studies have reported age, BSA, preoperative SpO_2, and CPB time as independent risk factors for poor prognosis.[3–8,17,24] For asymptomatic patients with TOF, an elective repair has been proposed as ideally timed between 3 and 6 months of age.[17] Our study also confirmed that age <6 months is not a risk factor for poor prognosis; in addition, age >2 years was a protective factor in our study, possibly because of the patients' favorable anatomical features and mild condition.

Our data revealed that the scoring system with an AUC of 0.78 (95% CI, 0.72–0.83) had an acceptable, but not excellent, predictability. This is understandable as patients with known risk factors were excluded to reduce the confounding factors, given that the main objective of this study was to estimate the prognostic value of ALC. After the scoring system, we also established another model without ALC. By comparing

Table 5. Demographic and Perioperative Data Before and After PSM

Variables	Before PSM			After PSM		
	ALC ≥4.36×10^9/L (n=529)	ALC <4.36×10^9/L (n=118)	SMD	ALC ≥4.36×10^9/L (n=117)	ALC <4.36×10^9/L (n=117)	SMD
Age, mo	8 (6–11)	8 (6–13)	0.24	8 (6–12)	8 (6–13)	<0.10
BSA, m^2	0.38 (0.34–0.41)	0.37 (0.33–0.42)	0.13	0.37 (0.34–0.40)	0.37 (0.33–0.41)	<0.10
SpO_2, %	89 (82–94)	85 (80–91)	0.26	86 (78–90)	85 (80–91)	<0.10
CPB time, min	97 (81–117)	97 (80–123)	<0.10	97 (79–118)	97 (80–123)	<0.10
ACC time, min	67 (55–84)	65 (54–85)	0.11	64 (53–83)	65 (54–85)	<0.10
T_{min}, ℃	30 (28–30)	30 (28–30)	0.26	30 (28–30)	30 (28–30)	<0.10

ACC indicates aortic cross-clamp; ALC, absolute lymphocyte count; BSA, body surface area; CPB, cardiopulmonary bypass; PSM, propensity score matching; SMD, standardized mean difference; SpO_2, blood oxygen saturation; and T_{min}, minimum temperature.

the AUC values of these 2 models, we concluded that the prediction model that included ALC was superior to the model without this variable. To further support this point, we also calculated the net reclassification improvement and integrated discrimination improvement, which is a modern and more sensitive statistical method, to evaluate how much better the addition of a biomarker is at predicting risk than an existing clinical model. The results further confirmed that ALC provided greater information for the clinical setting.

Before PSM, we further restricted the age to <2 years for 2 main reasons. First, being >2 years is a protective factor according to the analysis above, and there was only one child >2 years with a poor prognosis; therefore, limiting the age can reduce confounding factors. Second, ALC varies greatly with age in pediatric patients: at birth, ALC accounts for approximately 30% of the white blood cell count, and then gradually increases with age; at the age of approximately 2 years, ALC reaches a peak, accounting for approximately 60% of the white blood cell count, and then begins to decrease; after 6 years of age, the white blood cell classification is similar to that of adults. Therefore, we performed PSM and further examined patients aged <2 years. Moreover, we recalculated the cutoff value of ALC based on age-adjusted subjects and found that the cutoff point was unchanged.

Our study found that low preoperative ALC is closely related to the poor outcome of patients with TOF; meanwhile, length of hospital stay, length of postoperative stay, and medical cost are also increased, which is similar to results of previous studies.[12,14–16] Although the mechanical ventilation time and intensive care unit residence time were extended for patients with ALC <4.36×10^9/L in our study, the difference was not statistically significant. We speculate that this is mainly related to patient selection and study design. In our study, to eliminate confounding factors, we excluded patients with known risk factors, because these excluded cases often had low preoperative ALC. The main reasons for low preoperative ALC can be divided into 3 categories: decreased production, accelerated destruction, and lymphocyte redistribution. For decreased production, patients with TOF, especially those with complex malformations, are prone to malnutrition, microcirculatory damage, or tissue hypoxia, which can affect lymphocyte proliferation and differentiation and reduce ALC.[27,28] In terms of accelerated destruction, exposure to chronic hypoxia[29] and systemic inflammation[30] both can lead to the apoptosis of lymphocytes. Lymphocyte redistribution stress response, manifested by elevated cortisol and catecholamine levels, can lead to a redistribution of lymphocytes to lymphatic organs, commonly referred to as lymphocyte homing.[31] Moreover, previous studies have shown that patients with genetic syndromes are considered to have a disturbance in their adaptive immunity and, therefore, have low ALC.[12,32] According to the exclusion

Table 6. Outcomes of the Patients With Higher and Lower ALC Levels After PSM

Outcome	ALC≥4.36×10^9/L	ALC<4.36×10^9/L	OR (95% CI)	*P* Value
Poor prognosis, n (%)	9 (7.7)	24 (20.5)	3.500 (1.413–8.672)	0.007
MV time, h	18 (9–25.5)	19 (9.5–42)	1.007 (1.000–1.014)	0.065
LOIS, d	2 (1–4)	3 (1–5)	1.088 (0.988–1.198)	0.085
LOHS, d	15 (11.5–18.5)	15 (13–20.5)	1.033 (1.001–1.066)	0.043
LOPS, d	9 (7–11)	10 (7–12.5)	1.064 (1.005–1.126)	0.033
Cost, ¥ 1000	71 (63–84)	77 (63–98)	1.013 (1.002–1.024)	0.019

ALC indicates absolute lymphocyte count; LOHS, length of hospital stay; LOIS, length of intensive care unit stay; LOPS, length of postoperative hospital stay; MV, mechanical ventilation; OR, odds ratio; and PSM, propensity score matching.

criteria of our study, many patients with low preoperative ALC were excluded, such as those with complex malformations, genetic syndrome, and preoperative endotracheal intubation. These excluded patients had poor outcomes, which may explain why there was no difference in mechanical ventilation time and intensive care unit stay time in this study and why the outcome can cause the ALC count in reverse causality. However, even with such strict inclusion criteria, ALC still has a significant impact on short-term prognosis. Thus, it is considered a good indicator of adverse outcomes.

In addition, it remains unclear why patients with low ALC are more likely to have a poorer prognosis. Our data are unable to answer this question, but based on previous studies, the most widely accepted explanation is that a reduced ALC serves more as a surrogate indicator of general health and reflects a patient's physiological stress, such as malnutrition status, microcirculatory damage, or chronic hypoxia.[10,14,28] Furthermore, patients with low ALC may have been in a state of chronic low-level inflammation before surgery, coupled with the process of CPB destroying lymphocytes and redistributing lymphocytes to lymphoid or nonlymphoid organs (such as bone marrow), finally leading to further reduction of lymphocytes and exacerbating the inflammatory response after surgery.[33]

The advantages of this study are as follows. First, the sample size is relatively large, considering the low incidence of TOF. Second, a large number of potential confounding factors were controlled in this study through the study design and statistical analysis. In terms of study design, we excluded patients with known risk factors for poor prognosis, while these excluded cases often had low preoperative ALC. In terms of statistical analyses, we identified the independent risk factors by multivariable analysis and controlled these confounding factors using a PSM approach.

Conversely, this study had some limitations. First, the retrospective nature of the study might have led to the missing of important data. We were unable to include C-reactive protein and procalcitonin as markers because of excessive missing data. We also did not exclude all patients with genetic syndromes, or incorporate lymphocyte distribution, activation status (cluster of differentiation 69), or antibody titers associated with T/B-cell function because they were not routinely measured at Fuwai Hospital. Second, this was a single-center study, which may have introduced selection bias. More important, the age at repair in this center is mostly at 6 to 12 months, which may make the study less generalizable to some centers that favor elective TOF repair at 3 to 6 months. Third, we focused only on short-term outcomes and did not conduct a long-term follow-up of patients. Moreover, analyzing the performance of the scoring system with the same data used to develop the scoring system leads to overoptimistic estimates of the performance. Therefore, further multicenter prospective studies are needed to validate our findings.

In conclusion, ALC is a common, cheap, and easy-to-obtain variable with an excellent predictive value. Patients with low preoperative ALC levels are more likely to have a poor prognosis. A scoring system was constructed on the basis of the 5 factors significantly related to prognosis: age, BSA, CPB time, preoperative SpO_2, and ALC, and has a good prediction ability.

ARTICLE INFORMATION

Received August 25, 2020; accepted February 24, 2021.

Affiliations

Department of Anesthesiology (X.W., Q.L., Y.L., H.W., S.Y., F.Y.) and Center for Pediatric Cardiac Surgery, Fuwai Hospital, National Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences, and Peking Union Medical College, Beijing, China (Z.S.).

Sources of Funding

This work was supported by the National Nature Science Foundation of China (grant No. 81870070) and the Innovative Foundation for Graduate Students at Peking Union Medical College (grant No. 2019-1002-78).

Disclosures

None.

REFERENCES

1. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol*. 2019;48:455–463. DOI: 10.1093/ije/dyz009.
2. Zhao L, Chen L, Yang T, Wang T, Zhang S, Chen L, Ye Z, Luo L, Qin J. Birth prevalence of congenital heart disease in China, 1980–2019: a systematic review and meta-analysis of 617 studies. *Eur J Epidemiol*. 2020;35:631–642. DOI: 10.1007/s10654-020-00653-0.
3. Smith CA, McCracken C, Thomas AS, Spector LG, St LJ, Oster ME, Moller JH, Kochilas L. Long-term outcomes of tetralogy of Fallot: a study from the pediatric cardiac care consortium. *JAMA Cardiol*. 2019;4:34–41. DOI: 10.1001/jamacardio.2018.4255.
4. Li S, Zhang Y, Li S, Wang X, Zhang R, Lu Z, Yan J. Risk factors associated with prolonged mechanical ventilation after corrective surgery for tetralogy of Fallot. *Congenit Heart Dis*. 2015;10:254–262. DOI: 10.1111/chd.12205.
5. Mercer Rosa L, Elci OU, DeCost G, Woyciechowski S, Edman SM, Ravishankar C, Mascio CE, Kawut SM, Goldmuntz E. Predictors of length of hospital stay after complete repair for tetralogy of Fallot: a prospective cohort study. *J Am Heart Assoc*. 2018;7:e008719. DOI: 10.1161/JAHA.118.008719.
6. Sandoval N, Carreño M, Novick WM, Agarwal R, Ahmed I, Balachandran R, Balestrini M, Cherian KM, Croti U, Du X, et al. Tetralogy of Fallot repair in developing countries: international quality improvement collaborative. *Ann Thorac Surg*. 2018;106:1446–1451. DOI: 10.1016/j.athoracsur.2018.05.080.
7. Liu H, Zheng S, Zeng Z, Liu Z, Liu X, Shao Y. Association between perfusate oxygenation and acute lung injury in tetralogy of Fallot surgery. *Shock*. 2020;54:21–29. DOI: 10.1097/SHK.0000000000001475.
8. Egbe AC, Kothapalli S, Borlaug BA, Ammash NM, Najam M, Bajwa N, Tarek K, Mathew J, Connolly HM. Mechanism and risk factors for death in adults with tetralogy of Fallot. *Am J Cardiol*. 2019;124:803–807. DOI: 10.1016/j.amjcard.2019.05.048.
9. Silberman S, Abu-Yunis U, Tauber R, Shavit L, Grenader T, Fink D, Bitran D, Merin O. Neutrophil-lymphocyte ratio: prognostic impact in heart surgery: early outcomes and late survival. *Ann Thorac Surg*. 2018;105:581–586. DOI: 10.1016/j.athoracsur.2017.07.033.

10. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, Jeffrey RR, Buchan KG, El-Shafei H, Hillis GS. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J*. 2007;154:995–1002. DOI: 10.1016/j.ahj.2007.06.043.
11. Lomivorotov VV, Efremov SM, Boboshko VA, Leyderman IN, Lomivorotov VN, Cheung AT, Karaskov AM. Preoperative total lymphocyte count in peripheral blood as a predictor of poor outcome in adult cardiac surgery. *J Cardiothor Vasc An*. 2011;25:975–980. DOI: 10.1053/j.jvca.2010.12.006.
12. Cabrera AG, Dyamenahalli U, Gossett J, Prodhan P, Morrow WR, Imamura M, Jaquiss RDB, Bhutta AT. Preoperative lymphopenia is a predictor of postoperative adverse outcomes in children with congenital heart disease. *J Thorac Cardiovasc Surg*. 2009;138:1172–1179. DOI: 10.1016/j.jtcvs.2009.06.016.
13. Manuel V, Miana LA, Jatene MB. Predictive value of pre-operative neutrophil–lymphocyte ratio for children undergoing congenital heart surgery. *Cardiol Young*. 2020;30:1057. DOI: 10.1017/S1047951120000840.
14. Jones SM, McCracken C, Alsoufi B, Mahle WT, Oster ME. Association of preoperative cell counts with outcomes after operation for congenital heart disease. *Ann Thorac Surg*. 2018;106:1234–1240. DOI: 10.1016/j.athoracsur.2018.04.022.
15. Manuel V, Miana LA, Guerreiro GP, Tenório DF, Turquetto A, Penha JG, Massoti MR, Tanamati C, Junior APF, Caneo LF, et al. Prognostic value of the preoperative neutrophil-lymphocyte ratio in patients undergoing the bidirectional Glenn procedure. *J Cardiac Surg*. 2019;35:328–334. DOI: 10.1111/jocs.14381.
16. Xu H, Sun Y, Zhang S. The relationship between neutrophil to lymphocyte ratio and clinical outcome in pediatric patients after cardiopulmonary bypass surgery: a retrospective study. *Front Pediatr*. 2019;7:308. DOI: 10.3389/fped.2019.00308.
17. Mimic B, Brown KL, Oswal N, Simmonds J, Hsia TY, Tsang VT, De Leval MR, Kostolny M. Neither age at repair nor previous palliation affects outcome in tetralogy of Fallot repair. *Eur J Cardio-Thorac*. 2013;45:92–99. DOI: 10.1093/ejcts/ezt307.
18. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol*. 2007;165:710–718. DOI: 10.1093/aje/kwk052.
19. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005;58:475–483. DOI: 10.1016/j.jclinepi.2004.06.017.
20. Chu CC, Weng SF, Chen KT, Chien CC, Shieh JP, Chen JY, Wang JJ. Propensity score-matched comparison of postoperative adverse outcomes between geriatric patients given a general or a neuraxial anesthetic for hip surgery: a population-based study. *Anesthesiology*. 2015;123:136–147. DOI: 10.1097/ALN.0000000000000695.
21. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt C-E, Trouillet J-L, Bréchot N, Nieszkowska A, Dupont H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intens Care Med*. 2013;39:1704–1713. DOI: 10.1007/s00134-013-3037-2.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845. DOI: 10.2307/2531595.
23. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? *Circulation*. 2017;135:2369–2372. DOI: 10.1161/CIRCULATIONAHA.117.028307.
24. Savla JJ, Faerber JA, Huang YV, Zaoutis T, Goldmuntz E, Kawut SM, Mercer-Rosa L. 2-Year outcomes after complete or staged procedure for tetralogy of Fallot in neonates. *J Am Coll Cardiol*. 2019;74:1570–1579. DOI: 10.1016/j.jacc.2019.05.057.
25. Llamosas-Falcón L, Bermejo-Sánchez E, Sánchez-Díaz G, Villaverde-Hueso A, Posada de la Paz M, Alonso-Ferreira V, Alonso-Ferreira V. Tetralogy of Fallot in Spain: a nationwide registry-based mortality study across 36 years. *Orphanet J Rare Dis*. 2019;14:79. DOI: 10.1186/s13023-019-1056-y.
26. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. *Birth Defects Res A*. 2014;100:79–91. DOI: 10.1002/bdra.23218.
27. Nájera O, González C, Toledo G, López L, Cortés E, Betancourt M, Ortiz R. CD45RA and CD45RO isoforms in infected malnourished and infected well-nourished children. *Clin Exp Immunol*. 2001;126:461–465. DOI: 10.1046/j.1365-2249.2001.01694.x.
28. Aghdaii N, Ferasatkish R, Mohammadzadeh Jouryabi A, Hamidi SH. Significance of preoperative total lymphocyte count as a prognostic criterion in adult cardiac surgery. *Anesth Pain Med*. 2014;4:e20331. DOI: 10.5812/aapm.20331.
29. Sun J, Zhang Y, Yang M, Zhang Y, Xie QI, Li Z, Dong Z, Yang Y, Deng B, Feng A, et al. Hypoxia induces T-cell apoptosis by inhibiting chemokine C receptor 7 expression: the role of adenosine receptor A2. *Cell Mol Immunol*. 2010;7:77–82. DOI: 10.1038/cmi.2009.105.
30. Yndestad A, Damås JK, Oie E, Ueland T, Gullestad L, Aukrust P. Systemic inflammation in heart failure–the whys and wherefores. *Heart Fail Rev*. 2006;11:83–92. DOI: 10.1007/s10741-006-9196-2.
31. Thomson SP, McMahon LJ, Nugent CA. Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. *Clin Immunol Immunopathol*. 1980;17:506–514. DOI: 10.1016/0090-1229(80)90146-4.
32. de Hingh YC, van der Vossen PW, Gemen EF, Mulder AB, Hop WC, Brus F, de Vries E. Intrinsic abnormalities of lymphocyte counts in children with down syndrome. *J Pediatr*. 2005;147:744–747. DOI: 10.1016/j.jpeds.2005.07.022.
33. Tan TP, Arekapudi A, Metha J, Prasad A, Venkatraghavan L. Neutrophil-lymphocyte ratio as predictor of mortality and morbidity in cardiovascular surgery: a systematic review. *Anz J Surg*. 2015;85:414–419. DOI: 10.1111/ans.13036.