MedCrave
Step into the World of Research

Journal of Pediatrics & Neonatal Care

Research article

Open Access

Association between neutrophil-lymphocyte-ratio and oxygen delivery in patients after the Norwood operation

Abstract

Background: Both neutrophil-lymphocyte-ratio and renal oxygen extraction have been demonstrated to be associated with adverse events after cardiac surgery. The association between neutrophil-lymphocyte-ratio and renal oxygen extraction has not previously been studies. The aim of this study was to characterize the association between neutrophil-lymphocyte ratio and renal oxygen extraction.

Methods: High fidelity hemodynamic monitoring data was retrieved for patients who underwent the Norwood operation. Bayesian regression analyses were conducted to identify what hemodynamic variables, including renal oxygen extraction, were associated with neutrophil-lymphocyte ratio.

Results: A total of 27,270 datapoints were collected over 1,338 patient-hours for nine unique patients. Renal oxygen extraction ratio had an area under the curve of 0.72 to identify renal oxygen extraction of over 35%. An increase in renal oxygen extraction by 1 was associated with a 0.15 increase in the neutrophil-lymphocyte-ratio.

Conclusion: In patients after the Norwood procedure, there is a correlation between the neutrophil-lymphocyte-ratio and renal oxygen extraction. A neutrophil-lymphocyte-ratio of greater than 2.95 has fair-performance in identifying renal extraction of greater than 35%.

Volume 15 Issue 2 - 2025

Rohit S Loomba, Juan S Farias, Enrique Villarreal, Saul Flores

Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, USA

Correspondence: Rohit S Loomba, MD, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Received: May 24, 2025 | **Published:** July 17, 2025

Introduction

Monitoring of various parameters in critically ill patients is important to help characterize the probability of adverse events. Additionally, once adverse events occur, monitoring can help determine prognosis. These are particularly important in children after cardiac surgery.

Children with parallel circulation, wherein the saturation to blood in the pulmonary and systemic circulations is equal, are at among highest risk for adverse events, specifically those after a Norwood operation. There are data looking at the association of neutrophil-lymphocyte-ratio with the occurrence of various adverse events and overall prognosis after pediatric cardiac surgery.[1–5] As other studies have shown prognostic value of oxygen delivery indices but have not explored the association between oxygen delivery indices and neutrophil-lymphocyte-ratio.

The primary aim of this study was to characterize the association between neutrophil-lymphocyte ratio and systemic oxygen delivery using high-fidelity hemodynamic data in children after the Norwood operation.

Methods

Study design

This study protocol was approved by the institutional review board. It is in concordance with the Helsinki Declaration. This study was a single-center, retrospective study aimed to characterize the association between various clinical parameters and neutrophil-lymphocyte-ratio. The resulting model and being able to predict the neutrophil-lymphocyte-ratio was not necessarily the main aim of this study but rather to demonstrate the relationship between the independent variables and renal oxygen extraction.

Variables of interest

The variables of interest collected were as follows: central venous pressure, heart rate, respiratory rate, mean arterial blood pressure, arterial saturation by pulse oximetry, renal near infrared spectroscopy, peak airway pressure, mean airway pressure, positive end expiratory pressure, body temperature, fluid balance, epinephrine dose, norepinephrine dose, dopamine dose, dobutamine dose, vasopressin dose, nitroprusside dose, and nicardipine dose. Patient weight and gestational age were also collected.

All the data except for vasoactive doses were collected from the T3 software. T3 is software designed to integrate multiple data streams in real time in clinical settings. The data from all the streams can then be displayed by the software in a user-defined fashion. Additionally, T3 also estimates the venous saturation and then displays the probability of the venous saturation being under 30%, 40%, or 50% in a metric known as the index of inadequate delivery of oxygen. The T3 software collects data from the available streams at an interval of 5 seconds, thus offering high temporal resolution.

Central venous pressures were obtained by use of femoral lines terminating in the inferior caval vein. Line placement was confirmed by radiographs.

Renal near infrared spectroscopy values were collected. Near infrared spectroscopy values were obtained using the Casmed ForeSight Elite tissue oximeter.

Vasoactive doses were collected manually through the electronic medical record as charted. It is local practice to document every time an infusion dose has been changed and at regular intervals. Doses of all vasoactive infusions were collected for each timepoint at which the data from T3 were collected.

Submit Manuscript | http://medcraveonline.com

©2025 Loomba et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Copyright: ©2025 Loomba et al.

Fluid balance was collected manually through the electronic medical record as charted. It is local practice to update fluid balance hourly. Fluid balance for each timepoint at which T3 data were collected was collected as the fluid balance for the hour prior to that timepoint.

Some values were also calculated. Renal oxygen extraction was calculated as ((arterial saturation by pulse oximetry – renal near infrared spectroscopy)/ (arterial saturation by pulse oximetry)) x 100. Thus, if the arterial saturation were 80 and the renal near infrared spectroscopy value was 60, the renal oxygen extraction would be 25%. Oxygen consumption in ml/min was estimated using the LaFarge equation. Systemic blood flow was calculated by dividing the estimated oxygen consumption by the arteriovenous oxygen content difference. The renal near infrared spectroscopy value was used for this. Systemic vascular resistance was then calculated using the following equations: (mean arterial blood pressure – central venous pressure)/systemic blood flow.

Patient inclusion

Neonates with functionally univentricular hearts who underwent a Norwood operation were eligible for inclusion in this study. Data must have been collected and available for patients in T3 for patients to be included in this study. T3 was implemented locally on September 1st, 2022 and a final inclusion date of March 1st, 2023 was utilized. Only data while patients were intubated and mechanically ventilated were included as this allowed for airway pressures to be quantified. Data was available at five second intervals for patients with T3 data. Datapoints were included in the final analyses only if there was a central venous pressure and airway pressures available at that specific timepoint.

Statistical analyses

The primary statistical aim of the analyses was to model neutrophil-lymphocyte-ratio using the other collected data in order to quantitatively assess the association of the various parameters with central venous pressure. This was done utilizing a Bayesian linear regression. Neutrophil-lymphocyte-ratio was the dependent variable, and the following independent variables were included: central venous pressure, heart rate, respiratory rate, mean arterial blood pressure, arterial saturation by pulse oximetry, mean airway pressure, body temperature, fluid balance, epinephrine dose, norepinephrine dose, dopamine dose, dobutamine dose, vasopressin dose, nitroprusside dose, nicardipine dose, estimated systemic blood flow, renal oxygen extraction, and estimated systemic vascular resistance. The Jeffreys-Zellner-Siow prior was utilized. The top 10 most likely models were evaluated.

Next, a receiver operator curve analysis was done to determine to quantify the utility of the neutrophil-lymphocyte-ratio in predicting the binary variable of whether or not the renal oxygen extraction was greater than 35%. This was done as previous clinical studies have demonstrated that at an oxygen extraction between 30% and 40% and greater that the risk of adverse events (neurodevelopmental delay, need for intubation, acute kidney injury, hepatic insufficiency, necrotizing enterocolitis, cardiac arrest, and mortality increases.

Bayesian statistics were utilized rather than frequentist regressions for several reasons. The details of these are beyond the scope of this manuscript but in general Bayesian statistics allows for generating a distribution for all point estimates. This allows for the quantification of the probability of specific outcomes and models describing the outcomes. Bayesian models have also been demonstrated to be more well-fitted and reproducible.

Statistical analyses were conducted using JASP Version 0.16 (University of Amsterdam, Amsterdam, Netherlands). P-values are not presented as Bayesian statistical tools and not frequentist statistical tools were utilized.

Results

Cohort information

A total of 27,270 datapoints were included in the final analyses. These were collected from nine patients over a total of 1,338 patient hours (55.7 days). As per the inclusion criteria for retaining datapoints in the final analyses, central venous pressure and airway pressures must have been available for the data for a timepoint to be included.

Average gestational age was 38 weeks with two patients being premature. Average patient age at the time of the Norwood operation was 20 days. This was due to two patients getting their Norwood done closer to two months of life following a hybrid procedure. When these two patients are excluded the mean age at time of Norwood was two days. Of the nine patients for whom data was collected, two had an identified genetic anomaly (Table 1).

Table 1 Descriptive data regarding cohort

Principle cardiac diagnosis	
Hypo plastic left heart syndrome	5
Tricuspid atresia	2
Small left sided structures	2
Genetic anomaly	2
Premature	2
Age at Norwood (days)	20.5 ± 32.0
Weight at Norwood (kg)	3.3 ± 0.2

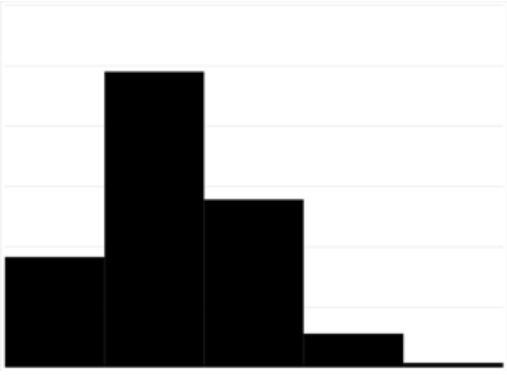

Figure 1 Roer histogram.

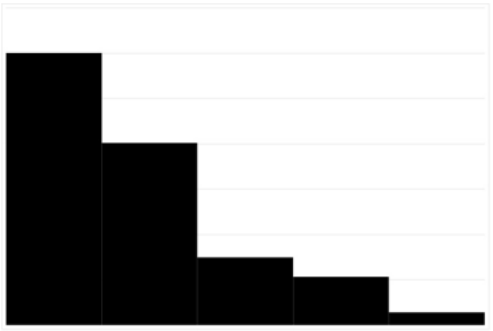

Figure 2 NLR histogram.

Citation: Loomba RS, Farias JS, Villarreal E, et al. Association between neutrophil-lymphocyte-ratio and oxygen delivery in patients after the Norwood operation. *J Pediatr Neonatal Care.* 2025;15(2):111–115. DOI: 10.15406/jpnc.2025.15.00595

Copyright: ©2025 Loomba et al.

Bivariate correlation between venous oxygen saturation and lactate

There was a weak but statistically significant negative correlation between renal oxygen extraction and the neutrophil-lymphocyte-ratio (correlation coefficient -0.319, $p< 0.01$).

Histograms demonstrating the distribution of renal oxygen extraction and neutrophil-lymphocyte-ratio values are contained in Figures 1 and 2, respectively.

Regression analysis

A Bayesian regression analysis was conducted with renal oxygen extraction as the dependent variable and the aforementioned collected variables as the independent variables. The best performing model had a 52% probability and retained the following independent variables: epinephrine dose, milrinone dose, vasopressin dose, sodium nitroprusside dose, mean airway pressure, arterial saturation by pulse oximetry, heart rate, respiratory rate, systemic vascular resistance, and renal oxygen extraction. The next most probable model had a probability of 21% and retained all the variables the most probable model did in addition to central venous pressure. By design, the most probable model had a Bayes Factor 10 of 1.00 and the second most probable model of 0.07.

With respect to the 10 most probable models, epinephrine dose, milrinone dose, vasopressin dose, nitroprusside dose, mean airway pressure, arterial saturation by pulse oximetry, heart rate, respiratory rate, systemic vascular resistance, and renal oxygen ratio were retained in 100% of models. Central venous pressure was retained in 34% of models while systemic blood flow was retained in 26% of models.

The regression coefficient for renal oxygen extraction was 0.15, indicating that an increase in renal oxygen extraction by 1 is associated with a 0.15 increase in the neutrophil-lymphocyte-ratio.

Receiver operator curve analysis

The neutrophil-lymphocyte-ratio had a 0.72 area under the curve for identifying a renal oxygen extraction of greater than 35%. The optimal cutoff point for neutrophil-lymphocyte ratio was 2.95. This cutoff point was 92% sensitive and 69% specificity.

Discussion

These analyses demonstrate that there is a correlation between neutrophil-lymphocyte-ratio and renal oxygen extraction. A neutrophil-lymphocyte-ratio greater than 2.95 had fair performance in identifying a renal oxygen extraction of greater than 35%.

The correlation between absolute neutrophil-lymphocyte-ratio and absolute renal oxygen extraction was not too strong but there was greater strength in the association of neutrophil-lymphocyte-ratio in identifying the binary endpoint of a renal oxygen extraction of greater than 35%.

In the pediatric population, the neutrophil-lymphocyte-ratio has been demonstrated to be associated with, and have prognostic implications in the setting of, several clinical occurrences such as pleural effusion after cardiac surgery, duration of mechanical ventilation after cardiac surgery, length of stay after cardiac surgery, low cardiac output after cardiac surgery, cardiac dysfunction, refractory Kawasaki disease, coronary artery lesions with Kawasaki disease, lymphatic anomalies after the Fontan procedure, carditis with Rheumatic fever, reactive airway disease, and necrotizing enterocolitis among others.[1–17]

This phenomenon is likely an association and not causal although the current data do not prove this. Many of the clinical settings in which neutrophil-lymphocyte-ratio has been demonstrated to have clinical significance are settings in which there may be inflammation or regional hypoxia.

In the setting of inflammation, neutrophils help mediate the inflammatory state along with other inflammatory cells. Neutrophils remain in circulation for a short period of time and change their morphology over the course of this relatively short period of time. Various signaling mechanisms facilitate the exit of neutrophils from the bone marrow and into the circulation. One such impetus for exit of neutrophils from the bone marrow is inflammation and neutrophils are the predominant cell type in early inflammation. Once at sites of inflammation, neutrophils can change phenotype and generate various subpopulations, indirectly and directly influencing the immune and inflammatory response. Ultimately these neutrophiles are removed by macrophages.[18,19] At sites of inflammation, often sites with regional hypoxia, neutrophils survive longer due to mechanisms that inhibit neutrophil apoptosis or phagocytosis.[20] Regional hypoxia due to other reasons, such as acute arterial occlusion, lead to similar neutrophil response.

The inflammatory response may be secondary to a process that is leading to an inadequacy of oxygen delivery or may be directly contributing to inadequacy of oxygen delivery due to increased oxygen consumption to sustain the inflammatory process. This is an important notion as it means that it is unclear whether the association of increasing neutrophil-lymphocyte-ratio with increasing renal oxygen extraction is the cause or the effect. It is plausible that decreased oxygen delivery may alter the differentiation and express of cells but it also plausible that increased oxygen consumption by the cells themselves as they perform their specific functions is leading to increased oxygen extraction. It is also very plausible that both are occurring simultaneously to some degree.

If inadequacy of oxygen delivery itself mediates an increase in neutrophil-lymphocyte-ratio, then the question is if this has clinical consequences in regard to immune and inflammatory response. Does this lead to increased susceptibility to infection? Does it alter the outcomes with infections that do occur? For adults who are already have a documented infection and sepsis, a higher neutrophil-lymphocyte ratio is associated with increased mortality. The current data do not explore these issues although they are logical considerations from such data and would be interesting questions to answer with future studies.

Regardless of whether or not increased neutrophil-lymphocyte-ratio is the result or cause of increasing oxygen extraction, it remains that neutrophil-lymphocyte-ratio is a relatively inexpensive, simple blood test that can help lend insight into underlying adverse processes that may be occurring or the prognosis of underlying adverse processes. The current data specifically pertain to the ability to use neutrophil-lymphocyte-ratio as a screen for increased renal oxygen extraction, concerning for inadequacy of oxygen delivery.

Monitoring the adequacy oxygen delivery is of utmost importance in all patients as organ function is dependent on this. Systemic oxygen delivery is the product of oxygen content and cardiac output. Out of these equations, the components that can be monitored clinically are hemoglobin, arterial saturation, venous saturation, and partial pressure of oxygen.[21–23] More routinely, continuously monitored indices such as hear rate, blood pressure, and respiratory rate are not included in these equations.[24] Monitoring the adequacy of systemic oxygen delivery requires both the arterial and venous saturations. The

Citation: Loomba RS, Farias JS, Villarreal E, et al. Association between neutrophil-lymphocyte-ratio and oxygen delivery in patients after the Norwood operation. *J Pediatr Neonatal Care*. 2025;15(2):111–115. DOI: 10.15406/jpnc.2025.15.00595

arterial saturation can be monitored by pulse oximetry or blood gas analysis while the venous saturation can be monitored by near infrared spectroscopy or blood gas analysis.[25–27] Such monitoring is important as monitoring of adequacy of oxygen delivery using a venous saturation, or an estimation of it, helps to determine the probability of adverse events including, but not limited to, developmental delay, acute kidney injury, hepatic insufficiency, extubation failure, cardiac arrest, and mortality.[28–35]

This study utilizes high-fidelity data captured at five second intervals, enabling for trends and associations to be effectively characterized. It also explores a novel aspect of neutrophil-lymphocyte-ratio. Thus, it is additive to the current literature. However, this study is not without its limitations. First, this is a single-center study and there could be factors not captured here that may be mediating associations that are related to center-specific practices. Second, this is retrospective in nature and so causality cannot be gauged. The absolute number of patients is low but the number of neutrophil-lymphocyte-ratio and renal oxygen extraction data pairs is quite high, and these are the "subjects" in the analyses. Thus, the analysis is adequately powered at this level. Although, patient specific factors which are accounted for in the regression cannot be confidently commented on due to the low number of patients.

Conclusion

In patients after the Norwood procedure, there is a correlation between the neutrophil-lymphocyte-ratio and renal oxygen extraction. A neutrophil-lymphocyte-ratio of greater than 2.95 has fair-performance in identifying renal extraction of greater than 35%.

Acknowledgments

None.

Funding

None.

Conflict of interest

Author declares that there are no conflicts of interest.

References

1 Gao P, Liu J, Wang X, et al. The association between neutrophil-lymphocyte ratio and poor outcomes following infant cardiac surgery. *BMC Cardiovasc Disord*. 2021;21(1):529.

2 Yakuwa K, Miyaji K, Kitamura T, et al. Neutrophil-to-lymphocyte ratio is prognostic factor of prolonged pleural effusion after pediatric cardiac surgery. *JRSM Cardiovasc Dis*. 2021;10:20480040211009438.

3 Iliopoulos I, Alder MN, Cooper DS, et al. Pre-operative neutrophil-lymphocyte ratio predicts low cardiac output in children after cardiac surgery. *Cardiol Young*. 2020;30(4):521–525.

4 Yin X, Xin M, Ding S, et al. Predictive role of perioperative neutrophil to lymphocyte ratio in pediatric congenital heart disease associated with pulmonary arterial hypertension. *BMC Surg*. 2021;21(1):3.

5 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.

6 Tian J, An XJ, Niu L. Analysis of the correlation between the neutrophil-lymphocyte ratio in peripheral blood and perioperative myocardial damage in pediatric patients with frequent ventricular premature beat. *Eur Rev Med Pharmacol Sci*. 2018;22(6):1752–1757.

7 Giray D, Hallioglu O. Are there any novel markers in acute rheumatic fever: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio. *Cardiol Young*. 2020;30(5):717–721.

8 Mu Y, Wang H. Association of neutrophil to lymphocyte ratio with preterm necrotizing enterocolitis: a retrospective case-control study. *BMC Gastroenterol*. 2022;22(1):248.

9 Aryani I, Yantie N, Gunawijaya E, et al. Correlation between neutrophil--to-lymphocyte ratio, platelet-to-lymphocyte ratio and mean platelet volume with severity of carditis in children with rheumatic fever. *Cardiol Young*. 2021:1–5.

10 Arwas N, Shvartzman SU, Goldbart A, et al. Elevated neutrophil-to-lymphocyte ratio is associated with severe asthma exacerbation in children. *J Clin Med*. 2023;12(9):3312.

11 Ozyilmaz S, Akgul O, Uyarel H, et al. The importance of the neutrophil-to-lymphocyte ratio in patients with hypertrophic cardiomyopathy. *Rev Port Cardiol*. 2017;36(4):239–246.

12 Moosmann J, Schroeder C, Cesnjevar R, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in Univentricular patients from birth to follow-up after Fontan-predicting lymphatic abnormalities. *Front Pediatr*. 2021;9:740951.

13 Ahmed M, El Amrousy D, Hodeib H, et al. Neutrophil-to-lymphocyte ratio as a predictive and prognostic marker in children with dilated cardiomyopathy. *Cardiol Young*. 2023;33(12):2493–2497.

14 Araujo F, Silva R, Oliveira CAL, et al. Neutrophil-to-lymphocyte ratio used as prognostic factor marker for dilated cardiomyopathy in childhood and adolescence. *Ann Pediatr Cardiol*. 2019;12(1):18–24.

15 Chu FL, Li C, Liu Y, et al. Peripheral blood parameters for predicting PICU admission and mechanical ventilation in pediatric inpatients with human parainfluenza virus-induced pneumonia. *J Med Virol*. 2023;95(4):e28752.

16 Manuel V, Miana LA, Guerreiro GP, et al. Prognostic value of the preoperative neutrophil-lymphocyte ratio in patients undergoing the bidirectional Glenn procedure. *J Card Surg*. 2020;35(2):328–334.

17 Farias JS, Villarreal EG, Savorgnan F, et al. The use of neutrophil--lymphocyte ratio for the prediction of refractory disease and coronary artery lesions in patients with Kawasaki disease. *Cardiol Young*. 2023;33(8):1409–1417.

18 Butterfield TA, Best TM, Merrick MA. The dual roles of neutrophils and macrophages in inflammation: a critical balance between tissue damage and repair. *J Athl Train*. 2006;41(4):457–465.

19 Rosales C. Neutrophil: A cell with many roles in inflammation or several cell types? *Front Physiol*. 2018;9:113.

20 Walmsley SR, Print C, Farahi N, et al. Hypoxia-induced neutrophil survival is mediated by HIF-1alpha-dependent NF-kappaB activity. *J Exp Med*. 2005;201(1):105–115.

21 Sheikholeslami D, Dyson AE, Villarreal EG, et al. Venous blood gases in pediatric patients: a lost art? *Minerva Pediatr (Torino)*. 2022;74(6):789–794.

22 Loomba RS. The oximetric approach to clinical care. *Pediatr Cardiol*. 2023;44(4):960–961.

23 Loomba RS, Flores S. Oximetry titrated care: this is the way. *Paediatr Anaesth*. 2022;32(3):485.

24 Dhillon S, Yu X, Zhang G, et al. Clinical hemodynamic parameters do not accurately reflect systemic oxygen transport in neonates after the Norwood procedure. *Congenit Heart Dis*. 2015;10(3):234–239.

25 Law MA, Benscoter AL, Borasino S, et al. Inferior and superior vena cava saturation monitoring after neonatal cardiac surgery. *Pediatr Crit Care Med*. 2022;23(7):e347–e355.

26 Dabal RJ, Rhodes LA, Borasino S, et al. Inferior vena cava oxygen saturation monitoring after the Norwood procedure. *Ann Thorac Surg*. 2013;95(6):2114–2120.

Copyright: ©2025 Loomba et al.

27 Loomba RS, Rausa J, Sheikholeslami D, et al. Correlation of near-infrared spectroscopy oximetry and corresponding venous oxygen saturations in children with congenital heart disease. *Pediatr Cardiol*. 2022;43(1):197–206.

28 Tweddell JS, Ghanayem NS, Mussatto KA, et al. Mixed venous oxygen saturation monitoring after stage 1 palliation for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2007;84(4):1301–1310.

29 Ghanayem NS, Hoffman GM. Near infrared spectroscopy as a hemodynamic monitor in critical illness. *Pediatr Crit Care Med*. 2016;17(8 Suppl 1):S201–S206.

30 Hoffman GM, Ghanayem NS, Scott JP, et al. Postoperative cerebral and somatic near-infrared spectroscopy saturations and outcome in hypoplastic left heart syndrome. *Ann Thorac Surg*. 2017;103(5):1527–1535.

31 Hoffman GM, Mussatto KA, Brosig CL, et al. Systemic venous oxygen saturation after the Norwood procedure and childhood neurodevelopmental outcome. *J Thorac Cardiovasc Surg*. 2005;130(4):1094–1100.

32 Joffe R, Al Aklabi M, Bhattacharya S, et al. Cardiac surgery-associated kidney injury in children and renal oximetry. *Pediatr Crit Care Med*. 2018;19(9):839–845.

33 Scott JP, Hoffman GM. Near-infrared spectroscopy: exposing the dark (venous) side of the circulation. *Paediatr Anaesth*. 2014;24(1):74–88.

34 Dorum BA, Ozkan H, Cetinkaya M, et al. Regional oxygen saturation and acute kidney injury in premature infants. *Pediatr Int*. 2021;63(3):290–294.

35 Takano H, Matsuda H, Kadoba K, et al. Monitoring of hepatic venous oxygen saturation for predicting acute liver dysfunction after Fontan operations. *J Thorac Cardiovasc Surg*. 1994;108(4):700–708.

Citation: Loomba RS, Farias JS, Villarreal E, et al. Association between neutrophil-lymphocyte-ratio and oxygen delivery in patients after the Norwood operation. *J Pediatr Neonatal Care*. 2025;15(2):111–115. DOI: 10.15406/jpnc.2025.15.00595