THE UTILIZATION OF NEUTROPHIL LYMPHOCYTE COUNT RATIO AS PREDICTOR OF NEONATAL SEPSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

BACKGROUND: Neonatal sepsis remains to be an important cause of neonatal morbidity and mortality and its diagnosis is difficult due to non-specific signs and symptoms that may mimic other infectious conditions. Blood culture, the gold standard in the diagnosis of sepsis, is limited by it being time-consuming and with high probability of false negative results.

OBJECTIVE: To investigate the usefulness of the NLR as a predictor in the diagnosis of neonatal sepsis and early - onset neonatal sepsis (EOS).

METHODS: Relevant publications from 2009 to 2019 that fulfilled the inclusion criteria were identified through electronic database search. Studies were analyzed and a meta- analysis was performed. The effect of NLR was calculated as a predictive factor for EOS.

RESULTS: Four observational studies were included with a total of 392 patients. Two studies were analyzed for EOS which included 242 patients. There is significant association between NLR and neonatal sepsis. The sensitivity and specificity of NLR to predict sepsis were 84.5% and 91%. The sensitivity and specificity of NLR to predict EOS were 71% and 66%.

CONCLUSION: NLR is an acceptable tool in predicting neonatal sepsis and EOS but its usefulness is limited due to the presence of bias and heterogeneity in the studies included.

RECOMMENDATIONS: Further studies, preferably local studies, to investigate and validate the usefulness of the NLR as a predictor of neonatal sepsis and EOS is recommended.

KEYWORDS: "neonatal sepsis", "early – onset neonatal sepsis", "neutrophil – lymphocyte ratio", "meta – analysis"

INTRODUCTION

Statement of the Problem

Infection remains to be an important cause of neonatal morbidity and mortality.[1] In 2018, the World Health Organization (WHO) recorded approximately five million neonatal deaths each year due to sepsis with 34 in 1000 births mortality rate.[2] In addition, almost 95% of the cases identified were from developing countries.[3]Especially in the neonatal population, delays in the diagnosis and initiation of appropriate antibiotics are critical because such delays can significantly worsen outcomes.[4]

The diagnosis of neonatal sepsis is difficult due to non-specific signs and symptoms that may mimic other infectious conditions.[1]Routine laboratory testing is done in any newborn with identifiable risk factors or signs and symptoms concerning sepsis. The gold standard in the diagnosis of neonatal sepsis is a positive culture from a normally sterile site and it would usually take 2 to 5 days for culture results to come out thereby delaying the diagnosis of sepsis. In addition, not all neonates with signs and symptoms of neonatal sepsis had positive cultures.[3] In a study done by Ruslie *et. al*, in neonates suspected to have sepsis, only 55.3% showed positive culture results.[3]

The neutrophil-lymphocyte ratio (NLR) is a novel parameter and is assumed to be a prognosticating factor in diseases such as inflammatory diseases like Kawasaki Disease and Systemic Lupus Erythematosus, cardiovascular diseases, cancer, and infections.[5] It is easily obtained and calculated from the complete blood count test. Several studies have found that the neutrophil – lymphocyte ratio outperforms other acute phase reactants such as the white cell count (WBC), neutrophil count and C-reactive protein (CRP) in the emergency room department.[5,6] Recent studies were also done with regards to the use of the NLR in the diagnosis of neonatal sepsis. The present study aimed to determine the usefulness of NLR as a predictor neonatal sepsis and early-onset sepsis in neonates.

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without proven bacteremia in the first month of life.[8] It can be divided into two major categories depending on the onset of symptoms. Early-onset sepsis presents within the first 72 hours of life.[8] It develops after delivery from organisms acquired before or during birth. On the other hand, late-onset sepsis presents after the 72nd hour of life. The source of infection is either hospital-acquired or community-acquired. [1,8]

The clinical manifestations of newborn infections vary and include subclinical infection, and mild to severe manifestations of focal or systemic infection.[1]According to the World Health Organization (WHO), neonatal sepsis can be diagnosed by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or because of suspected or proven infection. The clinical symptoms include temperature instability (hypothermia or hyperthermia), cardiovascular instability (bradycardia or tachycardia), presence of skin and subcutaneous lesions, respiratory instability (apnea or tachypnea), gastrointestinal symptoms (feeding intolerance, poor suck, or abdominal distention) and other non-specific signs and symptoms such as irritability, lethargy and hypotonia. Laboratory signs include WBC count of less than 4,000 x 109 cells/L or 20,000x109 cells/L, immature to neutrophil ratio of greater than 0.2, platelet count of <100,000 x 109 cells/L, CRP of >15mg/L, procalcitonin of >2ng/ml, hyperglycemia >180mg/dl or hypoglycemia <45mg/dl, and metabolic acidosis. However, in resource-limited settings with limited access to laboratory evaluations, this definition may not be applicable.[2]

The diagnosis of neonatal sepsis is complicated by its nonspecific clinical

symptomatology.[3] The gold standard in the diagnosis of sepsis is blood culture and should be done in all cases of suspected sepsis prior to starting of antibiotics. However, blood culture can time making it an unreliable tool in determining if treatment is needed in critical hours once the disease has begun.[7] Positive results can be influenced by several factors such as specimen collection and methods in culturing blood. Cultures may be negative in those who have received antibiotics previously or antenatally.[3]

Complete blood count is a common laboratory test done to screen for possible infection. Markers of infection that can be derived from the CBC include total leukocyte count, absolute neutrophil count and the immature to total neutrophil count. However, the absolute neutrophil count and the immature to total neutrophil count vary considerably during the neonatal period.[3,4,8] In addition, Poyoa *et al*. and Sierra et al. reported leukocyte level had low diagnostic value for neonatal sepsis. [9,10] In this study, leukocyte count was higher in confirmed sepsis than in suspected sepsis, but was not statistically significant.[3]In addition, according to the study done by Hornik, *et. al*, these markers have low sensitivities, making it a poor diagnostic marker to rule out early onset sepsis. [11]

A high index of suspicion is needed for early diagnosis of neonatal sepsis and treatment should be initiated without delay to prevent adverse outcomes of sepsis in the neonate. At present, starting empiric treatment with broad-spectrum antibiotics after a sepsis work-up in patients with clinical signs became a routine practice in neonatal care while awaiting results of the blood cultures sent.[3] Thus, a rapid diagnostic test that can differentiate neonates with and without sepsis will have a significant impact on neonatal care management.

Neutrophils and lymphocytes are important components of the immune system.[7] The NLR has been recently investigated as a biomarker for inflammation. It was found to be comparable with Erythrocyte Sedimentation Rate (ESR), CRP and WBC count as an indicator of systemic inflammation. The NLR has been used as a guide to prognosticate community-acquired pneumonia, ischemic heart disease, intravenous immunoglobulin (IVIG) resistant Kawasaki Disease, and cancer. [6]In general, neutrophils serve as a marker of ongoing non-specific inflammation, while lymphocytes act as a marker of the immune regulatory response. The NLR thus, represents the balance between inflammation and immune regulation, and is a biomarker of surgical stress, systemic inflammation, and sepsis, as the severity and clinical courses of such conditions correlate with neutrophilia and lymphocytopenia. In addition, in a study by Liu et al., it was reported that a high NLR is associated with more severe sepsis and higher mortality rate.[3]

OBJECTIVES OF THE STUDY

The general objective of this study was to investigate the usefulness of the neutrophil to lymphocyte ratio (NLR) as a predictor in the diagnosis of neonatal sepsis.

The study also aimed to determine the sensitivity and specificity of NLR using available studies on the utility of NLR in predicting early-onset neonatal sepsis.

METHODOLOGY

A systematic review and meta-analysis were done to synthesize the evidence for NLR as a predictor of early onset sepsis in neonates. Literature search used the following databases: PubMed, MEDLINE, EMBASE, CINAHL, HERDIN, Google Scholar, and the Cochrane Database of Systematic Reviews to look for relevant studies included in the study. The literature search used search terms containing "neutrophil-lymphocyte ratio", "early onset sepsis" and "neonatal sepsis". Combination

of terms was done using Boolean operators. Organizations, training hospitals, and professional societies were contacted for any additional published trials and unpublished data that may be included in this study.

All studies that met the following criteria were included in the study: (1) Retrospective or prospective case control, cross sectional, cohort study design investigating neonatal sepsis and early-onset neonatal sepsis from 2009 to 2019 according to the criteria set by the WHO, (2) Studies involving neonates ages 0 to 7 days old diagnosed to have neonatal sepsis and early-onset neonatal sepsis, and (3) Studies involving NLR as predictor of neonatal sepsis and early-onset neonatal sepsis.

Studies were excluded if (1) The effect of the outcome of interest is not assessed (2) Data is insufficient to provide or calculate pooled estimates (3) Studies or trials on animals other than humans, studies with different population and population with other alternative diagnoses.

Full text articles of the studies were obtained and assessed for eligibility for the study based on the set inclusion and exclusion criteria. The author extracted data onto a data extraction form, which included the following: (1) General Information: Study authors, published/unpublished, publication year, and journal, (2) Study design, (3) Study participants-age and sex, (4) Initial CBC parameters such as WBC, neutrophil and lymphocyte counts, (5) NLR and cut off value for patients diagnosed with early-onset neonatal sepsis as compared to those without neonatal sepsis, and (6) Sensitivity, specificity, p value, odds ratio and cut off ratio.

The following key terms were used: (“Neutrophils” AND lymphocyte ratio), (“neutrophil to lymphocyte ratio (NLR)” AND SEPSIS), (“neutrophil to lymphocyte ratio (NLR)” AND MORTALITY). Medical subject headings (MeSH) were also used to search the databases: (("neutrophils"[MeSH Terms] OR "neutrophils"[All Fields] OR "neutrophil"[All Fields]) AND ("lymphocytes"[MeSH Terms] OR "lymphocytes"[All Fields] OR "lymphocyte"[All Fields]) AND ("Ratio (Oxf)"[Journal] OR "ratio"[All Fields])) AND ("neonatal sepsis"[MeSH Terms] OR ("neonatal"[All Fields] AND "sepsis"[All Fields]) OR "neonatal sepsis"[All Fields]).

The review also included grey literature from the following databases: New York Academy of Medicine: Grey Literature, Sociological Abstracts, Science.gov, ProQuest Dissertations and Thesis, and WorldCat. Search for registered proposals and RCTs was done using websites such as www.clinicalTrials.gov. Cross-referencing of journals was also done. Data search also included searches from Google Scholar and the World Wide Web. Journals and articles published from 2009 to 2019 will be included in the study.

A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram was used to document the search process and the inclusion and exclusion of studies.

Studies included were appraised to assess risk of bias. However, due to the limited number of studies included in the study, a formal testing for publication bias was not feasible. The present study used the Newcastle – Ottawa Scale (NOS) in assessing the risk of bias. The NOS was developed to assess the quality of non-randomized studies with its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. The scale uses a 'star system' in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.[21]

The effect of heterogeneity of the studies was assessed by means of I^2. The predefined heterogeneity criteria were set as follows: low and not significant if the I^2 value is <40%; moderate with I^2 values of 40 to 60%; substantial heterogeneity at I^2 values 60 to 90% and considerable heterogeneity at 75% to 100%.[17] Due to the limited number of studies included in the analysis, possible sources of heterogeneity were not explored. The data was analyzed in the form of sensitivity, specificity and false-positive rates, odds ratio with their 95% confidence intervals (CIs). Meta-analysis was performed using the Review Manager 5.3 (Cochrane Collaboration, UK). To describe the percentage of total variation across the studies included in the study, heterogeneity was quantified using the I^2 test. Subgroup analysis was performed and methodological differences between studies were identified if heterogeneity was seen by visual inspection of the forest plot or a high I^2 value.

RESULTS

A systematic search was conducted to retrieve studies that will be included in the study. Search for grey literature was also done, however, there was no available study for review. A total of 20 studies were identified during the initial search. Eight studies that were not relevant to the present study were removed. Upon review of the titles and abstracts, eight studies that did not meet the inclusion criteria were excluded. A total of four studies were included in this meta-analysis. Flow chart of study selection is shown in Figure 1.

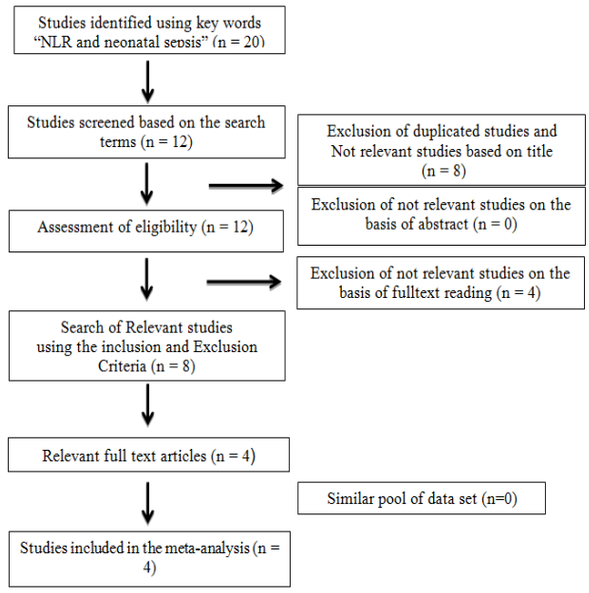

Figure 1. Systematic Review Process

Study Characteristics

The systematic search resulted in studies with different study designs, thus, upon careful consideration; the studies were confined to cross-sectional study designs. For this meta-analysis, studies included were those with reported use of NLR and early onset neonatal sepsis. The review included data from four (4) cross-sectional studies published during the period 2015 to 2019.

A total of four studies were included in the analysis. A total of 382 neonates were included in the analysis: 112 from the study of Can *et al* (2018), 120 from Wilar (2019), 70 from the study of Omran *et al* (2017), and 80 from Fang *et al* (2015). A summary of characteristics of the studies included are presented in Table 1 found on the next page.

Table 2 shows the summary of the results between the patients with neonatal sepsis and those without sepsis.

Table 2. Summary of Results Between Non – Neonatal Sepsis Group and Neonatal Sepsis Group

Study Author Year Country	**Non – Sepsis Group**	**Neonatal Sepsis Group**			
	Neutrophil – Lymphocyte Ratio (Mean and Standard Deviation)	**Neutrophil – Lymphocyte Ratio (Mean and Standard Deviation)**	**Sensitivity**	**Specificity**	**Cut – Off Point**
Can 2018 Turkey	0.21±0.12	2.88±0.16	97.4%	100%	6.76
Wilar 2019 Korea	0.82±0.32	2.82±2.29	83.3%	93.3%	1.245
Omran 2017 Egypt	1.6 ± 0.4	2.9 ± 1.7	80%	57.1%	2.7
Fang 2015 China	2.1 ± 0.6	11.45± 6.68	75%	84.2%.	12.64

TABLE 1: CHARACTERISTICS OF INCLUDED STUDIES				
First Author Surname Year Country	Study Title	Study Design	Population	Parameters Assessed and Findings
Fang 2015 China	Ratios of CD64 Expressed on Neutrophils, Monocytes, and Lymphocytes May Be a Novel Method for Diagnosis of Neonatal Sepsis	Prospective observational study design	80 neonates with neonatal sepsis (21 culture positive, 59 negative) were included	Ratios were calculated with these levels of CD64 expression. Blood culture and other laboratory CD4 ratios were calculated including the NLR, neutrophil to monocyte ratio, neutrophil - lymphocyte ratio to neutrophil monocyte ratio. Cut-off for NLR ratio is 12.64 with sensitivity of 75% and specificity of 84.2%.
Omran 2017 Egypt	Salivary C-Reactive Protein, Mean Platelet Volume and Neutrophil Lymphocyte Ratio as Diagnostic Markers for Neonatal Sepsis	Cross sectional study	70 full-term neonates were included, 35 were septic and 35 were non-septic	Mean platelet volume and neutrophil-lymphocyte ratio showed significant difference between septic neonates and controls. At a cut-off point of 2.7, neutrophil-lymphocyte ratio presented 80% sensitivity and 57.1% specificity
Can 2018 Turkey	The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis	Prospective observational study design	A total of 122 term neonates were included, 78 EOS group, 44 non - EOS	EOS group had significantly higher neutrophil counts, axillary temperature, neutrophil lymphocyte count ratio, platelet lymphocyte count ratio, C-reactive protein and procalcitonin levels compared with the control group. An NLR of 6.76 was determined as the predictive cutoff value of neonate EOS (sensitivity 97.4%; specificity 100%).
Wilar 2019 Korea	Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset neonatal sepsis	Cross sectional study	120 neonates who met the inclusion criteria, 90 in the EOS group and 30 in the non-EOS group.	EOS group had higher NLR level and greater eosinopenia than the non – EOS group. The diagnostic value of NLR in the EONS group (cutoff point, 1.24) showed83.3% sensitivity and 93.3% specificity.

Figure 2 shows the Risk of Bias analysis using the Newcastle-Ottawa Quality Assessment Scale. The studies included in the analysis exhibited low risk for bias. There are different parameters for the assessment such as Representativeness of Samples, Sample Size, Non-Respondents and Ascertain Risk of Exposure. A total of 10 stars can be obtained in the assessment with 10 being the highest. Each study included in the analysis garnered 8 stars which indicates low risk of bias.

	Representativeness	Sample size	Non-respondents	Ascertainment of exposure	Control of confounding	Assessment of outcome	Statistical test	Total
Wilar 2019	★	★	★	★★	--	★★	★	8
Omran 2018	★	★	★	★★	--	★★	★	8
Can 2017	★	★	★	★★	--	★★	★	8
Fang 2015	★	★	★	★★	--	★★	★	8

Figure 2. Risk of Bias Assessment Using Modified Newcastle-Ottawa

Neutrophil – Lymphocyte Count in Neonatal Sepsis

The pooled estimate for sensitivity and specificity of the four (4) studies on neonatal sepsis is shown in Figure 3. The NLR as a predictor of neonatal sepsis has high sensitivity at 0.86 (95% CI 0.70 – 0.94) and high specificity at 0.94 (95% CI0.47 – 1.0).

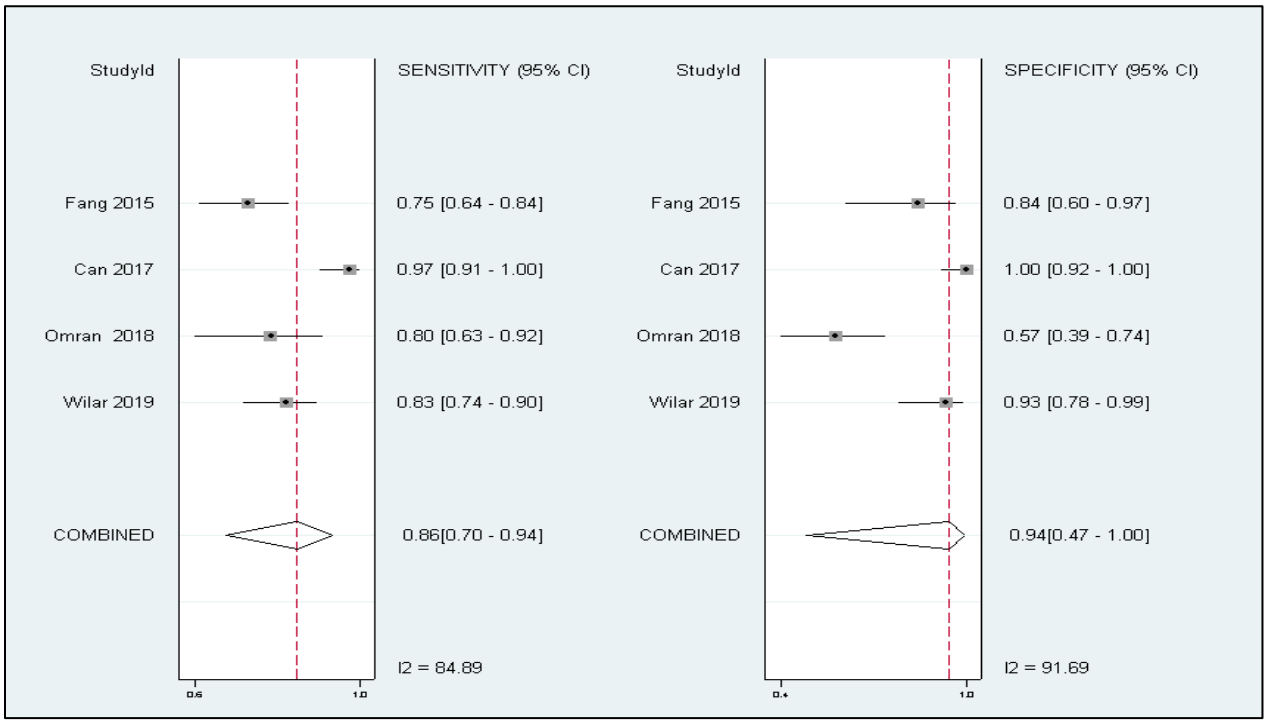

Figure 3: Forest Plot for Diagnostic Accuracy of NLR in Predicting Early Onset

Neonatal Sepsis

The area under the curve (Figure 4) shows high accuracy (AUC=0.93), suggesting that the NLR can be used as an acceptable diagnostic marker in the diagnosis of neonatal sepsis. All 4 studies have considerable heterogeneity at 84.9-91.7%.

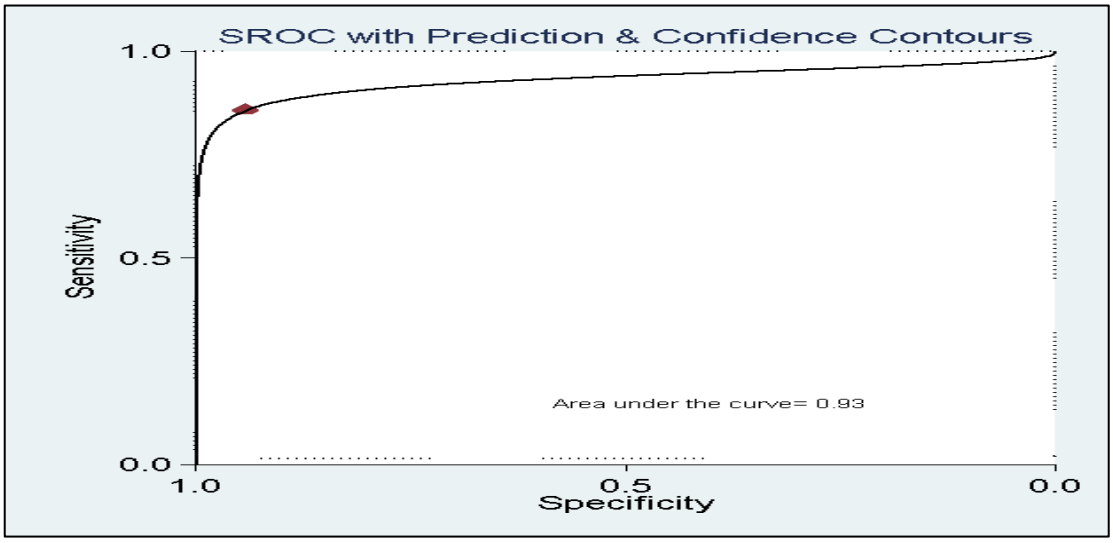

Figure 4: ROC Curve on the Diagnostic Accuracy of NLR in Predicting Neonatal Sepsis

The pooled estimate for sensitivity and specificity of two studies on early onset neonatal sepsis is shown in Figure 5. NLR in the diagnosis of early onset neonatal sepsis has a high combined sensitivity at 0.89 (95% CI 0.79 – 0.94) and high combined specificity at 0.97 (95% CI 87 – 1.0).

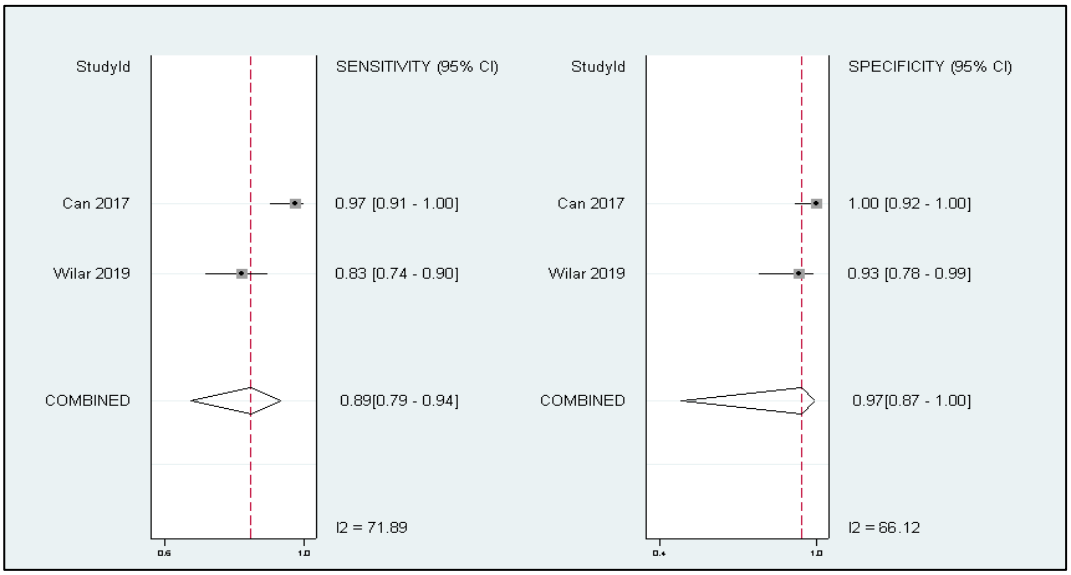

Figure 5: Forest Plot for Diagnostic Accuracy of NLR in Predicting Early Onset Neonatal Sepsis

The area under the curve shown in Figure 6 shows high accuracy (AUC=0.95). The 2 studies have substantial heterogeneity (71.9-86.1%).

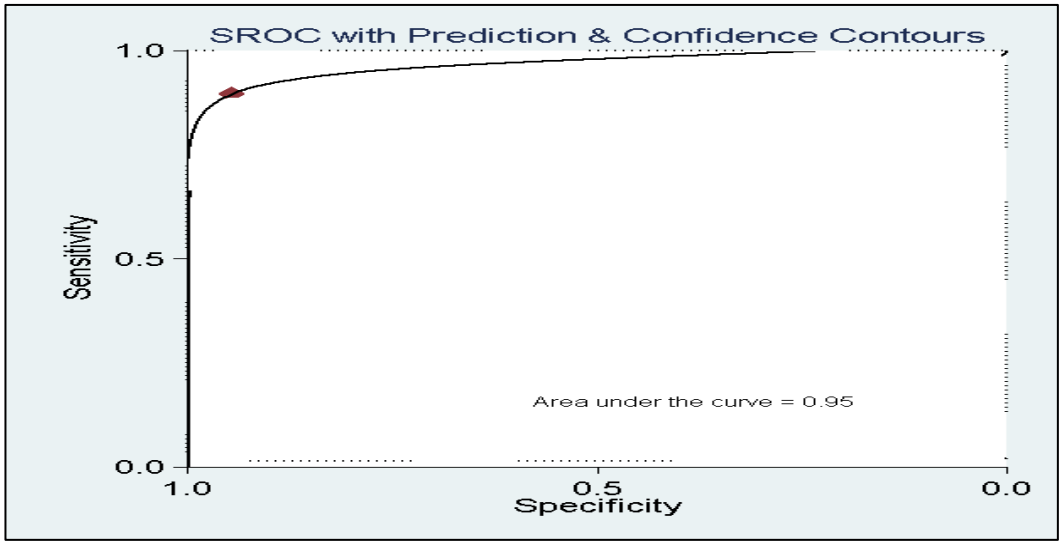

Figure 6: ROC Curve on the Diagnostic Accuracy of NLR in Predicting Early Onset Neonatal Sepsis

DISCUSSION

The diagnosis of early-onset neonatal sepsis remains to be a challenge to physicians due to its variable clinical presentation and can lead to substantial morbidity and mortality during the newborn period. Blood culture, which is the gold standard in the diagnosis of neonatal sepsis, is limited by being time-consuming and high probability of false negative results. Although several biochemical markers have been studied and proposed as potential markers for neonatal sepsis, the sensitivity and specificity of the tests were inadequate, and some results were inconclusive. Also these markers are expensive and not always readily available. Hence, it is necessary to find an immediate, cost-effective, and readily available marker for neonatal sepsis. The present study utilized parameters derived from the complete blood count (neutrophil count and lymphocyte count), which is a standard, routine and readily available test done in patients suspected to have infections, in the early diagnosis of early-onset neonatal sepsis.

There is growing evidence that NLR can be a promising predictor of conditions such as inflammatory conditions, cardiovascular diseases, cancer, and infections. The NLR is a simple and inexpensive marker of subclinical inflammation, which can be easily calculated from the differential white blood cell counts.[12]The present study combines current knowledge on the role of the NLR in the diagnosis of neonatal sepsis and early-onset neonatal sepsis and is the first systematic review and meta-analysis done investigating the predictive value of the NLR in the diagnosis of neonatal sepsis and early – onset neonatal sepsis.

The results of the present study showed significant association between neutrophil – lymphocyte count and early onset sepsis. The sensitivity and specificity of NLR to predict sepsis marker was 84.5% and 91%, respectively. Furthermore, the sensitivity and specificity of NLR to predict early-onset of sepsis was 71% and 66%. NLR are seen in early phase of sepsis and thus maybe of help in making a good diagnosis, especially when microbiological culture poses limitation in terms of time and low-positive rate.

The present study has some limitations such as the limited number of studies available for review. Hence, a funnel plot for asymmetry was not done which can lead to high risk of publication bias. The studies included in the analysis were observational in nature and risk of bias assessment and confounders might be present. Heterogeneity was also evident among the study categories and variables- both clinical and statistical. The possible sources of heterogeneity were ideally to be explored, however this was not possible due to the limited number of studies included in the analysis. The high heterogeneity results in this analysis may be partly due to differences in focused clinical outcomes of the studies. In addition, due to the lack of clinical data, the cut off value for the neutrophil to lymphocyte count ratio in the studies were different and the lack of raw data thereof for a computation of a new

cut off score from the analysis was not feasible.

CONCLUSION

Based on the present study, the NLR is a good diagnostic marker for the early diagnosis of neonatal sepsis given its high sensitivity and specificity. The NLR is higher among patients with early onset neonatal sepsis than those without neonatal sepsis. However, the heterogeneity of the studies included may pose limitations in the usefulness of NLR as a valid and accepted marker for early onset neonatal sepsis.

We recommend that prospective further studies be done to validate the usefulness of the NLR as a predictor for early – onset neonatal sepsis. Studies combining the effectiveness of the NLR with other markers of infection can also be done to increase the sensitivity and specificity of these markers combined in the diagnosis of early-onset neonatal sepsis.

BIBLIOGRAPHY AND REFERENCES

1. Robert M,Kleigman, MD. Nelsons textbook of Pediatrics. 20th International Edition. 2016 Elsevier. Chapters 93 – 109.

2. Fuchs A, Bielicki J, Mathur S, Sharlan M, Van Den Anker J. Antibiotic use for sepsis in neonates and children: 2016 evidence update. WHO-Reviews.

3. Ruslie RH, Tjipta DG, Samosir CT, Hasibuan BS. Bacterial pattern and role of laboratory parameters as marker for neonatal sepsis. IOP Conference Series: Earth and Environmental Science. 2018; 125, 012057. doi:10.1088/1755-1315/125/1/012057

4. Bhandhari V. Effective biomarkers for diagnosis of neonatal sepsis. *Pediatr Infect Dis J*.2014; 3 (3): 234-245

5. Yoon NB, Son C, Um SJ. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. *Ann Lab Med.*2013;33:105-10.

6. Richard L, Gomes C,Jarman I,*et al*. Neutrophil to lymphocyte count ratio as an early indicator of blood stream infection in the emergency department.EMJ Online. 2014; s 10.1136/emermed-2014-204071

7. Wilar R. Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset neonatal sepsis. *Korean J Pediatr*. 2019

8. AIIMS Protocol 2014. Neonatal sepsis. https://www.newbornwhocc.org/2014_pdf/Neonatal%20sepsis%202014.pdf

9. Cho HJ, So YB, SuYK, *et al*. A high neutrophil to lymphocyte ratio is associated with refractory Kawasaki disease. *Pediatr Int.* 2017 Jun;59(6):669-674

10. SeiichiroT, Takashi K, Yoichi K,Yusuke Y, Shigeaki N. A comparison of the predictive validity of the combination of

the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and other risk scoring systems for intravenous immunoglobulin (IVIg)-resistance in Kawasaki disease. PLOS ONE. 2017

11. Hornik CP, Benjamin DK, Becker KC, *et al*. Use of the complete blood cell count in late-onset neonatal sepsis. *Pediatr Infect Dis J*. 2012; 31:803–7

12. Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M, Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: A systematic review and meta-analysis.Am Surg J. https://doi.org/10.1016/ j.amjsurg.2019.04.018.

13. Omran A, Abdallah M,Saleh H, Amina A. Salivary C-reactive protein, mean platelet volume and neutrophil lymphocyte ratio as diagnostic markers for neonatal sepsis. Pedia J. 2017;94. 10.1016/j.jped.2017.03.006.

14. Fang D, Fan CH, Li, J,*et al*. Ratios of CD64 expressed on neutrophils, monocytes, and lymphocytes may be a novel method for diagnosis of neonatal sepsis. *Infect Dev Count J*. 2015. 9. 10.3855/jidc.4992.

15. Can E,Hamilçıkan S, Can C. The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Pedia Hema J*. 2017, 40. 1. 10.1097/MPH.0000000000001059.

16. Zahorec R. Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill. *BratislLekListy*. 2001; 102:5–14. PMID: 11723675

17. Higgins J, Green SP. Cochrane Handbook for Systematic Reviews of intervention. 2011Oxford: Wiley-Blackwell

18. Simundic*et al*. Measures of Diagnostic accuracy: Basic definition. EJIFCC.2009 Jan; 19(4): 203-2011 PMID:27683318

19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009 PLoS Med 6: e1000097 10.1371/journal.pmed.1000097

20. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. 2015. Stat Med 34: 343–360. 10.1002/sim.6342

21. Wells, GA *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp