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Peripheral blood neutrophil-to-lymphocyte ratio in preterm infants with intraventricular hemorrhage

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A R T I C L E I N F O

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A B S T R A C T

Objectives: Intraventricular hemorrhage (IVH) remains a major complication of prematurity, affecting 20–25% of premature infants of very low birth weight. Preterm infants with IVH are at risk for developing significant complications, including posthemorrhagic hydrocephalus and seizures. Multiple studies have reported an association between the neutrophil-to-lymphocyte ratio (NLR) in peripheral blood and outcomes after acute intracranial hemorrhage in adults. However, the prognostic value of the NLR in preterm infants, particularly those with IVH, has not been investigated previously.
Patients and methods: This retrospective, observational cohort study included premature infants with IVH and a neonatal reservoir placed between January 2013 and January 2018. For each patient, peripheral blood and available cerebrospinal fluid laboratory results within 50 days of IVH diagnosis were averaged. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Differences in NLR levels for patients with seizures or shunt placement were analyzed.
Results: Data for 13 surviving preterm infants (mean gestational age, 26.5 ± 3.0 weeks) were analyzed. The mean peripheral NLR (n = 13) was 1.6 ± 1.3 for all patients. Patients who experienced seizures had significantly higher peripheral blood NLR ($p = 1.2 \times 10^{-6}$, t-test) than those who did not, and an NLR > 3 correlated with seizure outcomes (p = 0.0035, Fisher's exact). Patients with sepsis or meningitis also had NLR values > 3 (p = 0.01 and 0.005, respectively) but there was no correlation between the sepsis/meningitis and seizures patients. No significant correlation was found between NLR and the development of hydrocephalus.
Conclusion: The development of seizures in preterm infants with IVH is known to significantly increase morbidity. In this study, higher peripheral blood NLR (> 3) correlated with the development of seizures, independent of sepsis or meningitis. Further prospective validation of the role of NLR as a predictive marker for seizures in preterm infants is warranted.

1. Introduction

Intraventricular hemorrhage (IVH) is the most common brain injury in premature infants of very low birth weight (VLBW, < 1500 g) and extremely low birth weight (ELBW, < 1000 g), and there are approximately 12,000 annual cases of IVH in these patients in the United States alone [1]. During gestation, the fetal germinal matrix undergoes rapid angiogenesis and acts as the primary supplier of neurons and glial cells to the developing brain. Germinal matrix activity peaks between 8 and 28 weeks and is complete around 32 weeks estimated gestational age (EGA) [2]. When a baby is born before 32 weeks EGA, the immature vessels of the germinal matrix are highly susceptible to rupture and subsequent IVH. Most IVH occurs within the first 72 h after birth when the infant is the most unstable and can experience systemic fluctuations of blood flow, volume, and intraventricular pressure because of parasympathetic immaturity [2]. Although advances in prenatal and neonatal care have improved morbidity and mortality rates drastically, IVH remains a major complication in approximately 20% of preterm infants [1].

IVH severity is graded on the Papile scale from I to IV [3]. Hemorrhage can be limited to the germinal matrix (grade I) or rupture through the ventricular wall into the ventricles (grades II to IV).

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Preterm infants with higher-grade IVH are at an increased risk of developing serious neurological complications, such as seizures and posthemorrhagic hydrocephalus (PHH) requiring ventriculoperitoneal shunt (VPS) placement [1]. Severe IVH (grades III and IV) is the most common cause of neonatal seizures in newborn preterm infants, and such seizures increase infant morbidity [4]. These infants can also develop symptomatic hydrocephalus within several days of birth, and the incidence of PHH in neonates with severe IVH can be as high as 25 to 35% [5]. Furthermore, many infants with severe PHH will require temporary cerebrospinal fluid (CSF) diversion and 72 to 90% will require permanent shunt implantation [5].

To date, there are very few tools other than the IVH grading system for clinicians to use to predict outcomes for IVH [6]. Advancements in traumatic brain injury (TBI) research have shown that there are similarities in the causes and inflammatory cascade produced in neonatal IVH and those of TBI [7]. Studies have shown an increase in key inflammatory cytokines, including interleukin (IL)-1α, IL-1β, IL-4, IL-6, IL-12, tumor necrosis factor (TNF)-α, chemokine ligand (CCL) CCL-3, CCL-9, and CXCL-10, in CSF following IVH [7–12]. Unfortunately, tests for these cytokines are costly and not readily available in most hospital laboratories.

The neutrophil-to-lymphocyte ratio (NLR) measured from a peripheral blood complete blood count (CBC) provides a simple, cost-effective index of inflammation. NLR has proven to be a reliable prognostic marker of morbidity, functional outcomes, and all-cause mortality in cancers, cardiovascular disease, renal disease, and cerebrovascular disease [8–11,13–29]. Several studies have reported an association between the peripheral blood NLR and outcomes following acute intracranial hemorrhage [16,25,30]. In addition, a study by Goksugur et al. [31] found that an NLR > 3 was an effective predictor of febrile seizures in pediatric patients between 6 months and 6 years of age. Although increasing attention has been paid to the prognostic value of NLR in adults, the prognostic value of the NLR in the preterm infant population, particularly in preterm infants with IVH, remains largely unknown. We hypothesized that an NLR > 3 in either the peripheral blood or the CSF, as described by Goksugur et al. [31], would be correlated with an increase in seizures and PHH (indicated by need for VPS placement) in these infants.

2. Materials and methods

2.1. Study, design, setting, and population

A retrospective review of the electronic medical records (EMR) for the period between January 1, 2013, and January 31, 2018, was performed to identify very premature infants (< 32 weeks EGA) diagnosed with IVH who underwent a neonatal reservoir placement at Joe DiMaggio Children's Hospital, a level III neonatal intensive care unit. Criteria for reservoir placement included: frontal-occipital ratio (FOR) > 0.55 plus 2/3 of the following: 1) bulging fontanelle; 2. sutures splayed > 3 mm; 3) bradycardia or apnea. This study was approved by the Memorial Healthcare System's Institutional Review Board (IRB) and was considered exempt from informed consent because of the retrospective nature and use of archival data.

2.2. Study protocol

The study population that met inclusion criteria was compiled from a query of the institution's EMR system, EPIC (EPIC Systems Corp; Verona, WI). After retrieval of patient charts, data collection was completed in a form standardized for data entry by a trained data abstractor supervised by a senior author (HS). Charts were specifically reviewed for patients with available peripheral blood (CBC panel with differential) laboratory results, and all patients without the relevant laboratory work within 50 days of IVH diagnosis were excluded from the study. To ensure data integrity and minimization of abstraction errors, approximately 10% of the abstracted data were randomly sampled, reviewed, and confirmed by a senior author (HS).

For all study patients, data were collected for the following: EGA at birth, birth weight, peripheral blood neutrophil and lymphocyte counts, CSF neutrophil and lymphocyte counts, IVH diagnosis date, IVH grade, and history of sepsis or meningitis. Outcome variables investigated were the development of seizures, defined as clinically positive findings of seizure activity confirmed by EEG, and placement of a VPS. Only patients who demonstrated seizure activity received an EEG. Criteria for VP shunt placement were weight > 2 kg and continuous need for tapping of reservoir. No infants received an endoscopic third ventriculostomy. The NLR for the peripheral blood, and for CSF, when available, was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. If multiple laboratory counts were collected for a patient, a mean NLR value was determined for the patient by averaging the NLR result from each panel acquired within 50 days of the patient's diagnosis of IVH.

2.3. Statistics

Study data were described with summary statistics (mean ± standard deviation). Linear regression analysis was used to correlate numerical data, including NLR levels for the peripheral blood vs. CSF and birth weight vs. EGA. Two-tailed t-tests determined any significant difference ($\alpha = 0.05$) in the NLR between the patients positive for seizures, sepsis, meningitis or VPS placement. Fisher's exact tests were used to determine whether there was a correlation between a NLR > 3 and seizure or VPS placement. Additionally, Fisher's exact tests were used to determine whether there was a correlation between birth weight (VLBW or ELBW) and seizure and VPS placement outcomes in this study population.

3. Results

From January 2013 to January 2018, 145 patients were diagnosed with IVH at our institution. Of those, 19 had a reservoir placed and 13 met inclusion criteria (See Consort Flow Diagram 1). Patients were excluded for the following reasons: lack of CBC data, no seizure outcome data, heart transplant and death. The last two were excluded

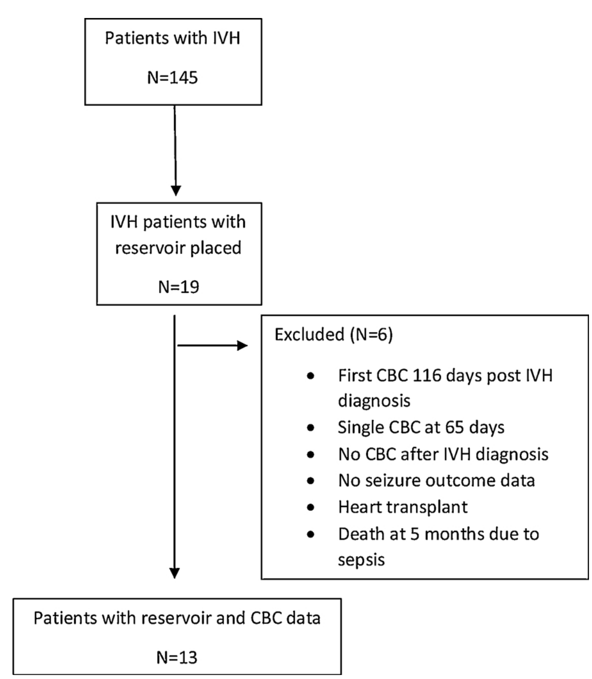

Diagram 1. Consort Flow Diagram. January 2013- January 2018.

Table 1
Patient study data for neonates diagnosed with IVH.

Patient	EGA (weeks)	Birth weight (g)	IVH grade (left, right)	Average blood NLR*	Average CSF NLR*	Seizures	Follow-up period (days)	Meningitis	Sepsis	Structural Abnormality on MRI
1	31	1640	III, III	0.43 ± 0.35	2.27 ± 0.45	N	533	N	N	None
2	30	1120	IV, I	0.81 ± 0.39	0.38	N	622	N	N	Porencephalic cyst, small CC, Chiari
3	24	695	IV, IV	3.68 ± 1.98	5.75 ± 6.54	Y	385	N	Y	Absence of CC and septum pellucidum
4	25	850	IV, IV	0.92 ± 0.15	–	N	1986	N	N	Absence of CC
5	23	600	I, IV	3.73 ± 4.63	–	Y	1262	N	Y	Chiari malformation
6	23	620	IV, IV	0.28 ± 0.39	0.45	N	665	N	Y	None
7	27	1100	III, III/IV	0.95 ± 0.18	1.00	N	472	Y	N	Partial absence of posterior body/splenium of CC
8	30	1735	II, II	1.66 ± 1.20	0.15 ± 0.14	N	1123	N	N	Chiari II, dysgenesis of CC
9	25	780	III, III	1.05 ± 0.60	15.23 ± 3.63	N	1122	N	Y	Partially absent septum pellucidum
10	30	1500	III, III	0.19 ± 0.19	3.11 ± 4.20	N	1081	N	N	Partially absent septum pellucidum
11	23	500	I, IV	2.83 ± 1.77	–	N	998	Y	N	Porencephalic cyst
12	27	1260	IV, III	3.43 ± 2.51	1.43	Y	272	N	N	Porencephalic cyst
13	26	920	III/IV, III	1.44 ± 1.19	0.19	N	306	N	N	None

CSF = cerebrospinal fluid; EGA = estimated gestational age; IVH = intraventricular hemorrhage; NLR = neutrophil-to-lymphocyte ratio; CC: corpus callosum.

* mean ± standard deviation.

because their NLRs were extremely large and potentially skewed the data too much for this small population. Patients were part of a consecutive cohort. The average number of days of follow-up was 784 with the shortest follow-up interval being 272 days and the longest was 1986 days (Table 1). The average EGA and birth weight were 26.5 ± 3.0 weeks and 1024 ± 409 g, respectively; 10 patients were considered very or extremely low birth weight (VLBW = 3/13, 77%; ELBW = 7/13, 54%) (Table 1). As expected, EGA and birth weight were significantly correlated (linear regression, $\beta = 129.74$, $p = 1.97 \times 10^{-6}$, adjusted $R^2 = 0.87$).

The mean peripheral NLR (n = 13) for the study group was 1.6 ± 1.3, and the mean CSF NLR (n = 10) was 3.0 ± 4.6 (Table 1). Of note, the peripheral blood NLR did not correlate with the CSF NLR (linear regression, $\beta = 0.28$, $p = 0.84$, adjusted $R^2 = -0.19$).

Patients who experienced seizures had significantly higher peripheral blood NLR (> 3) than those who did not ($p < 0.05$), and a peripheral blood NLR > 3 correlated with the development of seizures ($p < 0.05$) (Table 2). The presence of meningitis or sepsis did not correlate with seizure outcomes (p = 0.17 and 0.29, respectively). As expected, the presence of sepsis or meningitis was correlated with an increased NLR (p = 0.01, 0.005, respectively). The peripheral blood NLR in patients with a VPS placement was not significantly different (NLR < 3) ($p > 0.05$) than those who did not have a shunt placed, and an NLR > 3 did not significantly correlate with VPS placement ($p > 0.05$). Neither CSF NLR nor a CSF NLR > 3 correlated with seizure or VPS placement outcomes ($p > 0.05$). In addition, birth weights were not significantly different for patients with seizure or VPS placement outcomes ($p > 0.05$), and neither VLBW nor ELBW correlated with seizure or VPS placement outcomes (Fisher's exact tests, $p > 0.05$).

Interestingly, two patients (#3 and #5) developed both seizures and hydrocephalus, and these patients had the highest peripheral blood NLR in the surviving patient population.

4. Discussion

This study found that preterm infants with IVH who developed a seizure disorder had significantly higher values of peripheral NLR than those who did not have seizures. Also, there was a significant correlation observed between infants with NLR > 3 and seizure presentation. Patients with sepsis or meningitis had statistically significant increases in NLRs but there was no correlation between sepsis/meningitis and seizures. Lastly, two infants with a combination of seizures and hydrocephalus had the highest NLR of the study. In this small population, peripheral blood NLR significantly correlated with seizure outcomes, but sepsis, meningitis, EGA, birth weight, and CSF NLR did not.

IVH is a complication that occurs in 20% of preterm infants and is thought to be due to rupture of the fragile, immature vessels within the germinal matrix [2]. Once a hemorrhage occurs, the ensuing inflammatory response is characterized by microglial activation, cytotoxic inflammatory mediator release, increased capillary permeability, and recruitment of leukocytes from the peripheral blood [29]. This cascade has the potential to cause further damage to injured brain tissue in the acute time period following injury [31,32]. Studies directly measuring levels of chemokines and cytokines in the CSF of preterm infants with IVH have demonstrated elevations in inflammatory cell markers following IVH [7]. In the adult IVH population, elevations in NLR have correlated with worsened outcomes but there are no studies looking at the CSF NLR in these IVH patients [9]. While there is evidence suggesting that IVH causes inflammatory markers to be secreted in the CSF, our results did not indicate a statistically significant correlation between peripheral blood NLR and CSF NLR [7]. However, given the small sample size of our study, future research is needed to further assess this possible correlation.

Seizures significantly increase morbidity in preterm infants with IVH, and IVH remains the leading cause of neonatal seizures in the

Table 2
Statistical summary of NLR levels in neonates with a neonatal reservoir (IVH diagnosis) and patient outcomes for seizures and hydrocephalus (VPS placement).

	Overall	Seizures			Hydrocephalus		
		Positive	Negative	p-value	Positive	Negative	p-value
Patients n, %	13	3, 23.1%	10, 76.9%		10, 76.9%	3, 23.1%	
EGA, Weeks (n = 13)+	26.5 ± 3.0	24.7 ± 2.1	27.0 ± 3.1	*p=0.19*	26.0 ± 3.0	28.0 ± 2.6	*p = 0.33*
Birth weight, g (n = 13)+	1024 ± 409	852 ± 357	1077 ± 427	*p = 0.41*	950 ± 409	1273 ± 360	*p = 0.26*
CBC, mean NLR (n = 13)+	1.6 ± 1.3	3.6 ± 0.2	1.1 ± 0.8	$\boldsymbol{p = 1.2 \times 10^{-6}}$*	1.6 ± 1.3	1.8 ± 1.5	*p = 0.88*
CBC, NLR > 3 (n = 13)^	3/13	3/3	0/10	***p = 0.0035****	2/10	1/3	*p = 0.58*
CSF, mean NLR (n = 10)+	3.0 ± 4.6	3.6 ± 3.1	2.8 ± 5.1	*p = 0.81*	3.7 ± 5.5	1.3 ± 1.0	*p = 0.30*

mean ± standard deviation.
CBC = complete blood count, CSF = cerebrospinal fluid; EGA = estimated gestational age; IVH = intraventricular hemorrhage; NLR = neutrophil-to-lymphocyte ratio; VPS = ventriculoperitoneal shunt.
* Statistical significance at α = 0.05.
\+ T-test, two-tailed, unequal variance.
^ Fisher's exact test.

preterm infant population [4,30,34]. The presence of neonatal seizures in the preterm newborn directly correlates with adverse clinical outcomes. Seizures are also often predictive of poor neurologic outcomes and severe neurologic dysfunction later in life, including high rates of adult epilepsy and cognitive and motor deficits in those who survive [4,34–36]. Prompt diagnosis and successful early intervention in neonatal seizures is imperative to improving long-term neurological outcomes [36]. To date, there have been very few methods other than the current IVH grading system to assess outcomes and prognosis in the preterm IVH population. Therefore, a simple ratio calculated from peripheral blood samples has the potential to be an important prognostication tool for this population.

The NLR represents an informative index of systemic inflammation, and peripheral NLR is being increasingly studied as a potential predictor of morbidity and outcome in cardiovascular, oncologic, renal, cerebrovascular, and autoimmune inflammatory diseases [8–11,13–29]. The relationship between the peripheral neutrophil and lymphocyte count in the setting of systemic inflammation was initially described by Zahorec et al. [12] in patients after major abdominal surgery. The authors found that the peripheral NLR was a rapid, efficient, and reliable marker of stress severity [12]. They also found that the NLR strongly correlated with patients with sepsis or meningitis. In subsequent studies, the NLR was associated with poor postoperative outcomes and lower overall survival in patients after major surgery [14–18]. To date, multiple studies have supported the role of the NLR as a prognostic tool, demonstrating worse outcomes with higher NLR values [8–11,13–29]. Furthermore, the NLR has been found to be effective in the diagnosis of familial Mediterranean fever [19], ulcerative colitis [8], and Alzheimer disease [26]. Several studies in adult populations have demonstrated that the NLR is a positive predictor of in-hospital mortality and overall poor outcomes in patients after intracranial hemorrhage) [9,10,28,29]. Because of its proven value and low cost compared with more expensive markers of inflammation, such as IL-6, IL-8, IL-1β and TNF-α, the use of NLR as a prognostic marker is promising [7].

Currently, there is a paucity of data available on the utility of NLR for predicting outcomes after neurologic injury in the pediatric population, especially in preterm infants. In this study population, a greater NLR was observed in patients with an increased risk of seizures. To the best of our knowledge, in epilepsy, this correlation has only been reported previously in differentiating simple and complex febrile seizures. In a study by Goksugur et al., the NLR for simple febrile seizures was 2.18 versus 3.8 for complex febrile seizures (p = 0.024). This study also found a statistically significant difference in NLR for patients with seizures (NLR = 3.6) versus non-seizure patients (NLR = 1.6, $p < 0.0001$). Results of the study by Goksugar et al. supports results from our study. However, our study adds to the body of literature by focusing on a different population of infants with neonatal seizures, whereas the study by Goksugar et al. examined simple and complex febrile seizures.

The utility of NLR in predicting outcomes in so many disease processes lies in its relationship to the function of the immune system. Although this relationship has yet to be fully elucidated, there are a few salient points. The immune system has innate and adaptive arms (Petrone, 2017). The innate immune system is activated rapidly after an acute injury and causes neutrophils to migrate from peripheral lymphatic organs to the brain (Petrone 2017). Next, the adaptive immune system, which consists more of T lymphocytes that activate slowly, takes over. Increasingly, we are understanding that there are probably different populations of neutrophils and not all neutrophils are associated with a positive innate inflammatory response. There may be subsets of neutrophils that cause a detrimental inflammatory reaction after the initial injury (Hazeldine 2015). Therefore, the NLR may be capturing a mismatch between the innate and adaptive immune system that causes over activation of the innate response and poor activation of the adaptive response (Petrone 2017). This mismatch, in turn, is responsible for worsened outcomes (Petrone 2017). In the setting of neonatal IVH and inflammation, this detrimental immune response could play a role in predisposing a child to developing a seizure disorder [33].

Our findings suggest that NLR could possibly be utilized as a simple predictive marker for identifying preterm infants at risk of seizures, allowing for early diagnosis and intervention as well as improving the prognostic value of IVH grade alone.

This study was limited by its retrospective use of archival data. Therefore, as with any retrospective study, incomplete, absent, or erroneous record-keeping may have affected the reported results. In particular, this study excluded patients without CBC follow-up data which may have introduced bias into the study as patients who did not have CBC follow-up data may have had better clinical outcomes than the cohort studied, and therefore may have had no need for repeat blood work. Also, as an author, the data abstractor was not blinded to the study objective. This was a preliminary feasibility study and was limited to only 13 cases that met the inclusion criteria. Nevertheless, the results offer new insights that may aid in the management and prognostication of outcome in premature infants with IVH. A larger prospective study is warranted to assess the utility of peripheral NLR as a prognostic marker in the preterm infant population.

5. Conclusion

This is the first study to assess the utility of peripheral NLR as a predictive marker of outcomes in the population of preterm infants with IVH. Rates of seizures in this cohort correlated with higher NLR (> 3). This is an important finding because neonatal seizures increase morbidity in the preterm infant population, and early diagnosis and prompt intervention is imperative. The NLR is a simple and cost-effective measurement of inflammation, and further prospective validation of its role as a predictive marker is warranted.

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References

[1] P. Ballabh, Intraventricular hemorrhage in premature infants: mechanism of disease, Pediatr. Res. 67 (1) (2010) 1.
[2] P. Ballabh, A. Braun, M. Nedergaard, Anatomic analysis of blood vessels in germinal matrix, cerebral cortex, and white matter in developing infants, Pediatr. Res. 56 (2004) 117.
[3] L.-A. Papile, J. Burstein, R. Burstein, H. Koffler, Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm, J. Pediatr. 92 (4) (1978) 529–534.
[4] F. Pisani, C. Spagnoli, Acute Symptomatic Neonatal Seizures in Preterm Neonates (etiologies and Treatments), Sem Fetal Neonatal Med, Elsevier, 2017.
[5] P. Chittiboina, H. Pasieka, A. Sonig, P. Bollam, C. Notarianni, B.K. Willis, A. Nanda, Posthemorrhagic hydrocephalus and shunts: what are the predictors of multiple revision surgeries? Clinical article, J. Neurosurg. Pediatr. 11 (1) (2013) 37–42.
[6] S. Robinson, Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts: a review, J. Neurosurg. Pediatr. 9 (3) (2012), https://doi.org/10.3171/2011.12.PEDS11136.
[7] G. Habiyaremye, D.M. Morales, C.D. Morgan, J.P. McAllister, T.S. CreveCoeur, R.H. Han, M. Gabir, B. Baksh, D. Mercer, D.D. Limbrick, Chemokine and cytokine levels in the lumbar cerebrospinal fluid of preterm infants with post-hemorrhagic hydrocephalus, Fluids Barriers CNS 14 (1) (2017) 35.
[8] M. Celikbilek, S. Dogan, O. Ozbakır, G. Zararsız, H. Kücük, S. Gürsoy, A. Yurci, K. Güven, M. Yücesoy, Neutrophil–lymphocyte ratio as a predictor of disease severity in ulcerative colitis, J. Clin. Lab. Anal. 27 (1) (2013) 72–76.
[9] A. Giede-Jeppe, T. Bobinger, S.T. Gerner, J.A. Sembill, M.I. Sprügel, V.D. Beuscher, H. Lücking, P. Hoelter, J.B. Kuramatsu, H.B. Huttner, Neutrophil-to-lymphocyte ratio is an independent predictor for in-hospital mortality in spontaneous intracerebral hemorrhage, Cerebrovas Dis. 44 (1-2) (2017) 26–34.
[10] F. Wang, L. Wang, T.-t. Jiang, J.-j. Xia, F. Xu, L.-j. Shen, W.-h. Kang, Y. Ding, L.-x. Mei, X.-f. Ju, Neutrophil-to-lymphocyte ratio is an independent predictor of 30-Day mortality of intracerebral hemorrhage patients: a validation cohort study, Neurotox. Res. (2018) 1–6.
[11] Y. Yu, H. Wang, A. Yan, H. Wang, X. Li, J. Liu, W. Li, Pretreatment neutrophil to lymphocyte ratio in determining the prognosis of head and neck cancer: a meta-analysis, BMC Cancer 18 (1) (2018) 383.
[12] R. Zahorec, Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill, Bratisl. Lek. Listy 102 (1) (2001) 5–14.
[13] F. Imtiaz, K. Shafique, S.S. Mirza, Z. Ayoob, P. Vart, S. Rao, Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population, Int. Arch. Med. 5 (1) (2012) 2.
[14] R. Palin, A. Devine, G. Hicks, D. Burke, Association of pretreatment neutrophil–lymphocyte ratio and outcome in emergency colorectal cancer care, Ann. R. Coll. Surg. Engl. 100 (4) (2018) 308–315.
[15] S. Walsh, E. Cook, F. Goulder, T. Justin, N. Keeling, Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer, J. Surg. Oncol. 91 (3) (2005) 181–184.
[16] M. Stotz, A. Gerger, F. Eisner, J. Szkandera, H. Loibner, A. Ress, P. Kornprat, W. Zoughbi, F. Seggewies, C. Lackner, Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer, Br. J. Cancer 109 (2) (2013) 416.
[17] P. Vaughan-Shaw, J. Rees, A. King, Neutrophil lymphocyte ratio in outcome prediction after emergency abdominal surgery in the elderly, Int. J. Surg. 10 (3) (2012) 157–162.
[18] E. Dilektasli, K. Inaba, T. Haltmeier, M.D. Wong, D. Clark, E.R. Benjamin, L. Lam, D. Demetriades, The prognostic value of neutrophil-to-lymphocyte ratio on mortality in critically ill trauma patients, J. Trauma Acute Care Surg. 81 (5) (2016) 882–888.
[19] A.U. Uslu, K. Deveci, S. Korkmaz, B. Aydin, S. Senel, E. Sancakdar, M. Sencan, Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res. Int. 2013 (2013).
[20] M. Biyik, R. Ucar, Y. Solak, G. Gungor, I. Polat, A. Gaipov, O.O. Cakir, H. Ataseven, A. Demir, S. Turk, Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis, Eur. J. Gastroenterol. Hepatol. 25 (4) (2013) 435–441.
[21] H. Kayadibi, E. Sertoglu, M. Uyanik, S. Tapan, Neutrophil-lymphocyte ratio is useful for the prognosis of patients with hepatocellular carcinoma, World J. Gastroenterol. 20 (28) (2014) 9631.
[22] J.Gd.M. Monteiro Júnior, Dd.O.C. Torres, M.C.F.C. da Silva, C.Md.H. Martins, I.K. da Silva, M.E.M. do Nascimento, A.C.O. dos Santos, U.R. Montarroyos, D.C.S. Filho, Prognostic value of hematological parameters in patients with acute myocardial infarction: intrahospital outcomes, PLoS One 13 (4) (2018) e0194897.
[23] Y. Yigit, S. Yilmaz, A. Akdogan, H. Halhalli, A. Ozbek, E. Gencer, The role of neutrophil–lymphocyte ratio and red blood cell distribution width in the classification of febrile seizures, Eur. Rev. Med. Pharmacol. Sci. 21 (2017) 554–559.
[24] X. Lu, S. Wang, G. Zhang, R. Xiong, H. Li, High neutrophil-to-Lymphocyte ratio is a significant predictor of cardiovascular and all-cause mortality in patients undergoing peritoneal Dialysis, Kidney Blood Press. Res. 43 (2) (2018) 490–499.
[25] S. Tonyali, C. Ceylan, S. Yahsi, M.S. Karakan, Does neutrophil to lymphocyte ratio demonstrate deterioration in renal function? Ren. Fail. 40 (1) (2018) 209–212.
[26] M.E. Kuyumcu, Y. Yesil, Z.A. Oztürk, C. Kizilarslanoğlu, S. Etgül, M. Halil, Z. Ulger, M. Cankurtaran, S. Arıoğul, The evaluation of neutrophil-lymphocyte ratio in Alzheimer's disease, Dement. Geriatr. Cogn. Disord. 34 (2) (2012) 69–74.
[27] E. Sahan, S. Polat, Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion, Turk Kardiyol. Dern. Ars. 42 (4) (2014) 415.
[28] C. Tao, X. Hu, J. Wang, J. Ma, H. Li, C. You, Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage, Biomark. Med. 11 (1) (2017) 33–42.
[29] S. Lattanzi, C. Cagnetti, C. Rinaldi, S. Angelocola, L. Provinciali, M. Silvestrini, Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage, J. Neurol. Sci. 387 (2018) 98–102.
[30] R.D. Sheth, G.R. Hobbs, M. Mullett, Neonatal seizures, J. Perinatol. 19 (1) (1999) 40.
[31] S. Goksugur, N. Kabakus, M. Bekdas, F. Demircioglu, Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types, Eur. Rev. Med. Pharmacol. Sci. 18 (2014) 3380–3385.
[32] E. Mracsko, R. Veltkamp, Neuroinflammation after intracerebral hemorrhage, Front. Cell. Neurosci. 8 (2014) 388.
[33] F. Pisani, C. Facini, A. Pelosi, S. Mazzotta, C. Spagnoli, E. Pavlidis, Neonatal seizures in preterm newborns: a predictive model for outcome, Eur. J. Paediatr. Neurol. 20 (2) (2016) 243–251.
[34] M.S. Scher, Neonatal seizure classification: a fetal perspective concerning childhood epilepsy, Epilepsy Res. 70 (2006) 41–57.
[35] K.T. Kahle, K.J. Staley, The Bumetanide-sensitive Na-K-2Cl Cotransporter NKCC1 As a Potential Target of a Novel Mechanism-based Treatment Strategy for Neonatal Seizures, (2008).
[36] A.B. Petrone, V. Gionis, R. Giersch, T.L.J.N. Barr, Immune biomarkers for the diagnosis of mild traumatic brain injury, Neuro Rehabil. 40 (4) (2017) 501–508.