MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 10(7) pp. 193-197, July, 2022
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

Predictive Value of Delta Neutrophil Index, Interleukin 8 and C-Reactive Protein for Septic Patients

Pavlina Peneva[1*], Silviya P. Nikolova[2], Yana Bocheva[3]

[1]St. Marina University Hospital – Varna, Medical University – Varna (Bulgaria)

[2]Department of Social Medicine and Healthcare Organization, Medical University – Varna (Bulgaria)

[3]Department of Clinical Laboratory and Immunology, St. Marina University Hospital – Varna, Medical University – Varna (Bulgaria)

***Corresponding Author's E-mail: p.peneva@abv.bg; Pavlina.Peneva@mu-varna.bg**

Abstract

In recent years, there have been an increasing number of studies on the Delta Neutrophil Index — DNI, C Reactive Protein – CRP and Interleukin 8 – IL8 as early markers for developing sepsis and risk of death. The study aimed to examine DNI, CRP and IL-8 in septic and non-septic patients and determine their predictive value as markers for sepsis. A prospective non-interventional single-centre clinical follow-up was performed. The study was conducted from January 2017 to July 2018 in a Bulgarian ICU in the city of Varna. DNI is a significantly critical marker for developing sepsis (Exp (B)=1.329, p= 0.007). DNI has an association with developing sepsis (r=0.363, p=0.001). ROC analysis showed a DNI value of 1.4(the bestcut-off value 1.4), with 73% sensitivity and 87% specificity (AUC 0.764, 95% CI 0.650-0.878, p=0.0001). CRP is a significant marker for severity of infection and shows the likelihood of sepsis events (Exp(B)=1.016, p=0.0001). The ROC curve results demonstrate that CRP, with 82% sensitivity and 76% specificity, predict sepsis development (AUC 0.885, 95% CI 0.813-0.956, p -0.0001). There is a correlation, indicating an IL-8 increase as a marker for sepsis (r = 0.461. P = 0.0001). IL8 was significantly higher in sepsis groups than in the control group (t=3,537, p<0.001). Our results show that DNI, CRP and IL-8 are reliable indicators of high predictability for the development of sepsis, and their careful monitoring will help in the early detection of these patients and their timely treatment.

Keywords: CRP, DNI, IL8, Infection, Sepsis, Septic shock

INTRODUCTION

Sepsis is a severe syndrome in emergency medicine caused by a serious infection in the body. The current definition of sepsis characterises it as a life-threatening organ dysfunction due to a dysregulation in the body's response to infection, according to the latest Sepsis-3 Task Force guidelines (Singer et al., 2016; Levy et al., 2018). The global burden of sepsis is difficult to ascertain, although a recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths (Rudd et al., 2020).

Early diagnosis is a challenging and crucial factor (Park et al., 2020; Seok et al., 2012; Park, 2021). Treatment of sepsis and septic shock is even more difficult. Difficulties are caused by the sometimes unclear clinical picture, long course of infection, polymorbidity of patients, and different organism responses (Miedema et al., 2011; Meyer, 2015; Eichberger and Resch, 2022).

Acute viral and bacterial lung infections are among the most severe body infections with a risk of complications. Pneumonia is a serious disease and the most common cause of sepsis, septic shock and varying lengths of stay

in the intensive care unit. About 1/3 (35%) of patients with community-acquired pneumonia (CAP) at the time of hospitalisation present themselves with a sepsis clinic. Approximately 35–50% of the septic shock cases are of pulmonary origin (Kim et al., 2015) (Meyer, 2015).

In recent years, there have been an increasing number of studies on the Delta Neutrophil Index — DNI, CRP and IL-8 as markers for developing sepsis, septic shock and risk of death (Moniruzzaman et al., 2020; Park et al., 2017; Zhou et al., 2015; Yousef et al., 2014).

AIMS AND OBJECTIVES

Our study aimed to examine DNI, CRP and IL-8 in patients with non-sepsis patients with infections and sepsis and septic shock patients and determine their predictive value as markers for detecting and distinguishing septic from non-septic patients.

METHODS

A prospective non-interventional single-centre clinical follow-up was performed. All participants were included in the study after written informed consent. The study was conducted from January 2017 to July 2018 in a Bulgarian ICU in the city of Varna and approved by the Ethics Committee for Clinical Trials at the Medical University – Varna, Bulgaria.

The study included 82 patients (50 males, 32 females) with a mean age of 63.7 ± 13.6 years. Of these, 37 participants with a mean age of 66.2 ± 10.5 (22 males and 12 females) had infections without sepsis criteria — group I, serving as a control group. The remaining group of patients with sepsis criteria, a total of 45, were divided into two groups: group II — patients with sepsis without septic shock, a total of 26 with a mean age of 61.3 ± 15.0 (16 males and 10 females), and group III — septic shock patients, a total of 19 with a mean age of 62.2 ± 17.3 (12 males and 7 females). An analysis of the localisation of the leading infection in the three groups revealed pneumonia: for the group without sepsis (25 patients – 68%), for the septic group (32 patients – 71%).

All septic patients met the Sepsis-3 Task Force criteria (2016).

The study included patients with laboratory constellation for systemic inflammation (SIRS), aged over 18 years, regardless of concomitant comorbidity.

Exclusion criteria were pregnancy, age < 18 years and > 80 years and the presence of malignancies, including haematological diseases.

Peripheral blood counts were examined in all patients at inclusion, taking into account the main haematological and morphological parameters: haemoglobin, erythrocytes, DCC data for leukocytes, platelets. Blood samples were taken by vein puncture in a 2 mL vacutainer and analysed within the first hour on an ADVIA 2120i (Siemens) haematology analyser, after which DNI (Delta Neutrophil Index) was calculated by the formula:

DNI = (New% + Eo%) – PMN%

In healthy individuals, the DNI value is close to 0. because there are normally no immature granulocytes in the blood; hence, the difference between the two fractions is about 0. The DNI calculation was performed in all patients on the first and the fifth day.

DNI represents an automatic analysis of the fraction of immature granulocytes obtained as a difference in the fraction of myeloperoxidase cells, Eo and Neu, calculated by myeloperoxidase (MPO) cytochemical reaction in the MPO channel and the fraction of mature polymorphonuclear leukocytes measured in the nuclear lobularity channel by the reflected light beam. The calculation of immature granulocytes includes promyelocytes, myelocytes and metamyelocytes without blasts.

The device differentiates various subpopulations of blood cells through a flow cytometry process with two independent methods (two channels with different readings) for white blood cell (WBC) analysis – myeloperoxidase channel and lobular/nuclear density channel (Harris et al., 2005; Nahm et al., 2008; Seok et al., 2012).

C-reactive protein (CRP) was tested from venous blood on ADVIA 1800 and OLYMPUS AU 400 analysers. Interleukin 8 was tested by a complex ELISA data installation with BioTech (UK) devices with ready-to-use kits for Human IL-8 ELISA, Diaclone, France. Reference values for IL-8 ranged from 1 to 29 pg/mL as specified by the manufacturer.

The statistical analysis was performed using the Statistical Package for personal computer SPSS for Windows, version 23. We used Kolmogorov-Smirnov normality test to examine the distribution of the variables included in the analysis. An Independent T-test was applied to compare the average values of the markers included in the study for the investigated septic and control groups. Correlation analysis was used to study the relationships between clinical indicators and determine the strength of their influence. The estimation of the strength of the dependence between the variables is based on the Pearson coefficient (r) results. Regression analysis (R) was used to study the functional relationships between quantified factors. Logistic regression was applied in the cases of variable qualitative results. We used ROC curve analysis to determine the accuracy and specificity of the predictability for sepsis development.

RESULTS AND DISCUSSION

The values indicate that DNI is a significantly critical

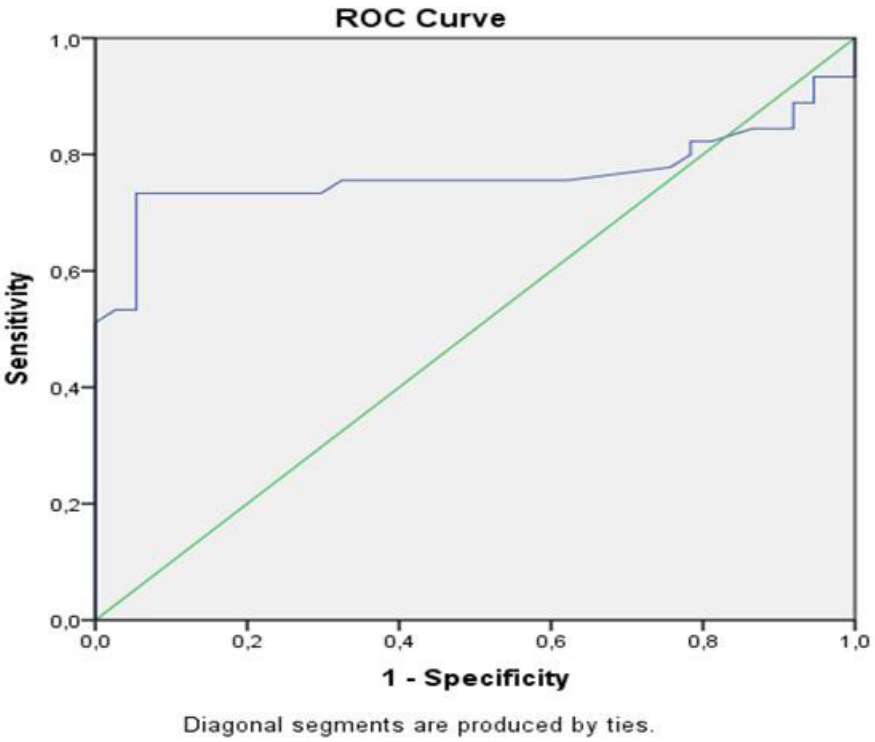

Figure 1. ROC curve for predictability of sepsis according to DNI values (AUC 0.764; 95% CI 0.650-0.878. p=0.0001)

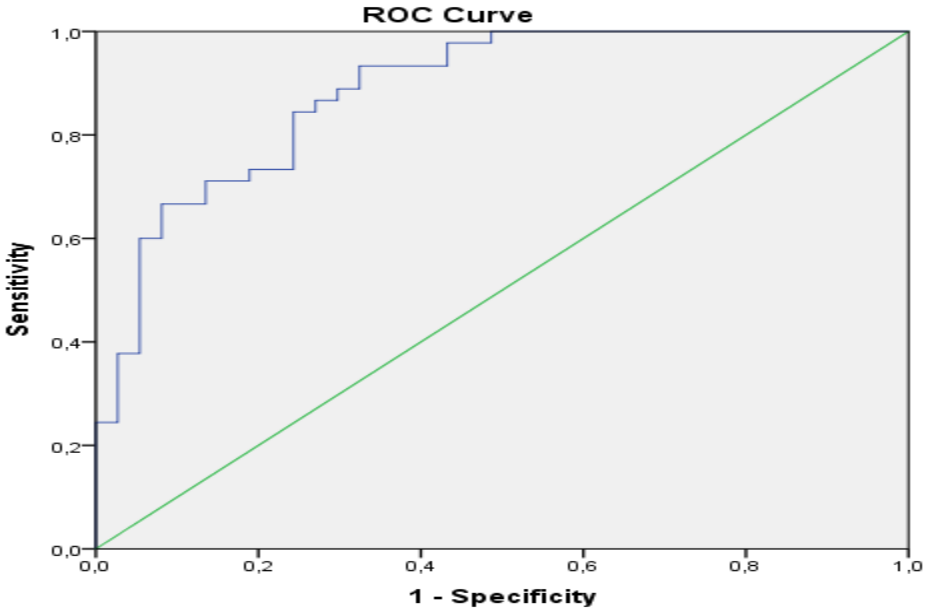

Figure 2. ROC curve for predictability of sepsis according to CRP values (AUC 0.885, 95% CI 0.813-0.956, p=0.0001)

marker for determining the severity of infection. Thus, in the group of infections without sepsis, its predictability was 7.5% (Exp (B) = 0.752, p = 0.007). The DNI predictability was significantly higher in the group of sepsis without septic shock — 32% (Exp (B) = 1.329, p = 0.007). DNI indication for the development of septic shock shows the highest predictability of 43% (Exp (B) = 1.430, p = 0.001). DNI has a statistically significant association with the type of developed infection afterwards and the severity of the condition (r = 0.363, p = 0.001).

We investigated the ROC curve for DNI values above

which sepsis development can be assumed with high probability. ROC analysis showed a DNI value of 1.4 (the best cut-off value 1.4), with 73% sensitivity and 87% specificity (AUC 0.764, 95% CI 0.650 - 0.878, p = 0.0001) (Figure 1).

CRP is a significant marker for determining the severity of infection and shows the likelihood of sepsis events (Exp (B) = 1.016, p = 0.0001) and septic shock (Exp (B) = 1.017, p = 0.0001). Similarly, CRP shows the probability of infection (Exp (B) = 0.984, p = 0.001). The ROC curve results demonstrate that CRP values above 135 mg/L, with 82% sensitivity and 76% specificity, predict sepsis development (AUC 0.885, 95% CI 0.813 - 0.956, p -0.0001) (Figure 2).

The correlation analysis of the three groups— with sepsis-free infectious patients, patients with sepsis without septic shock and septic shock patients, found a moderately strong and positive correlation, indicating an IL-8 increase as a marker for sepsis development (r = 0.461. P = 0.0001). Using the Independent t-test to compare the mean values of two independent samples (t = 3.537. P <0.001), we found IL-8 mean values in all septic patients were significantly higher.

For the sepsis-free infectious patients' group, the mean value for IL-8 was 49.20 ± 11.6 pg/mL, and for septic patients — 350.6 ± 65.8 pg/mL. Logistic regression analysis was performed at a later stage to determine the predictive power of interleukin 8 for sepsis development. The results showed that as the IL-8 values increased by one unit, the probability of developing sepsis increased 8-fold (Exp (B) = 8.089, p = 0.0001).

The correlation analysis performed by the Pearson method showed a strong positive correlation between IL-8 and DNI (r = 0.575, p = 0.0001), which indicates that the increase in both indicators is parallel to the development of sepsis. Similarly, CRP and IL 8 increased in parallel during sepsis (r = 0.453, p = 0.0001).

CONCLUSIONS

Our results show that DNI, CRP and IL-8 are reliable indicators of high predictability for the development of sepsis and septic shock, and their careful monitoring and analysis will help in the early detection of these patients and their timely treatment. A significant advantage is the speed and low cost of the required tests.

LIMITATIONS

Several limitations of the present study deserve consideration. First, the study had a relatively small sample size and was conducted at the Intensive Care Unit of one hospital. Second, patients were not selected randomly but purposefully and were further examined for changes in blood parameters during sepsis. Third, the frequency and duration of the DNI and IL8 follow-up were another limitation due to the differences in their values at the beginning of the infection. Baseline values would more clearly shape the growth curve and would probably be useful at a very early stage of the infection – within hours or a day – sometimes enough time to unfold the picture of sepsis. Finally, not all patients with sepsis were included in the sample. Patients with some specific diseases were excluded from the study (i.e. patients with oncological diseases) because their DNI and IL8 values were higher and were likely to mislead the average trend of the collected data.

Conflict of Interest: The authors report no conflict of interest.

Financial Disclosure: None reported

REFERENCES

Eichberger J, Bernhard R (2022). "Reliability of Interleukin-6 Alone and in Combination for Diagnosis of Early Onset Neonatal Sepsis: Systematic Review." Frontiers in Pediatrics 10 (March): 840778. https://doi.org/10.3389/fped.2022.840778.

Harris N, Jolanta K, Alexander K (2005). "The ADVIA 2120 Hematology System: Flow Cytometry-Based Analysis of Blood and Body Fluids in the Routine Hematology Laboratory." Laboratory Hematology 11 (1): 47–61. https://doi.org/10.1532/LH96.04075.

Kim H, Yonggoo K, Kwan HK, Chang DY, Jin WK, Hae KL (2015). "Use of Delta Neutrophil Index for Differentiating Low-Grade Community-Acquired Pneumonia From Upper Respiratory Infection." Annals of Laboratory Medicine 35 (6): 647–50. https://doi.org/10.3343/alm.2015.35.6.647.

Levy Mitchell M., Laura EE, Andrew R (2018). "The Surviving Sepsis Campaign Bundle: 2018 Update." Critical Care Medicine 46 (6): 997–1000. https://doi.org/10.1097/CCM.0000000000003119.

Meyer NJ (2015). "Finding a Needle in the Haystack: Leveraging Bioinformatics to Identify a Functional Genetic Risk Factor for Sepsis Death*." Critical Care Medicine 43 (1): 242–43. https://doi.org/10.1097/CCM.0000000000000664.

Miedema KGE, Eveline SJM, de Bont, Rob FM, Oude E, Michel J. van Vliet, Claudi S. M. Oude Nijhuis, Willem A. Kamps, and Wim J. E. Tissing (2011). "The Diagnostic Value of CRP, IL-8, PCT, and STREM-1 in the Detection of Bacterial Infections in Pediatric Oncology Patients with Febrile Neutropenia." Supportive Care in Cancer 19 (10): 1593–1600. https://doi.org/10.1007/s00520-010-0987-6.

Moniruzzaman, Mohammad, Ashesh Kumar Chowdhury, ASM Areef Ahsan, Md Zakiur Rahman, Saimun Nahar Rumana, Md Abdullah Yusuf, and Gobindo Chandra Saha. 2020. "Role of Interleukin-6 and Interleukin-8 Cytokines as Early Diagnostic Markers of Sepsis." Bangladesh J. Infectious Dis. 6 (2): 34–38. https://doi.org/10.3329/bjid.v6i2.46102.

Nahm CH, Jong WC, Jongwook L (2008). "Delta Neutrophil Index in Automated Immature Granulocyte Counts for Assessing Disease Severity of Patients with Sepsis." Annals of Clinical and Laboratory Science 38 (3): 241–46.

Park JH, Hyeong Ju B, Keum HL, Jong WL, Andreas K, Michael E, Jae Il S (2017). "Delta Neutrophil Index (DNI) as a Novel Diagnostic and Prognostic Marker of Infection: A Systematic Review and Meta-Analysis." Inflammation Research 66 (10): 863–70. https://doi.org/10.1007/s00011-017-1066-y.

Park SY, Jin SL, Jihyu O, Ji-Young P (2020). "Delta Neutrophil Index as a Predictive and Prognostic Factor for Candidemia Patients: A Matched Case-Control Study." BMC Infectious Diseases 20 (1): 396. https://doi.org/10.1186/s12879-020-05117-0.

Park, Chang-Eun (2021). "Diagnosis and Prognosis of Sepsis." Korean Journal of Clinical Laboratory Science 53 (4): 309–16. https://doi.org/10.15324/kjcls.2021.53.4.309.

Rudd KE, Sarah CJ, Kareha MA, Katya AS, Derrick T, Daniel RK, Danny VC, et al. (2020). "Global, Regional, and National Sepsis Incidence and Mortality, 1990–2017: Analysis for the Global Burden of Disease Study." The Lancet 395 (10219): 200–211. https://doi.org/10.1016/S0140-6736(19)32989-7.

Seok Y, Jong RC, Juwon K, Young KK, Jongwook L, Jaewoo S, Sue JK, Kyung-A L (2012). "Delta Neutrophil Index: A Promising Diagnostic and Prognostic Marker for Sepsis." Shock 37 (3): 242–46. https://doi.org/10.1097/SHK.0b013e3182454acf.

Singer M, Clifford SD, Christopher WS, Manu SH, Djillali A, Michael B, Rinaldo B, et al. (2016). "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)." JAMA 315 (8): 801. https://doi.org/10.1001/jama.2016.0287.

Yousef A, Abd Al-Maksoud, Ghada AS, Maaly MM (2014). "The Value of Admission Serum IL-8 Monitoring and the Correlation with IL-8 (-251A/T) Polymorphism in Critically Ill Patients." ISRN Inflammation 2014 (March): 1–7. https://doi.org/10.1155/2014/494985.

Zhou M, Shupeng C, Jialin Yu, and Qi Lu. 2015. "Interleukin-8 for Diagnosis of Neonatal Sepsis: A Meta-Analysis." Edited by Qiang Ding. PLOS ONE 10 (5): e0127170. https://doi.org/10.1371/journal. zpone.0127170.