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C-reactive protein is a more valuable marker in predicting the severity of complications in measles-affected children compared to blood cell count-derived inflammatory indices

C-reaktivni protein je pouzdaniji pokazatelj od inflamacijskih indeksa izvedenih iz krvne slike u predviđanju teških komplikacija kod dece obolele od malih boginja

Marija Stojiljković*†, Mirjana Miljković*

***General Hospital of Leskovac, Pediatric Department, Leskovac, Serbia; †University of Niš, Faculty of Medicine, Niš, Serbia**

Abstract

Background/Aim. Measles is a contagious disease with a good prognosis; however, severe complications may sometimes develop. C-reactive protein (CRP) and blood cells count-derived inflammatory indices – granulocyte-lymphocyte ratio (GLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), mean platelet volume (MPV)/platelet count ratio (MPR), red blood cell distribution width (RDW), and MPV are the indicators related to the clinical outcome in various inflammatory diseases. The aim of the study was to analyze the values of CRP, blood cell count, GLR, PLR, MLR, MPR, RDW, and MPV in measles-affected children compared to healthy controls and between measles-affected children with complicated and severely complicated measles form. A particular aim of the paper was to assess the suitability of inflammatory-derived markers for predicting the severity of the disease. **Methods.** The study included 55 measles-affected children who developed complications (examination group), while the control group included 30 healthy children. The first peripheral blood count, obtained on the first hospitalization day (before treatment), was used for further analyses. **Results.** The white blood cells, lymphocytes, monocytes, and platelets count were significantly lower, while GLR, PLR, MPR, and CRP were significantly higher in measles-affected children ($p < 0.05$). In severely complicated measles form, significantly higher values of granulocytes, CRP, GLR, and PLR were documented, including lower lymphocytes ($p < 0.05$). A linear regression analysis showed that CRP was the only indicator with predictive significance for the severity of the course of measles. **Conclusion.** The blood cell count-derived inflammatory indices should not be crucial in assessing the severity of measles in children. CRP was the most valuable predictive factor for the development of the severe course of measles in measles-affected children.

Key words:
blood cells; blood platelets; child; c-reactive protein; leukocytes; measles; prognosis; severity of illness index.

Apstrakt

Uvod/Cilj. Male boginje (MB) su infektivno oboljenje koje u pojedinim slučajevima može dovesti do razvoja ozbiljnih komplkacija opasnih po život. Kao pouzdani pokazatelji kliničkog ishoda u mnogim inflamacijskim bolestima pokazali su se C-reaktivni protein (CRP) i indeksi inflamacije izvedeni iz krvne slike: odnos granulocita i limfocita (GLO), odnos trombocita i limfocita (TLO), odnos monocita i limfocita (MLO), odnos srednje zapremine trombocita (SZT) i broja trombocita (STO), varijacije u veličini u volumenu eritrocita (VVE) i SZT. Cilj rada bio je da se analiziraju vrednosti CRP-a, broja krvnih ćelija, GLO, TLO, MLO, STO, VVE, i SZT kod dece sa MB i uporede sa vrednostima kod zdrave dece, kao i da se ove vrednosti analiziraju i uporede između dece sa lakšim i teškim komplikacijama MB. Poseban cilj rada bio je da se proceni adekvatnost navedenih markera inflamacije za predviđanje težine MB. **Metode.** Ispitivanu grupu činilo je 55 dece obolele od MB, sa komplikacijama, a kontrolnu grupu činilo je 30 zdrave dece. U daljem istraživanju korišćen je prvi uzorak krvi, uzet prvog dana hospitalizacije (pre lečenja). **Rezultati.** Broj belih krvnih zrnaca, limfocita, monocita i trombocita bio je značajno niži, dok su vrednosti GLO, TLO, STO i CRP-a bile značajno više kod dece obolele od MB ($p < 0,05$). Kod dece sa težim komplikacijama MB zabeležene su značajno više vrednosti granulocita, CRP-a, GLO, TLO i niže vrednosti limfocita ($p < 0,05$). Metodom linearne regresije pokazano je da je

Correspondence to: Marija Stojiljković, Palikuća bb, 16 000 Leskovac, Serbia. E-mail: marijastojiljkovic986@gmail.com

vrednost CRP-a bila jedini pouzdan pokazatelj u prognozi nastanka teške forme MB. **Zaključak.** Broj krvnih ćelija i indeksi inflamacije izvedeni iz krvne slike ne bi trebalo da budu presudni u proceni ozbiljnosti kliničkog toka MB kod dece. CRP je pozdaniji pokazatelj u predviđanju razvoja težeg oblika bolesti kod dece obolele od MB.

Ključne reči:
krv, ćelije; trombociti; deca; c-reaktivni protein; leukociti; morbili; prognoza; bolest, indeks težine.

Introduction

Measles is an infectious disease caused by the highly contagious measles virus (MV). It is a preventable disease, and accelerated immunization against MV had a significant impact on reducing death caused by measles worldwide. However, measles still poses a public health problem. In 2018, more than 140,000 people died from measles, mostly children under 5 years of age [1]. From 2016 to March 2019, the European Region reported 114,682 measles cases [2].

As an infectious disease, measles generally has a good prognosis; however, severe complications may sometimes develop. The most common measles complications include pneumonia, croup, gastroenteritis, otitis media, conjunctivitis, and stomatitis. Rarely, uncommon complications such as encephalitis, myocarditis, pneumothorax, appendicitis, and subacute sclerosing panencephalitis may occur and can be very serious, life-treating, and require special treatment and care [3, 4].

Measles is a systemic inflammatory disease with general immune suppression which extends to more than two years after acute infection [5, 6]. The severe inflammatory process contributes to weak adaptive response (suppression of lymphocyte proliferation, altered cytokine profiles, immune modulation, and inhibition of hematopoiesis) and immune response imbalance [7–9].

Numerous inflammatory processes in the skin, respiratory mucosa, lung, conjunctivae, and liver are accompanied by the release of many pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, which can induce profound changes in C-reactive protein (CRP) synthesis and cytopoiesis of the hematic cells [5, 6, 10].

The level of CRP is a widely used marker of inflammation in clinical practice. Increased levels of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α), secreted mainly by macrophages and neutrophils, perform transcriptional induction of the CRP gene. CRP is mainly synthesized in hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. CRP plays an important role in inflammatory processes during infection, including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly IL-6 and TNF-α [11].

These inflammation-induced changes are manifested in hematopoiesis and granulocyte, lymphocyte, and platelet (PLT) counts in the peripheral blood [7, 8]. The granulocyte count can reflect the inflammatory state in the body. The more severe inflammation, the higher the granulocyte count will be. At the same time, a more intensive inflammatory reaction will cause a lower lymphocyte count. The severity of inflammation reflects changes in the granulocyte-lymphocyte ratio (GLR). PLT to lymphocyte ratio (PLR) reflects changes in PLT and lymphocyte counts. It can demonstrate the severity of infectious diseases and the degree of thrombosis in in the body [12]. In clinical work, three laboratory parameters indicate PLT activation: the count of PLTs; mean PLT volume (MPV), the average size of PLTs, which reflects their production in the bone marrow; PLT cell distribution width (PDW), the index of inhomogeneity of the size of the PLTs. In healthy populations, MPV and PLT counts are in an inverse relationship. Therefore, reactive thrombocytosis is followed by lower values of MPV and PDW. Higher MPV is considered an indicator of PLT activation and aggregation. However, in an inflammation process, PLTs are quickly spared at the site of infection, and bone marrow accelerates the release of immature, larger PLTs [13, 14]. Inflammation and oxidative stress suppress erythrocyte maturation in the bone marrow and reduce the red blood cell (RBC) life span. As a consequence, large, premature RBCs (reticulocytes) are released into the circulation, and RBC distribution width (RDW) in the peripheral blood is elevated [15].

Recent studies have indicated that several inflammatory indices derived from blood cell count may be used in estimating the severity of inflammation as predictive markers in the diagnosis and prognosis of patients with inflammation (cardiovascular diseases, diabetes, malignancy) [16–18]. The novel inflammatory biomarkers include the following ratios: GLR, PLR, RDW, MPV, monocytes to lymphocytes (MLR), and MPV/PLTs count (MPR). These indices are inexpensive and easily calculated indicators of the systematic inflammatory response. Many studies have confirmed their usefulness in predicting sepsis in children [19], early onset neonatal sepsis [20], infective endocarditis [21], death risk in children with severe hand, foot, and mouth disease [22], and mortality in pediatric intensive care [23]. Furthermore, in other infectious diseases, these indices have the diagnostic and prognostic value in children with infectious diseases such as rotavirus-positive gastroenteritis [24], febrile seizures [25], Kawasaki disease [26], hepatitis A [27], otitis media [28], febrile urinary tract infection [29], and acute pyelonephritis [30].

While reviewing the literature, we found that Solmaz et al. [31] documented the utility of MPV only for determining inflammation in measles-affected children. Güzelçiçek and Demir [32] documented that only PLR was associated with the measles outcome in children.

The diagnostic and prognostic utility of CRP and GLR, PLR, MPV, MLR, MPR, and RDW has not been evaluated yet in measles-affected children with various severe forms of measles. The aim of the study was to analyze the values of CRP and GLR, PLR, MLR, MPR, RDW, and MPV in mea-

sles-affected children compared to healthy children and between two groups of measles-affected children, severely complicated and non-severely complicated. A particular aim of the paper was to assess the suitability of CRP and these blood cell count-derived inflammatory markers for predicting the severity of the disease.

Methods

During the outbreak of measles in Jablanica District, from October 2017 to July 2018, 110 children were affected. In the Pediatrics Department of the General Hospital Leskovac, 89 (80.9%) measles-affected children were clinically examined, and 55 (50%) were hospitalized and clinically treated. The criteria for hospitalization were the presence of measles complications and the parents' consent for hospital treatment. This retrospective, medical record-based study was conducted at the Pediatrics Department, General Hospital Leskovac, Serbia, and included 55 measles-affected, hospitalized children who developed complications and 30 healthy control children. The inclusion criteria for the study group were measles-affected children who developed complications. Exclusion criteria were measles-affected children without complications and children with chronic conditions (rheumatic, autoimmune, gastroenterological, hematological, malignant, nephrological, endocrinological, and neurological diseases). The control group included only healthy children. There were children for specialist outpatient pediatric examination in whom blood analyses were needed. These were the children who were referred to specialists due to suspicion of a disease that was excluded by diagnostic and clinical trials (anemia, short stature, impaired glucose, lipid metabolism, and hypothyroidism). Exclusion criteria for the control group were the presence of any infectious or chronic disease. Written informed consent was obtained from the parents of each child. The study was approved by the Ethics Committee of the General Hospital Leskovac (No 352/2 from January 20, 2021).

On admission to Pediatrics Department, clinical examination and venous puncture for laboratory analysis were performed. The diagnosis of measles was based on the World Health Organization criteria [3]. In cases of confirmed contact with the measles-affected and typical clinical manifestation (generalized erythematous/maculopapular rash, fever above 38 °C, cough, coryza, and conjunctivitis), measles was diagnosed. The diagnosis was made by a pediatrician and infectious disease specialist. Moreover, serological confirmation was performed in all cases at the Institute for Virology, Vaccines, and Serums "Torlak" in Belgrade. The detection of specific IgM antibodies in serum confirmed the diagnosis of measles.

Complications (diarrhea, dehydration, laryngitis, bronchitis, purulent conjunctivitis, and stomatitis) were determined by anamnestic data and physical examination. Otitis media was confirmed by an otoscopic examination. Pneumonia was confirmed by a chest radiograph with the presence of pulmonary infiltrates. The central nervous system was considered to be affected if lethargy, irritability, febrile seizures, disorientation, or other neurological deficits were present.

After diagnosing measles complications, the severity of complications and clinical conditions was assessed for every child. The clinical severity of measles was classified into two categories: complicated and severely complicated. The severely complicated group included children with convulsions, children who were lethargic or unconscious, chest indrawing with a respiratory rate of 60 breaths per min or more (oxygen saturation below 92% on room air), stridor in a calm child, severe dehydration, and severe malnutrition. The measles group with complications included children with rapid breathing (40 or more breaths per min for children older than 1 year or 50 or more breaths per minute for children under 1 year), moderate dehydration, laryngeal stridor only when a child was crying, mouth ulcers affecting the intake of food or fluids, pus draining from eyes, and acute otitis media.

Peripheral venous blood samples were collected in ethylenediaminetetraacetic acid tubes on the first hospitalization day. These results were chosen for further investigations. The complete blood count was analyzed on the Pentra ES 60 Horiba device. CRP was determined on Erba Mannheim XL 600 device.

The following laboratory data were noted: white blood cells (WBC), granulocyte, lymphocyte, and monocyte count and percentages, RBCs count, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), RDW, and PLT count. GLR was calculated by dividing the absolute granulocyte count by the absolute lymphocyte count. PLR was calculated by dividing the absolute PLT count by the absolute lymphocyte count. MLR was calculated by dividing the absolute monocyte count by the absolute lymphocyte count. MPR was calculated by dividing the machine-calculated MPV by the PLT count.

Statistical analysis

The data were analyzed using descriptive statistical methods: frequency, percentage, mean ± standard deviation, and 95% confidence interval (CI) for Exp(B), depending on the type and variable distribution. Kolmogorov-Smirnov's test confirmed the deviation from the normality of data distribution. Relation between variables was measured using non-parametric Mann-Whitney *U* test and *t*-tests. The logistic regression (Enter model) was performed to determine the predictive importance of significant variables for the severely complicated measles form. Variables with statistical significance between non-severely complicated and severely complicated measles forms were included in a linear regression entry method. All analyses were conducted with SPSS version 17.0 (SPSS INC, NC). Statistical significance was set at $p < 0.05$.

Results

A total of 55 hospitalized measles-affected children were included in the study. The mean age of the measles group (n = 55) was 22.85 ± 23.94 months. The mean age of the non-severely complicated group and the severely com-

plicated group was 23.84 ± 26.02 and 20.65 ± 19.03 months, respectively. As shown in Table 1, there were no significant differences between the groups regarding age and sex ($p > 0.05$).

Measles-affected children had significantly higher values of WBC, percentage of granulocytes, PLT, MCV, GLR, PLR, MPR, and CRP compared to the control group ($p = 0.010$, $p = 0.001$, $p = 0.0001$, $p = 0.004$, $p = 0.0001$, $p = 0.022$, $p = 0.002$, $p = 0.0001$). Absolute counts and percentages of lymphocytes and monocytes were significantly lower in measles-affected children compared to the control group ($p < 0.005$) (Table 2).

The percentage of granulocytes was significantly higher ($p = 0.014$), while the number and percentage of lymphocytes were significantly lower ($p < 0.01$) in the severely complicated measles group. The values of inflammatory indices, GLR, PLR, and CRP were significantly higher in the severely complicated group compared to the non-severely complicated group ($p = 0.018$, $p = 0.012$, $p = 0.002$, respectively) (Table 3).

Additionally, variables with statistical significance between the non-severely complicated and severely complicated measles forms were included in the linear regression entry method. As a result, the value of CRP had a predictive effect on the development of the severe form of measles (Table 4).

Table 1

Age and gender of the patients

Variables	Control group	Measles group			*p*-value	
		total	NSC	SC	MG vs. CG	SC vs. NSC
Age (months) mean ± SD	24.9 ± 25.86	22.85 ± 23.94	23.84 ± 26.02	20.65 ± 19.03	0.740	0.913
Gender						
male, n (%)	14 (46.66)	27 (49.09)	22 (57.89)	5 (29.41)	0.9893	0.096
female, n (%)	16 (53.33)	28 (50.90)	16 (42.10)	12 (70.58)		

SD – standard deviation; NSC – non-severely complicated measles group; SC – severely complicated measles group; MG – measles group; CG – control group; n – number.

Table 2

Laboratory tests and blood cell count-derived inflammatory indices performed in measles-affected children and the control group

Parameters	Control group (n = 30)	Measles group (n = 55)	*p*-value	Reference range
WBC (10^9/L)	9.110 ± 2.803	7.560 ± 3.378	0.010*	6.0–16.0
RBC (10^{12}/L)	4.402 ± 0.449	4.631 ± 0.547	0.053	4–5
Hgb (g/L)	124.970 ± 16.243	113.580 ± 15.081	0.002*	109–138
Hct (%)	36.567 ± 4.427	34.553 ± 3.736	0.029*	28.8–39
MCV (fL)	81.437 ± 6.498	74.649 ± 11.461	0.004*	73.8–89.4
RDW (%)	12.587 ± 0.945	13.371 ± 2.992	0.167	11.9–16.2
PLT (10^9/L)	323.030 ± 84.272	249.710 ± 90.752	< 0.001*	150–450
MPV (fL)	8.253 ± 0.686	8.207 ± 1.144	0.841	6.9–11.3
Granulocytes (%)	40.547 ± 17.577	55.536 ± 18.728	0.001*	42–76
Granulocyte count (10^9/L)	3.481 ± 1.627	4.155 ± 2.684	0.400	1–8.5
Lymphocytes (%)	53.493 ± 16.751	39.818 ± 17.442	0.001*	11–49
Lymphocyte count (10^9/L)	5.111 ± 2.651	3.010 ± 1.903	< 0.001*	4–12
Monocytes (%)	5.640 ± 2.091	4.318 ± 2.636	0.005*	0–10
Monocyte count (10^9/L)	0.546 ± 0.310	0.336 ± 0.297	< 0.001*	0.3–1.0
GLR	0.724 ± 0.401	2.005 ± 1.800	< 0.001*	
MLR	0.129 ± 0.058	0.129 ± 0.099	0.424	
PLR	81.906 ± 51.737	114.949 ± 85.456	0.022*	
MPR	0.026 ± 0.009	0.038 ± 0.017	0.002*	
CRP (mg/L)	1.823 ± 1.329	15.320 ± 20.066	< 0.001*	0–5

WBC – white blood cell; RBC – red blood cell; Hgb – hemoglobin; Hct – hematocrit; MCV – mean corpuscular volume; RDW – red cell distribution width; PLT – platelet; MPV – mean platelet volume; GLR – granulocyte/lymphocyte ratio; MLR – monocyte/lymphocyte ratio; PLR – platelet/lymphocyte ratio; MPR – mean platelet volume/platelet count ratio; CRP – C-reactive protein. Values are expressed as mean ± standard deviation. Mann-Whitney *U* test.
***statistically significant difference.**

Table 3

Laboratory tests and cell count-derived inflammatory index performed in non-severely complicated and severely complicated measles form (MF) groups

Parameters	Non-severely complicated MF (n = 38)	Severely complicated MF (n = 17)	*p*-value	Reference range
WBC (10^9/L)	7.539 ± 2.8792	7.606 ± 4.3974	0.792	6.0–16.0
RBC (10^{12}/L)	4.5895 ± 0.58399	4.7241 ± 0.45699	0.591	4–5
Hgb (g/L)	113.21 ± 16.313	114.41 ± 12.294	0.870	109–138
Hct (%)	34.537 ± 4.0802	34.588 ± 2.9336	0.978	28.8–39
MCV (fL)	75.879 ± 9.5345	71.900 ± 14.8832	0.542	73.8–89.4
RDW (%)	13.855 ± 2.061	12.288 ± 4.3107	0.616	11.9–16.2
PLT (10^9/L)	254.21 ± 90.690	239.65 ± 92.849	0.466	150–450
MPV (fL)	8.355 ± 1.1332	7.876 ± 1.1311	0.211	6.9–11.3
Granulocytes (%)	51.211 ± 17.2446	65.206 ± 18.7687	0.014	42–76
Granulocyte count (10^9/L)	3.731 ± 1.7444	5.104 ± 3.9868	0.702	1–8.5
Lymphocytes (%)	43.745 ± 16.645	31.041 ± 16.3577	0.010*	11–49
Lymphocyte count (10^9/L)	3.380 ± 1.9636	2.181 ± 1.5000	0.014*	4–12
Monocytes (%)	4.597 ± 2.5008	3.694 ± 2.8964	0.101	0–10
Monocyte count (10^9/L)	0.375 ± 0.3187	0.248 ± 0.2262	0.093	0.3–1.0
GLR	1.5593 ± 1.289	3.0009 ± 2.36028	0.018*	
MLR	0.121110 ± 0.073	0.147006 ± 0.1421789	0.649	
PLR	100.7352 ± 78.568	146.7194 ± 93.91298	0.012*	
MPR	0.03782 ± 0.017	0.03724 ± 0.015092	0.750	
CRP (mg/L)	10.626 ± 16.222	25.812 ± 24.1045	0.002*	0–5

For abbreviations see under Table 2.

Table 4

Linear regression analysis of predictors for severe measles form

Variables	B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Lymphocytes (%)	0.269	0.156	2.994	1	0.084	1.309	0.965	1.776
Lymphocyte (count)	-0.732	0.457	2.562	1	0.109	0.481	0.196	1.179
Granulocytes (%)	0.191	0.140	1.866	1	0.172	1.210	0.920	1.591
PLR	0.004	0.005	0.586	1	0.444	1.004	0.994	1.014
CRP	0.066	0.026	6.149	1	0.013*	1.068	1.014	1.125
GLR	0.347	0.408	0.726	1	0.394	1.415	0.637	3.147
Constant	-22.959	13.956	2.706	1	0.100	0.000		

PLR – platelet/lymphocyte ratio; CRP – C-reactive protein; GLR – granulocyte/lymphocyte ratio; CI – confidence interval.
***statistically significant difference.**

Discussion

In searching for parameters useful for predicting the measles course, it is necessary to know the immunological mechanism involved in the inflammatory process. That implies migration and infiltration of neutrophils and PLTs into the perivascular space, which regulates the inflammation process in tissue via the cytokine network. Neutrophils are the first effector cells at the site of inflammation. They are involved in the removal of extracellular pathogens and the activation and control of other immune cells, especially PLTs [5–7, 33]. Blood monocytes, as a part of the innate immune system, migrate into the inflamed tissue and differentiate into macrophages and dendritic cells [34]. Defective lymphoproliferation, increased activation and apoptosis of uninfected lymphocytes induce significant lymphopenia in MV infection. De Vries RD et al. [35] hypothesized that measles immune suppression is, in fact, a "numbers game". They considered that measles immune suppression is a result of immune cell depletion "which is masked by the rapid proliferation of MV-specific and bystander lymphocytes". Recently published above-mentioned studies confirmed a significantly higher prognostic value of blood cell count-derived inflammatory indices in accessing the severity of inflammation than the count of particular types of blood cells.

CRP is a well-known marker of inflammation widely used in clinical practice. Elevated CRP levels are typical for bacterial infections but may also be recorded in some viral infections [36, 37]. In our study, the values of CRP corresponded to the severity of the inflammation, and it was the only valuable predictor for severely complicated measles forms in measles-affected children. The MV is the initiator of the inflammatory process, which causes extensive epithelial damage. These epithelial lesions are a favorable environment for the development of bacterial infection in immunocompromised children. It causes complications such as pneumonia and croup. These conditions cause the severe form of measles and represent the most common complications in the group of children with serious complications in our study. Therefore, elevated CRP is probably a result of bacterial superinfection or severe viral infections in response to elevated pro-inflammatory cytokines IL-1, IL-6, and TNF-α. Griffin

DE et al. [38] documented higher values of CRP in measles patients with pneumonia, which remained elevated for a long time, while CRP values in MV meningitis and encephalitis remained normal. It is caused by a direct viral invasion of the brain or an abnormal immune response to CNS antigens.

Altered peripheral blood cell count was confirmed in our study, and the results indicated the participation of the white blood cell subset in the pathogenesis of measles. Previous research by Solmaz et al. [31] showed significantly lower values of leukocytes, neutrophils, and PLTs in measles-affected children without significant differences in blood-derived indices NLR (neutrophil-lymphocyte ratio) and PLR. A recently published study by Güzelçiçek and Demir [32] on measles-infected children in comparison with healthy controls has shown a lower number of WBC and neutrophils, MPV and NLR, and higher number of lymphocytes and CRP. Only PLR was associated with the outcome of disease. A study by Kim et al. [39] has shown that the measles patients had lower leukocytes, neutrophils, and lymphocyte counts than the healthy group. In our study, we demonstrated significantly lower WBC, lymphocyte, monocyte, and PLT counts and a high granulocyte count in the measles group. A significantly higher count of granulocytes and the value of GLR confirm their participation in the measles pathogenesis. Defective lymphoproliferation and apoptosis of uninfected lymphocytes induce significant lymphopenia, which correlates with the severity of the disease [8, 9]. Changes in the total leukocyte pool present in our respondents, especially in granulocyte and lymphocyte counts, affected the values of GLR as well. The changes in GLR values were associated with more severe forms of measles. Nonetheless, the values of granulocytes, lymphocytes, and GLR were not valuable predictors of severely complicated measles forms in measles-affected children. This “numbers game” may be the reason why lymphocytes do not significantly change their numerical relationship with neutrophils, monocytes, and PLTs.

Increased levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 are responsible for reactive thrombocytosis and the severe course of measles. Activated PLTs release IL-1α, IL-1β, TGF-β1, macrophage inflammatory protein, platelet-derived growth factor. In addition, they express the surface molecules (E selectin, P selectin) involved in the chemotaxis of neutrophils, T-lymphocytes, natural killer cells, and macrophages [40, 41]. In inflammation, the bone marrow produces immature, larger PLTs followed by lower values of MPV. In this study, only the values of PLR were associated with a more severe measles form and followed the severity of the inflammatory process. Leukocyte shifts during the immune response (neutrophilia, lymphopenia) change the value of PLR. However, PLR was not a suitable predictive factor for severely complicated measles forms. A recent study has suggested that PLT activation may be a consequence of enhanced bacterial lipopolysaccharide in circulation. As measles is a viral infection, this may be the reason for a weaker activation of PLTs. CRP is a much more sensitive marker of inflammation than an indicator of PLT activation [41]. In the study of Solmaz et al. [31], the level of MPV was proved to be lower in measles-affected children. We demonstrated only a significantly lower PLT count in measles-affected children and higher MPR, which did not differ significantly in severe measles forms. Viruses can infect megakaryocytes, which leads to apoptosis of megakaryocytes, decreased production of PLTs, difficult maturation, and decreased expression of thrombopoietin receptor [40–42]. In our study, MPV was similar in measles-affected children and healthy controls, and in severe form vs. non-severe measles form. Data about usefulness in other inflammatory diseases in pediatrics are divergent. Nonetheless, PLR values differed significantly between the examined groups. In response to some viruses, PLTs can be activated. All these processes contribute to the increase in PLT consumption and removal and lead to thrombocytopenia [40, 42]. However, virus-induced PLT activation modulates the shape of immune responses, which may be one reason for the long-term immunosuppression present in measles-infected children [41].

The RDW is recognized as a biomarker of subclinical infection. The results of some studies showed that RDW positively correlated with inflammatory markers such as erythrocyte sedimentation and CRP levels. However, results of studies in the pediatric population are various, and RDW did not show as good a prognostic marker as in the adult population [43–45]. In our study, RDW did not show any significant relationship with inflammation severity.

A retrospective study and a small study group (n = 55), especially a small number of children with a seriously complicated form of measles (n = 17), limit the value of the results. Another limiting factor may be the time from the onset of symptoms to hospital admission and blood sampling. Some children had received antipyretics and antibiotics due to fever before hospital admission. Changes in the population of WBC and PLTs reflect the body’s response to the inflammatory and infectious process that can be modified by pharmacological treatment. Hence, data about the usefulness of these inflammatory biomarkers are various and remind us that laboratory results should be interpreted following the clinical conditions of every particular child. It is necessary to determine the cut-off values of CRP and tested ratios in measles-affected children who require hospital admission.

Conclusion

The results demonstrated that CRP was the most valuable predictor of severely complicated measles forms in measles-affected children. The blood cell count-derived inflammatory indices (GLR, MLR, PLR, and MPR) are not reliable predictive factors. The significance of the CRP value and blood-derived inflammatory parameters for predicting the severity of measles should be further examined in other multicenter studies with a larger study group.

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