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# Prognostic value of hematological parameters in childhood respiratory tract infections

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## ABSTRACT

**Introduction.** Respiratory tract infections (RTIs) represent a growing burden among pediatric populations, as their potential progression towards acute respiratory insufficiency (ARI), which requires hospitalization and can be light-threatening without adequate supportive measures. Several recent studies have tried to investigate the role of non-invasive depictable parameters, such as those easily determined through a complete blood count (CBC), in the prediction of potentially complicated RTIs. The aim of the current study is to assess whether changes in hematological parameters can predict the development of respiratory insufficiency in children with RTIs.
**Material and methods.** A retrospective study was conducted on 80 patients hospitalized for RTIs, divided into two groups based on their complication by ARI: children with RTI and ARI (group 1-30 patients) and children with RTI, uncomplicated with ARI (group 2-50 patients). Patients with a previously known chronic or hematological disorder were excluded from the study. A CBC was carried out in each patient and C-reactive protein (CRP) values were also determined. Moreover, RT-PCR testing for SARS-COV2 infection was carried out in each child.
**Results.** There were no significant differences in most of the hematological parameters analyzed between the two groups, with the exception of mean corpuscular hemoglobin concentration (MCHC), which exhibited lower values in study group 1. Insignificant differences in parameters of CBC were also found when performing a separate analysis on the subgroup of patients infected with SARS-COV2. However, significantly higher CRP values were found in subjects with RTIs complicated by ARI. An important decrease in hemoglobin levels, under 10 mg/dl, was not positively associated with a complicated outcome of RTIs.
**Conclusion.** Hematological parameters, with the exception of MCHC, are not predictive of ARI in children diagnosed with RTIs. A separate analysis on cases diagnosed with SARS-COV2 infection revealed similar, insignificant results. Further studies, conducted on larger populations, could provide more data regarding the role of hematological parameters in the prediction of RTIs'severity.

**Keywords:**

## INTRODUCTION

Respiratory tract infections (RTIs) represent a significant burden in both pediatric and adult ages, especially when they are recurring (1). These are divided into upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) and can have an acute or chronic evolution. Commonly encountered among children at any age, they can range from a mild self-limited to a severe potentially life-threatening event, in case of the development of an acute respiratory insufficiency (ARI) (2).

Acute URTIs usually have a viral etiology, most of the incriminated agents including rhinovirus, adenovirus, coxsackievirus, influenza and parainfluenza viruses, respiratory syncytial virus (RSV), middle east respiratory syndrome coronavirus (MERS-CoV)

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and human metapneumovirus (3). The bacterial origin of these conditions, although less frequent, is highly dependent upon age, the most frequent pathogens involved being group A beta-hemolytic streptococci, group C beta-hemolytic streptococci, Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydia pneumoniae. Common symptoms of these include local symptoms, such as nasal congestion and obstruction, sneezing, coughing, and dysphagia. However, general symptoms such as fever, fatigue, and headaches can manifest as well. Sometimes, prolonged expiration or even wheezing can appear, as a result of upper airway obstruction (4).

LRTIs are caused by an infection of the lower airway tract and lung parenchyma and include bronchiolitis, bronchitis, and pneumonia (5). Their viral etiology is overlapping with the one of URTIs, as every URTI can present a descendent evolution. Bacterial etiology is miscellaneous and involves pathogens such as Hemophilus influenzae, Staphylococcus aureus, and Klebsiella pneumonia, along with the atypical bacterial infections Legionella pneumophila, Mycoplasma pneumoniae, Chlamydophila pneumoniae and Chlamydia psittaci (3). The distinction between URTI and LRTI is important due to the main complications the latter can impose, which evolve around respiratory distress and failure (4).

Prediction of possible complicated evolution of RTIs is still challenging, but recent literature data has tried to focus on miscellaneous laboratory data which might predict an unfavorable outcome, including hematological parameters, easily measured through an automatic hemoleucogram. Particularly, red blood cell indexes have recently been regarded as potential indicators of unfavorable outcomes in various viral respiratory tract infections (6).

Changes in red blood cell indexes might also be related to the influence of pro-inflammatory cytokines which impair red blood cell production and maturation of its precursors or to intra-infectious anemia which usually manifests as a decrease in hemoglobin (Hb), and/or hematocrit values. Furthermore, acute, transitory anemia can overlap a chronic anemia (7). It is well known that anemia can be silent for a prolonged period of time, as the body's natural response is to slowly decrease hemoglobin levels until a non-tolerable level is reached (8). Prompt and correct diagnosis and treatment for both the source of anemia and the anemia itself are crucial because prior research has shown that children with anemia are more susceptible to lower RTIs. Moreover, a child with an URTI is more prone to develop pneumonia when diagnosed with acute anemia (9).

This study aimed to assess whether changes in red blood cell parameters (erythrocyte count, hemoglobin, hematocrit, MCV, MCH, and RDW) can predict the development of respiratory insufficiency in children with RTIs. A secondary objective was to assess potential changes in other hematological parameters, such as leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets, and their correlation with a simple or complicated RTI.

## MATERIAL AND METHODS

### Study population

We conducted a retrospective study, which involved 80 patients with RTIs aged 25 days to 17 years, admitted to the Pediatrics Clinic I from the Targu Mures Emergency Clinical County Hospital, Romania, between September 2020 to February 2022. This study included patients with a diagnosis of URTI (tonsillitis, laryngitis, pharyngitis, sinusitis, and otitis media) or LRTI (bronchiolitis, bronchitis, and pneumonia) based on clinical data (signs and symptoms) and imagistic investigations, when needed (thoracic X-ray). Vital indicators such as heart rate, blood pressure, and temperature were measured in each patient prior to admission. Depending on the saturation levels registered at the moment of admission ($O_2$ saturation levels lower than 92% or at least 92%), the patients were divided into two study groups: children with RTI and ARI (group 1-30 patients) and children with RTI, uncomplicated with ARI (group 2-50 patients).

Patients with genetic syndromes, congenital malformations of the respiratory tract, or any previously known chronic disorder were excluded, as well as those with a history of any type of hematological condition before admission. Furthermore, patients in which a hematological malignancy or an immune deficiency was later diagnosed were also left out of the study.

### Laboratory data

A complete blood count (CBC), which measures the absolute numbers of erythrocytes, leukocytes, and platelets as well as neutrophils, monocytes, lymphocytes, eosinophils, and basophils was carried out in each patient. Special attention was given to erythrocyte indices, which included hemoglobin (Hb), hematocrit (Htc), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), MCH concentration (MCHC), and red cell distribution width (RDW). Furthermore, in each patient inflammatory markers were assessed, which included at least the C-reactive protein. Moreover, considering the epidemiological context and the respiratory clinical features, all patients underwent reverse transcription-polymerase chain reaction (RT- PCR) testing for SARS-COV2 infection. In those with clinical and paraclinical data suggestive of a bacterial etiology, blood cultures and/or sputum cultures were also analyzed, depending on the clinical setting and the possibility of appropriate patient collaboration (for the later ones).

### Ethics

The research was approved by the Ethics Committee of the Târgu Mureș Emergency Clinical County Hospital (No. 8833/2021), respecting the principles of the declaration of Helsinki. Prior to admission, one of the parents or the child's legal guardian signed an informed consent which acknowledged the approval of medical data use for research and scientific purposes. We did not include patients in the study whose legal guardians refused to sign the informed consent.

### Statistical analysis

The statistical analysis was carried out using the GraphPad Prism 9 software. The Shapiro-Wilk normality test was performed to assess Gaussian or non-Gaussian distribution of the studied variables, and descriptive statistics were utilized for parameters such as mean, median, and their corresponding standard deviations. Mean comparison was conducted using the unpaired t-test with Welch's correction for parameters complying to a Gaussian distribution or the Mann-Whitney test for those with a non-Gaussian distribution pattern. The Chi-square test was applied to evaluate contingency tables. The significance threshold of the p-value was established at 0.05, which corresponded to a confidence interval of 95%.

## RESULTS

As previously mentioned, out of the 80 patients included in the study, ARI was identified in 37.5% (n=30) of the cases, whereas 62.5% (n=50) of the children did not present with O2 saturation levels lower than 92%.

Slightly more male patients were found to suffer from ARI, 21.25% (n=17) as opposed to female patients (16.25%, n=13). However, the difference was insignificant (p=0.4528).

Furthermore, there was no significant difference in terms of mean age between the

study groups. The mean age of the entire study group was 3,065 ± 4,229 SD years.

In our study, patients belonging to group 1 had a mean heart rate of 152,2 ± 22,25 SD beats/minute (bpm), compared to 139,3 ± 25,57 SD bpm for the non-ARI study group. The p-value was 0,0423, showing a significant discrepancy. Comparisons of vital parameters have been provided in Table 1. Significant decrease in Oxygen saturation was expectable in group 1 (p<0.001). Patients belonging to study group 2 had marginally higher values than study group 1, in terms of body temperature with a mean of 36,95 ± 1,012 (SD) C compared to 36,56 ± 0,8755 (SD) C (p=0.021), as represented as well in Table 1.

Comparison of hematological parameters between the two study groups revealed mostly insignificant results, those are mentioned in Table 2. There were no significant differences between the two study groups in terms of leukocyte count, absolute values of cells identified among the leukocyte formula, nor among red blood cell count or most of their indexes. However, a significant correlation between elevated CRP values and study group 1 (with ARI) was demonstrated and expected (25. 06 ± 65.43 versus 13.74 ± 30.29, p=0.032). The only other significant result was represented by a descending trend in MCHC, positively correlated with ARI (p<0.001. All other parameters, namely erythrocytes, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets as well as erythrocyte indices such as hemoglobin, hematocrit, MCV, MCH, and RDW presented with a p-value > 0.05 (see Table 2) demonstrating the null hypotheses, which means that there is no correlation between RTI associated with ARI or non-ARI and any modification of those specific parameters.

In terms of etiology, out of the entire study population, 51 patients (63.75%) presented a viral origin of the URTI or LRTI diagnosed, out of which 20 also developed ARI. Bacterial etiologies were suspected

**TABLE 1.** Comparison of vital signs between children with ARI and children without ARI

| Parameter | With acute respiratory insufficiency (n=30)<br>Mean ± SD (median) | Without acute respiratory insufficiency (n=50)<br>Mean ± SD (median) | P - value |
|---|---|---|---|
| Heart rate (bpm) | 152,2 ± 22,25<br>(146,5) | 139,3 ± 25,57<br>(140,0) | * 0,0423 |
| SpO2 (%) | 89,13 ± 7,505 (90,00) | 97,00 ± 3,264<br>(97,00) | * <0,0001 |
| Temperature (˚C) | 36,56 ± 0,8755<br>(36,30) | 36,95 ± 1,012<br>(36,50) | * 0,0219 |

*Legend: SpO2%: oxygen saturation in the blood*
*n = number, SD = standard deviation, *Mann–Whitney test was used*

**TABLE 2.** Comparison of hematological parameters and CRP values between children with ARI and children without ARI

| Parameter | Group 1 (n=30) Mean ± SD (median) | Group 2 (n=50) Mean ± SD (median) | P – value |
|---|---|---|---|
| CRP (mg/L) | 25,06 ± 65,43 (3,685) | 13,74 ± 30,29 (1,3) | * 0,0322 |
| Leukocytes ($10^3$/L) | 12,74 ± 12,51 (5,661) | 12,93 ± 6,292 (11,37) | * 0,9626 |
| Neutrophiles ($10^3$/L) | 6,283 ± 4,615 (5,09) | 5,669 ± 4,841 (4,22) | * 0,4873 |
| Lymphocytes ($10^3$/L) | 4,745 ± 3,013 (3,945) | 5,342 ± 3,714 (4,105) | * 0,5953 |
| Monocytes ($10^3$/L) | 1,244 ± 0,7971 (1,1) | 1,378 ± 0,944 (1,205) | * 0,6727 |
| Eosinophiles ($10^3$/L) | 0,163 ± 0,3955 (0,06) | 0,2698 ± 0,3787 (0,095) | * 0,2816 |
| Basophiles ($10^3$/L) | 0,06367 ± 0,08323 (0,03) | 0,0486 ± 0,04785 (0,03) | * 0,7444 |
| Platelets ($10^3$/L) | 404,5 ± 236,7 (380) | 405,5 ± 175,7 (385,5) | 0,9843 |
| Erythrocytes ($10^6$/L) | 4,654 ± 1,21 (4,505) | 4,258 ± 0,6465 (4,24) | * 0,1568 |
| Hemoglobin (g/dL) | 14,98 ± 16,4 (11,95) | 11,93 ± 2,013 (12,1) | * 0,9626 |
| Hematocrit (%) | 36,92 ± 7,966 (36,85) | 35,28 ± 5,048 (35,45) | * 0,6300 |
| MCV (fL) | 80,44 ± 9,849 (79,5) | 83,46 ± 9,157 (82,2) | 0,1777 |
| MCH (pg) | 26,96 ± 4,13 (26,85) | 28,48 ± 4,07 (28) | 0,0651 |
| MCHC (g/dL) | 31,93 ± 2,592 (32,6) | 33,56 ± 1,869 (33,45) | * 0,0004 |
| RDW (fL) | 43,51 ± 10,61 (42,25) | 43,71 ± 8,609 (41,30) | * 0,6763 |

*Legend: CRP = C-reactive protein, MCV = mean cellular volume, MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, RDW = red cell distribution width, n = number, SD = standard deviation*
** Mann–Whitney test was used*

in 29 cases, which accounted for 36.25% of the study population. Out of these cases, 10 were hospitalized with ARI. These numbers have been represented in Figure 1.

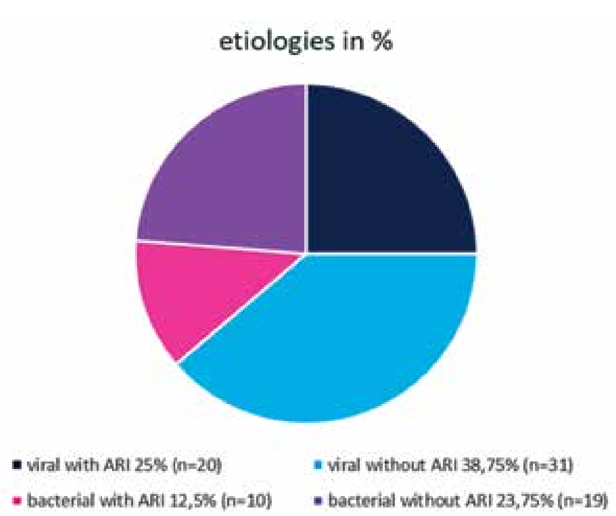


**FIGURE 1.** Prevalence of viral or bacterial etiologies and their complication with ARI in the entire study sample

We identified a SARS-Cov2 infection among 21 patients. Out of those 23,81% (n=5) developed ARI. We also tried to perform a separate comparison of hematological parameters on patients with this viral infection, but no significant differences were found in these cases in relation to the development of ARI.

There was a clear correlation between a diagnosis of bronchitis and pneumonia and the development of ARI (p=0.042 and p=0.047), as opposed to URTIs which did not significantly correlate with low O2 saturation levels (p>0.05).

We further tried to analyze whether a decrease in Hb levels, under a threshold of 10 g/dl, posed an additional risk for the development of ARI. Analysis of hemoglobin values revealed that only 13 patients had Hgb values <10 mg/dl. Out of these, only four also developed ARI, hence the p-value of 0.4072 is not significant.

## DISCUSSION

These days, RTIs, particularly LRTIs seem to be a common ailment among pediatric populations from all around the world, and they're a growing burden in countries such as Germany, the USA, the UK, and Sweden (10). Respiratory tract infections still represent the most common cause of pediatric hospitalization, with the male sex being apparently more likely than the female sex to experience overall morbidity and mortality during childhood. Boys were admitted to hospitals more frequently than girls in young children, according to a 2009 Danish study that looked at gender disparities in hospitalization rates for respiratory tract infections, but the opposite ratio was found in teenagers and young adults aged between 15 and 25 (11). Moreover, young age seems to be a risk factor for complicated RTIs, due to a continuous development of immune system response at this age, as well as constant exposure to pathogens (12). Our study also identified a slightly higher prevalence of ARI among the male sex, but without significant disparities between the two genders. However, our study revealed no significant age differences between the two research groups, therefore excluding low age as a risk factor for ARI.

The ARI study group had high heart rates and poor oxygen saturation, which were recorded.

Given that all of these are symptoms of severe respiratory insufficiency, both were anticipated in study group 1.

Acute respiratory insufficiency represents the life-threatening complication of respiratory tract infections, and often requires oxygen supplementation (usually at oxygen saturation levels lower than 92%) and adjuvant supportive therapy, in the form of corticosteroids (13) . Hypoxemia is defined as arterial oxygen saturation below 90% as measured by pulse oximetry. Diagnosing hypoxemia is a straightforward, non-invasive procedure that does not require much training and it can represent a useful screening tool in each RTI. The correlation between hypoxemia and child mortality rates emphasizes the need for early detection and the possible benefit of therapy (14). As also identified in our study, the most common causes of ARI in children are related to LRTIs (15). Large families, late birth orders, crowding, low birth weight, starvation, vitamin A deficiency, lack of breastfeeding, pollution, and early age are risk factors that raise the prevalence and severity of lower respiratory tract infections in underdeveloped countries (16).

The prediction of possible adverse outcomes of RTIs might enlighten which are the patients at risk for requiring hospitalization. Recently, various studies have focused on hematological parameters as potential non-invasive biomarkers of inflammation associated with RTIs, which are also able to distinguish between viral and bacterial etiologies of RTIs (17,18). Moreover, several parameters including neutrophil-lymphocyte ratio (NLR) or RDW have been regarded as predictors of adverse outcomes of the recently trending SARS-COV2 infection (19,20). The current study tried to assess whether hematological parameters, easily depictable through an automatic CBC can be significantly modified in relation to ARI. We did not find any significant differences in terms of hematological parameters between the two study groups with one exception (MCHC). Even though the levels assessed were still within the normal range, MCHC values were significantly lower in patients with RTIs complicated with ARI. Anemia has been regarded as a potential risk factor for LRTIs, with low red blood cell indexes found in patients diagnosed with LRTI (21), but in our study, only 13 of the 80 patients presented hemoglobin levels below 10 mg/dl. Furthermore, in only four of these patients O2 saturation levels under 92% were measured, and therefore no correlation with ARI was proven. An earlier study suggests that anemic children have a 5.57 times higher likelihood of developing a LRTI than non-anemic children but does not provide a correlation with respiratory distress (22).

Our study also tried to separately assess the impact of hematological parameters changes on the evolution of RTIs caused by SARS-COV2 infection. Lower leukocyte and neutrophil counts, lymphopenia, reactive lymphocytosis, dysplastic changes of granulocytes, and dysplastic changes of platelets were all reported in association with Covid-19 in children who were studied in the past, but they were non-specific and non-diagnostic (23). Patients with COVID-19 can apparently be monitored for hematological alterations that can foretell their requirement for further care and risk of developing severe disease. Lymphocytopenia causes subtle hematological alterations, and severely ill individuals have neutrophilia, lymphocytopenia, high D-dimer, extended PT, and reduced fibrinogen, all of which indicate a poor prognosis (24). RDW increase has so far indicated a poorer prognosis for the course of this infection, but a decrease in Hgb and Htc levels has been reported in those who required hospitalizations but recovered from the disease. These studies however were conducted on adult populations (25,26). Within our study, we identified lymphopenia in just over half of the cases diagnosed with SARS-COV2 infection, but there were no significant differences between the two study groups for any of the hematological parameters analyzed.

In the present research, there was a discernible link between elevated CRP levels and study group 1 (children with ARI), which is expectable, given that those subjects presented a more severe RTI that resulted in ARI. Some studies have demonstrated that children with ARI and RTIs might have a more favorable evolution when their CRP levels are greater, suggesting that CRP may act as a protective factor, while other suggest that higher CRP levels might be indicative of a more severe outcome, especially in RTIs of viral origin (27,28). Moreover, we identified significant changes in vital parameters in the study group of RTIs and ARI, which was not unexpected, considering that there is a link between tachycardia, elevated temperatures, and infectious processes. One study conducted at Oxford University in 2009 reported a heart rate increase by 9.9–14.1 bpm for every 1°C increase in temperature (29).

Although limited by the relatively small sample size, our study analyzed potential differences of multiple hematologic parameters in relation to ARI in the setting of RTIs. These included absolute values of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils,

basophils, platelets, as well as erythrocyte indices (erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, and RDW). In order to avoid the influence of previously known disorders on the aforementioned parameters, we excluded patients with previously known chronic disorders or hematological conditions. Furthermore, a separate analysis was conducted on those cases diagnosed with SARS-COV2 infection, given recent data which demonstrated that several hematological parameters have been linked to its severity. The major limitation of our study remains the number of patients included and its unicentric character. Moreover, we would have benefitted from the investigation of other parameters linked to inflammation and iron-deficiency anemia, such as ferritin and transferrin. A separate analysis on age groups could have also brought new information into light, but due to the small sample and a mean age of around 3 years, further division of subjects included would have likely been subject to bias errors.

## CONCLUSION

RTIs are one of the leading causes of morbidity worldwide and are becoming a growing worry for kids of all ages. Our study sought to identify whether changes in hematological parameters, including red blood cell indices, can be predictive of potential unfavorable evolution in children with RTIs, manifested through ARI. We did not identify any significant differences between patients with uncomplicated RTIs and those who also developed ARI, with the exception of MCHC, which exhibited slightly lower levels in the latter group. A separate analysis on cases diagnosed with SARS-COV2 infection revealed similar, insignificant results. However, there are a limited number of cases available in the literature on this matter, and it has been well-known that children with anemia are more prone towards developing RTIs. Therefore, further studies, performed on larger populations, enrolling patients from different geographical areas, are warranted to provide new insights in the roles of hematological parameters in the prediction of RTIs' evolution.

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