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Comparison of Clinical and Laboratory Characteristics of COVID-19 and Respiratory Diseases of Other Etiology in Hospitalized Children

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Abstract: Today, respiratory diseases are one of the most widespread pathologies of children, causing maximum morbidity. The aim of our study was to determine and analyze differences in clinical and laboratory data and outcomes among children hospitalized with respiratory diseases of COVID-19 and other etiologies. For this purpose, 164 patients under the age of 17 were involved in the study. Patients were divided into two groups: Group I included 89 (54.3%) patients diagnosed with CKD (upper respiratory tract diseases of various etiologies), Group II included 75 (45.7%) patients diagnosed with COVID-19 (PCR positive) pneumonia. During the clinical examination, intoxication, indigestion, auscultatory changes in the lungs, loss of sense of smell, muscle pains, etc., upper respiratory tract damage syndrome, catarrhal symptoms, rhinitis, hyperemia of yawning at various levels during CRX were more manifested during the clinical examination. In both comparison groups of sick children, the main leading symptoms in general were fever 122 (74.4%), cough 133 (81.1%). An increase in the concentration of pro-inflammatory cytokines (IL-1β, IL-6, Il-18) was observed in the blood of patients during both pathologies. Cytokine levels were more prominent increased during COVID-19 compared to ARDs. This indicates the severity of the inflammatory process during COVID-19. The study of the level of pro-inflammatory cytokines in the blood serum of COVID-19 patients allows to determine the progress and severity of the inflammatory process.

Keywords: Acute Respiratory Diseases, COVID-19, Children, Clinical Indicators

1. Introduction

One of the main directions in the fight for children's health is acute respiratory diseases (ARDs), which occupy one of the leading places in the structure of children's pathology [1, 2]. ARDs is a group of diseases with high infectivity, characterized by upper and lower respiratory tract damage, inflammation and various degrees of intoxication.

Due to high prevalence, ARDs remain one of the serious health problems in many countries of the world. Scientific interest to this pathology and it's socio-economic importance are determined by the wide spread of ARDs, the high level of morbidity and the risk of developing serious complications, the active involvement of the child population in the epidemic process, as well as the greatest economic damage in the entire infectious disease structure.

Considering the widespread of ARDs in pediatric practice, high risk of development of their recurrent and severe forms (pneumonia, bronchiolitis), the problem of effective prevention and treatment remains actual. For this reason, early diagnosis of respiratory diseases in children and determination of the mechanisms of adaptation disorders are important issues of modern pediatric pulmonology.

It is known that viruses play an important role in the etiological structure of acute respiratory diseases [3]. Respiratory infections (RI) include both upper and lower respiratory tract infections. RI can cause weakening of the functional activity of the immune system in children,

prolongation, chronicity, and aggravation of the inflammatory process. Given that the genetic structures of viruses are constantly changing, and as a result of this change, new types of viruses are formed, the children's immune response to them can be different. As a result, viruses reduce both immunological reactivity in the body and cause many complications more easily in organisms with a weakened immune system. So, in recent years, a new viral agent has been discovered in the world: SARS-CoV-2. SARS-CoV-2 is a highly infectious respiratory virus. At the end of 2019 and at the beginning of 2020, the SARS-CoV-2 virus, which spread to the world from the city of Wuhan (China), posed a global threat to health and society in the world, and created an emergency situation of international importance [4]. It turned out that coronaviruses can cause many diseases in humans, from a mild form of acute respiratory infection to a severe acute respiratory syndrome (Severe acute respiratory syndrome), accompanied by symptoms of damage to other organs and systems.

According to the researchers, COVID-19 is more satisfactory in children than in adults in contrast to other respiratory viruses, where disease manifestations are often more severe in children. Studies conducted in different countries have revealed that COVID-19 in children is mostly symptomless and has a mild course [5, 6]. Nevertheless, even without symptoms of the disease, the spread of the virus in children can continue for a very long time, and thus they are the main potential source in the continuation of the pandemic [7]. This is an important difference between COVID-19 and other respiratory infections. Despite all this, the clinical profiles and pathophysiology of COVID-19 in children remain unclear, indicating the importance of continuing scientific and experimental studies.

Thus, the revealing of early clinical diagnostic criteria for respiratory diseases in children has the great scientific and practical importance.

The purpose of the study was to compare the clinical features, laboratory data and outcomes in children with coronavirus disease 2019 (COVID-19) and other acute respiratory diseases.

2. Materials and Methods

The study was conducted in 2019-2022 at Educational Therapeutic Clinic of Azerbaijan Medical University and Children's Infectious Diseases Hospital № 7. 164 sick children between the ages of 1 month and 17 years were involved in the research to implement the tasks. 35 healthy children were formed the control group.

Based on clinical, epidemiological data, instrumental and laboratory examinations, patients were divided into two groups: 89 (54.3%) children diagnosed with ARDs (upper respiratory tract infections of various etiologies) were included in group I, 75 (45.7%) children diagnosed with COVID-19 pneumonia (PCR positive) were included in group II. The age composition of the children included in the study was as follows: 26 (15.9%) were children under 1 year old, 71 (43.3%) - 1-3 years old, 67 (40.9%) over 3 years old. Among patients with ARDs, 68.5% of patients were 1-3 years old, 4.5% - under 1 years old, 27.0% of patients were over 3 years old. Among childrem with COVID-19, 57.3% were over 3 years old, 29.3% were under 1 year old, and 13.3% were paients of 1-3 years old. In ARDs, young children (1-3 years) prevailed, in COVID-19 - children under 1 year and over 3 years old. Gender distribution was as following: 91 (55.5%) of the examined patients were boys, 73 (44.5%) were girls; 17 (48.6%) of healthy children were boys, 18 (51.4%) were girls.

Patients included in the study were selected according to the inclusion and exclusion criteria.

2.1. Inclusion Criteria

Children treated with moderate and severe acute respiratory diseases were included in the study. The diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) of a nasopharyngeal smear.

2.2. Exclusion Criteria

Patients with bronchial asthma, autoimmune diseases, cystic fibrosis, primary and acquired immunodeficiency and COVID-19 (PCR) positive patients with asymptomatic mild course of disease were excluded.

2.3. Examination Methods

Examination methods include complaint and anamnestic data, epidemiological (obtained from the history of the disease and parents), clinical data. At the same time, instrumental and laboratory examinations were performed (general and biochemical analysis of blood), the level of cytokines in blood serum was determined and analyzed. A typical diagnosis of COVID-19 was established by polymerase chain reaction (PCR) of a nasopharyngeal swab according to protocol. Examinations were carried out during the acute period of the disease.

In order to assess the levels of circulating cytokines (Il-1β, IL-6, IL-18) in blood serum, reagent kits from the company "Vektor Best" (Russian Federation) were used by the enzyme-linked immunosorbent assay (IFA) method. Measurements were carried out on the "Stat Fax 303+" device.

2.4. Statistical Processing

Statistical data processing was carried out using the methods of variation (U-Mann-Whitney), discriminant (Pearson's Chi-square), correlation (Rho-Spearman), dispersion (F-Fisher and F-S-Fisher-Snedekor tests) tests. All statistical calculations were carried out in MS EXCEL-2019 and IBM Statistics SPSS-26 programs. The null hypothesis was rejected at $p < 0.050$.

3. Results and Their Discussion

Differences in clinical data and laboratory results among hospitalized children during the study were determined, analyzed, and compared. The acute period of the disease is

characterized by relevant disorders.

The analysis of the epidemiological anamnesis of the COVID-19 (PCR) positive patients showed that the vast majority of the disease cases described in children were related to contact with family members or other sick children. This clearly shows human-to-human transmission. As for the seasonal nature, the majority of upper respiratory tract infections patients applied in autumn and winter (39.3% and 42.7%, respectively), but COVID-19 patients applied in summer and autumn (57.3% and 42.7%, respectively), and we think that this distribution can be expained with the fact that COVID-19 is characterizied by the possibility of outdoor transmission, but the respiratory diseases rate peaks are in the fall and winter. 81 (49.4%) of the examined patients applied to the hospital in the first 3 days of the disease. 74 children (45.1%) were admitted to the hospital on days 4-7 of the disease, and 9 (5.5%) patients were admitted to the hospital later than the 7th day after the onset of clinical manifestations. When the patients were admitted to the hospital, respiratory movements were counted in 1 minute, SpO2 level was determined by pulse oximetry "Pulse Oximeter CMS50C" device, which is a simple and reliable screening method to assess hypoxemia. Patients with a positive COVID-19 (PCR) test but without clinical or radiological signs of the disease were considered asymptomatic. We did not include asymptomatic patients in our study. In the patients included in the study, typical multisystem inflammatory syndrome (MIS-C), the fact of death was not recorded.

Clinical assessment showed that in patients with COVID-19, intoxication, indigestion, auscultatory changes in the lungs, weakened breathing, wheezing, Loss of sense of smell and taste, muscle pains, etc., and in patients with ARDs syndrome of damage to the upper respiratory tract at different levels, catarrhal symptoms, rhinitis, hyperemia of throat are more common. In both comparison groups, fever was noted in 122 (74.4%) and cough in 133 (81.1%) cases. SPO2-97.5±0.2% was recorded in patients during ARDs, SPO2-95.9±0.4% during COVID-19 (table 1).

Table 1. *Clinical signs observed in ARDs and COVID-19 (PCR) positive patients.*

Clinical symptoms	Patient group		$P\chi^2$	pU
	ARDs	COVID-19		
	n=89	n=75		
	absolute number, %	absolute number, %		
Temperature	56 (62,9%)	66 (88,0%)	<0,001*	<0,001*
Cough	59 (66,3%)	74 (98,7%)	<0,001*	<0,001*
loss of appetite	44 (49,4%)	72 (96,0%)	<0,001*	<0,001*
Fatigue	71 (79,8%)	74 (98,7%)	<0,001*	<0,001*
Dyspnea	9 (10,1%)	13 (17,3%)	0,176	0,178
Hyperemia of throat	68 (76,4%)	25 (33,3%)	0,001*	0,001*
Rinit	57 (64,0)	1 (1,3%)	<0,001*	<0,001*
Diarrhea	1 (1,1%)	7 (9,3%)	0,015*	0,015 *
Vomiting	9 (10,1%)	14 (18,7%)	0,116	0,117
Sluggishness	–	21 (28,0%)	–	<0,001*
Cyanosis	–	8 (10,7%)	–	0,005*
Muscle pain	–	13 (17,3%)	–	<0,001*
Loss of sense of smell and taste	–	5 (6,7%)	–	0,044 *
Headache	–	7 (9,3%)	–	0,016 *
Muscle hypotonia	–	16 (21,3%)	–	<0,001*

Note: the statistical significance of the differences between the indicators of the groups:
$P_{\chi 2}$ –according to Chi-square Pearson test
Pu - according to the Mann-Whitney u test
* – "0" hypothesis is rejected

As can be seen from Table 1, intoxication symptoms prevailed during COVID-19, and catarrhal symptoms prevailed during ARDs, there was no noticeable shortness of breath in patients with ARDs. The clinical signs identified during COVID-19 in children compared to patients with ARDs can be explained by the specific features of the pandemic virus. X-ray examination of the lungs is considered one of the main examination methods in respiratory diseases. As a result of the X-ray examination, the strengthening of the lung pattern in 119 (85.0%) and the expansion of the lung roots - in 140 (100%) children were revealed, in COVID-19 (PCR) positive patients, infiltrative shadowing of various sizes in the lungs were found in 75 (53.5%) children: 49 (65.3%) patients had one-sided pneumonia, 26 (34.7%) patients had bilateral pneumonia, 3 (3.3%) children had “ground-glass opacities” symptome.

During the analysis of laboratory data, relative lymphocytosis, a slight increase in the level of ESR and CRP were found in the majority of hospitalized children with ARDs, but the changes were not statistically significant. During the analysis of laboratory parameters in COVID-19 (PCR) positive patients, moderate lymphocytosis, thrombocytopenia tendency, a slight increase in CRP and ESR levels were observed. However, many of these laboratory findings during COVID-19 are nonspecific and similar with ordinary pneumonia (table 2).

Table 2. *Comparative analysis of hemogram indicators in ARDs and COVID-19 (PCR) positive patients.*

		n	Mean	Std. Error	Min	Max	P_F	P_U
Leukocytes q/l	ARD	89	11,0	0,6	3,03	44,71	< 0,001*	<0,001*
	COVID-19	75	8,0	0,4	3,1	23,3		
Neutrophils #	ARD	89	4,9	0,4	0,1	22,19	0,003 *	0,003 *
	COVID-19	60	3,4	0,3	0,5	12,2		
Lymphocytes #	ARD	89	4,7	0,4	0,75	31,05	0,311	0,208
	COVID-19	72	4,1	0,4	0,4	18,7		
Erythrocytes q/l	ARD	89	4,74	0,05	3,65	6,22	< 0,001*	<0,001*
	COVID-19	75	4,38	0,07	2,86	5,55		
Trombocytes q/l l	ARD	89	352,2	11,7	120	673	< 0,001*	<0,001*
	COVID-19	75	284,2	13,5	48	796		
ESR mm/Hour	ARD	87	18,7	1,8	2	90	0,634	0,656
	COVID-19	75	17,6	1,4	3	65		
CRP mq/l	ARD	73	11,5	2,5	0,05	121,7	0,227	0,195
	COVID-19	68	7,9	1,6	0,06	69		

* Note: statistical significance of the difference between the indicators of the groups:
PF – According to the F-Fisher criterion
PU – according to theMann-Whitney U test
* – "0" hypothesis is rejected

At the next stage of the study, ROC-analysis was performed based on the sensitivity and specificity indicators of WBC and PLT. Based on the ROC curve, it was determined that the area of the curves for WBC indicator was 0.319±0.041; 95% CI: upper and lower bounds, 0.238 -0.401, respectively: p<0.001, which can be evaluated as an indicator with high specificity and sensitivity. The area of the ROC curve of PLT was 0.319±0.042; 95% CI: upper and lower bound 0.237-0.401, respectively: p<0.001 (graph 1).

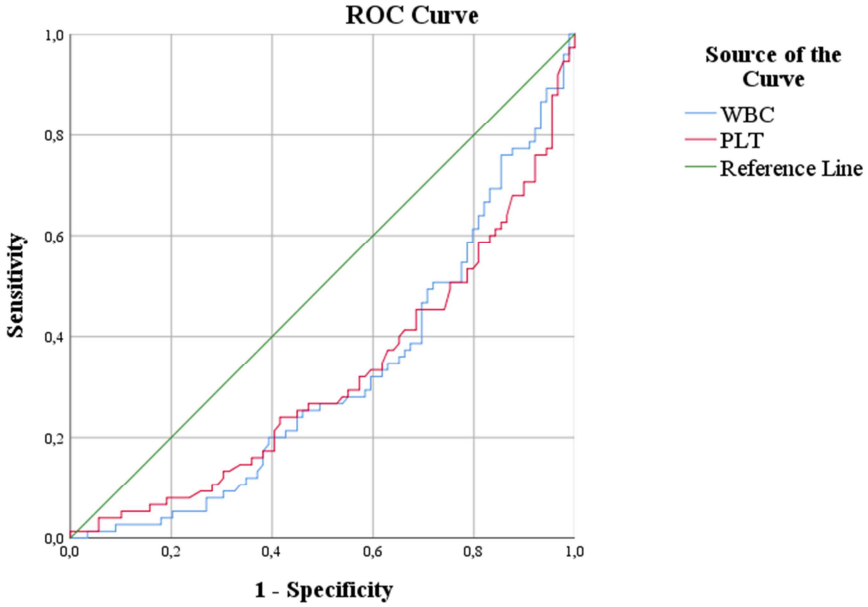

Figure 1. *Results of ROC analysis of laboratory indicators in ARDs and COVID-19 (PCR) positive patients.*

Table 3. *Results of ROC analysis of laboratory indicators in ARDs and COVID-19 (PCR) positive patients.*

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
WBC	0,319	0,041	< 0,001	0,238	0,401
PLT	0,319	0,042	< 0,001	0,237	0,401

The functional change caused by the hypersecretion of cytokines involved in inflammatory processes is the basis of the pathogenesis of acute respiratory diseases. Studying the role of cytokines in ARDs has been fundamental to understanding the causes of the severe and complex course of these diseases.

Taking into account the important role of cytokines in the regulation of inflammatory processes, in the next stage of the study, the examination and analysis of some cytokines (IL-1β, IL-6, IL-18) in the blood serum in ARDs (n=30) and in

COVID-19 (PZR) positive patients (n=75) were perfomed.

The level of pro-inflammatory cytokines in COVID-19 (PCR) positive patients was found to be significantly different compared to the corresponding indicators of ARDs patients (table 4).

Table 4. *Comparison of cytokine levels in ARDs and COVID-19 (PCR) positive patients.*

		Control	ARDs	COVID-19
	N	15	30	75
IL-1β pg/ml	M	0,55	1,05	1,84
	Me	0,05	0,00	0,30
	Q1	0,00	0,00	0,05
	Q3	1,40	1,90	1,90
P			0,938	0,013*
p_1				0,008*
IL-6 pg/ml	M	1,63	2,56	3,97
	Me	1,10	1,70	3,30
	Q1	0,60	1,00	1,40
	Q3	1,70	3,50	5,90
P			0,044*	0,001*
p_1				0,025*
IL-18 pg/ml	M	231,9	186,5	421,5
	Me	218,0	186,0	410,8
	Q1	155,5	53,7	282,0
	Q3	310,4	288,2	510,7
P			0,185	<0,001*
p_1				<0,001*

Comparison of cytokine levels in ARDs and COVID-19 (PCR) positive patients

P – with the indicators of the control group (according to the Mann-Whitney U test)

P_1 – with indicators of the ARDs group (according to the Mann-Whitney U test)

* – "0" hypothesis is rejected

As can be seen in Table 4, there are significantly higher median levels of IL-1β, IL-6, IL-18 during COVID-19 compared to ARDs. The levels of these cytokines are correspondingly increased during COVID-19 compared to ARDs. The mean of IL-1β in patients with ARDs was 1.05 pg/ml, and mean structural indicators compared to COVID-19 were as median 0.00 pg/ml (0.00-1.90 in the 1st and 3rd quartiles). In COVID-19 patients, the mean of IL-1β was 1.84 pg/ml, and the mean structural indicators were as median 0.30 pg/ml (0.05-1.90 in the 1st and 3rd quartiles) compared to the ARDs (p=0.008).

Mean of IL-6 level was 2.56 pg/ml during ARDs compared to COVID-19, median was 1.70 pg/ml (1.00-3.50 in the 1st and 3rd quartiles); during COVID-19, the mean of this cytokine was 3.97 pg/ml, median of the average structural indicators was 3.30 pg/ml (in the 1st and 3rd quartiles were 1.40-5.90) (p=0.025).

In patients with ARDs, mean of IL-18 was 186.5 pg/ml, the median was 186.0 pg/ml (53.7-288.2 in the 1st and 3rd quartiles); in patients with COVID-19 the mean of IL-18 was 421.5 pg/ml in the acute period of the disease, the median was 410.8 pg/ml (282.0-510.7 in the 1st and 3rd quartiles) compared to the average structural indicators (p =0.001).

Thus, it is clear from our research that an increase in the concentration of pro-inflammatory cytokines was observed in the blood of patients during both the studied pathologies. In comparison, the level of cytokines was especially higher in COVID-19 (PCR) positive patients. The increase in the level of cytokines is directly related to the activity of the inflammatory process. This indicates that the immune system is quickly activated to resist the invasion and damage of the pathogen in children during the growth and development period.

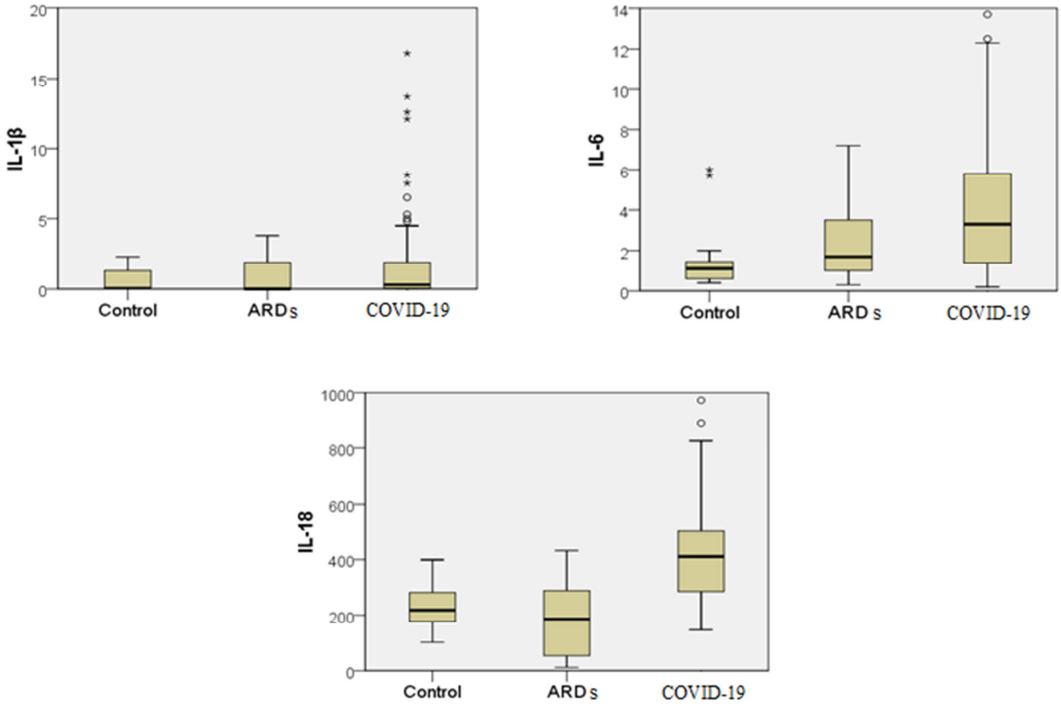

Figure 2. *Diagram of the average levels of cytokines in ARDs and COVID-19 (PCR) positive patients.*

In the next stage of our study, ROC-analysis was performed based on the sensitivity and specificity indicators of cytokines in the studied patients.

According to the results of ROC analysis, all indicators have statistical significance. Based on the ROC curve, it was found that the area under the curve of the IL-1β was 0.665±0.073; 95% CI: upper and lower bound, 0.522-0.808, respectively: p=0.008. The area under the ROC curve of the IL-6 was 0.640±0.058; 95% CI: upper and lower bound 0.527-0.754, respectively: p=0.025, which can be considered diagnostically significant. The area under the ROC curve of the IL-18 was 0.862±0.039; 95% CI: upper and lower bound, 0.787 - 0.938, respectively: p=0.001, which also can be considered statistically significant (graph 3).

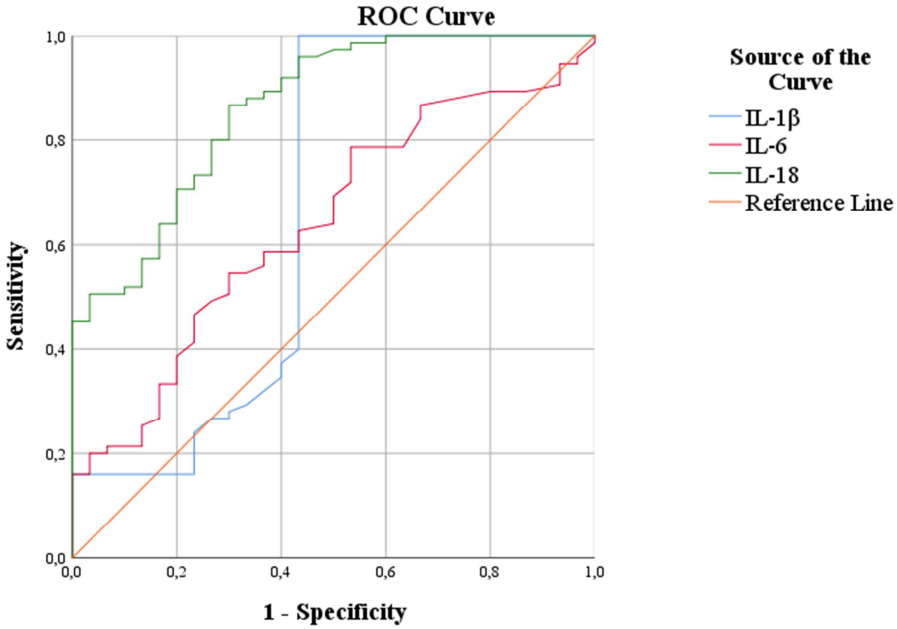

Figure 3. *Integrated indicator of ROC-specificity and sensitivity of cytokines in ARDs and COVID-19 (PCR) positive patients.*

Table 5. *Integrated index of ROC-specificity and sensitivity of cytokines in ARDs and COVID-19 (PCR) positive patients.*

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IL-1β	0,665	0,073	0,008	0,522	0,808
IL-6	0,640	0,058	0,025	0,527	0,754
IL-18	0,862	0,039	< 0,001	0,787	0,938

According to ROC calculations, the mentioned cytokines have high specificity and sensitivity, and can be independent prognosticators in the early diagnosis of ARDs, in particular, for COVID-19.

In the next stage of the research, correlations between clinical and laboratory indicators were studied (table 6).

Table 6. *Assessment of correlations between some indicators in ARDs and COVID-19 (PCR) positive patients.*

		WBC	NEUT	LYM	RBC	PLT	ECS	CRP	IL-1β	IL-6	IL-18
Condition	ρ (Rho)	0,092	-0,060	0,061	0,317**	-0,140	0,057	-0,040	0,256**	0,254**	0,371**
	P	0,242	0,466	0,444	0,000	0,075	0,469	0,636	0,008	0,009	0,000
Sluggishness	ρ (Rho)	0,246**	0,048	0,177*	0,344**	-0,001	0,054	-0,049	0,267*	0,161	0,213
	P	0,004	0,605	0,044	0,000	0,990	0,536	0,581	0,021	0,169	0,067
Cyanosis	ρ (Rho)	0,171*	-0,029	0,129	-0,077	0,090	0,066	-0,058	0,099	0,055	-0,032
	P	0,048	0,752	0,143	0,377	0,301	0,448	0,520	0,397	0,640	0,786
Muscle hypotonia	ρ (Rho)	0,154	0,083	0,086	0,311**	-0,073	0,042	-0,004	0,202	0,172	0,183
	P	0,075	0,368	0,329	0,000	0,403	0,627	0,960	0,083	0,140	0,115
Weakness of reaction	ρ (Rho)	-0,048	-0,069	-0,052	-0,193*	0,007	0,042	-0,112	0,129	-0,043	0,133
	P	0,579	0,459	0,554	0,025	0,935	0,627	0,211	0,270	0,713	0,254
Cough	ρ (Rho)	0,026	-0,004	0,157*	-0,008	-0,041	0,081	-0,032	0,166	0,123	0,213*
	P	0,738	0,959	0,046	0,915	0,604	0,303	0,705	0,091	0,213	0,029
Dyspnea	ρ (Rho)	0,162*	0,051	0,136	-0,081	-0,050	0,012	0,084	0,093	-0,026	0,019
	P	0,038	0,538	0,085	0,305	0,526	0,876	0,322	0,346	0,793	0,844
loss of appetite	ρ (Rho)	-0,171*	-0,117	-0,068	0,224**	0,255**	0,023	-0,118	0,051	0,096	0,406**
	P	0,028	0,155	0,394	0,004	0,001	0,776	0,163	0,607	0,329	0,000

		WBC	NEUT	LYM	RBC	PLT	ECS	CRP	IL-1β	IL-6	IL-18
Muscle pain	ρ (Rho)	-0,145	0,046	0,342**	-0,007	-0,124	0,147	0,136	0,110	-0,010	0,059
	P	0,095	0,617	0,000	0,931	0,155	0,091	0,127	0,346	0,934	0,618
Vomiting	ρ (Rho)	-0,019	-0,124	-0,047	-0,161*	-0,154*	-0,036	-0,109	0,024	-0,005	0,069
	P	0,814	0,132	0,551	0,040	0,049	0,651	0,197	0,806	0,960	0,486
Diarrhea	ρ (Rho)	0,053	-0,059	0,076	0,262**	-0,110	-0,061	-0,190*	0,046	-0,004	0,118
	P	0,499	0,472	0,336	0,001	0,162	0,441	0,024	0,645	0,964	0,229
Temperature	ρ (Rho)	-0,192*	-0,036	0,218**	-0,144	-0,140	-0,036	0,087	0,219*	-0,027	0,009
	P	0,014	0,660	0,005	0,067	0,073	0,652	0,303	0,025	0,785	0,928
Loss of sense of smell and taste	ρ (Rho)	-0,091	-0,045	-0,193*	0,042	-0,058	-0,078	0,047	0,192	0,052	0,057
	P	0,295	0,631	0,027	0,628	0,505	0,367	0,601	0,098	0,659	0,628
Headache	ρ (Rho)	0,038	0,106	-0,197*	-0,008	0,023	0,239**	0,097	-0,026	0,070	-0,019
	P	0,662	0,251	0,024	0,929	0,796	0,005	0,276	0,828	0,551	0,871
Rinorea	ρ (Rho)	0,227**	0,161*	0,170*	0,246**	0,195*	0,014	0,118	-0,056	-0,180	-0,201*
	P	0,003	0,050	0,031	0,001	0,012	0,861	0,164	0,570	0,066	0,039
Hyperemia of throat	ρ (Rho)	0,134	0,206*	-0,001	0,215**	0,081	0,077	0,057	-0,031	-0,081	-0,198*
	P	0,087	0,012	0,987	0,006	0,302	0,327	0,503	0,752	0,411	0,043
Fatigue	ρ (Rho)	-0,077	-0,102	0,034	0,288**	-0,151	0,047	0,167*	-0,007	0,092	0,217*
	P	0,328	0,218	0,669	0,000	0,054	0,551	0,048	0,942	0,353	0,026

Note: ρ (Rho)- correlation coefficient (ρ-Spearman criterion)
p - statistical significance of the correlation coefficient * -"0" hypothesis is rejected

4. Discussion

Today, respiratory diseases remain one of the main causes of hospitalization in children in the world. Despite the successes achieved in the fight against these diseases, there is an increasing trend of respiratory tract diseases of various etiologies in children.

The high frequency of respiratory system infections in children is associated with epidemic causes (high infectivity of viral infections, increased frequency of contacts with a large number of serotypes of pathogens), on the one hand, and with transient functional anomalies, features of the immune system that have not yet been fully formed, on the other hand. The relationship between clinical and laboratory indicators of respiratory diseases in children and the pathogenesis of the disease is still being studied.

In the course of our research, it was determined that the majority of patients during KRX were children of early age (1-3 years), and during COVID-19, children were from the group of up to 1 year and over 3 years of age. According to many authors, ARDs have the highest morbidity rate in early-aged children and is characterized by a number of serious complications (pneumonia, bronchiolitis) [8,9,10]. In children at this age, the anatomical and physiological structure of the respiratory organs, the characteristics of the adaptation period, the immaturity of the general and local immune system, specific and non-specific protective factors, etc. insufficient formation are the main factors that cause respiratory tract diseases.

Relatively high morbidity rates of COVID-19 in patients under 1 year of age can be explained by their frequent hospitalization for epidemiological reasons and increased risk of developing complications. Dong Y (2020) and colleagues reported that infants are more susceptible to infection during COVID-19 [7]. We think that these characteristics in infants and adults can be explained by age differences in their immune system activity and maturity.

The clinical characteristics of the patients examined in our study reflect the clinical course of acute respiratory diseases. Commonly, the main symptom in both comparison groups was fever 122 (74.4%), the second most common symptom was cough 133 (81.1%) [11]. Upper respiratory tract injury syndrome, catarrhal symptoms, and rhinitis were more common during ARDs [3,11]. The clinical signs observed in children with COVID-19 (PCR) positive pneumonia were typical for the studied pathology [5, 12].

During our observations, along with respiratory symptoms, some symptomes, characteristic of COVID-19, such as muscle pain (in 13 (17.3%) cases), loss of sence of smell and taste (anosmia, ageusia) (in 5 (6.7%) cases), and headache (in 7 (9.3%) cases) were observed. None of these symptoms are present in other respiratory diseases. There are limited data on loss of sence of smell and taste during COVID-19 in children. Siddiqui M., et al (2021) in their retrospective studies reported that loss of sense of smell was the main presenting symptom in children with COVID-19 (PCR) positive patients [11]. Gastrointestinal symptoms such as diarrhea and vomiting were more common during COVID-19 compared to the other comparison group. A number of researchers have suggested that the absence of gastrointestinal symptoms in patients with COVID-19 is an important subjective finding that differentiates it from other viral diseases [11].

Thus, the clinical features of COVID-19 compared to ARDs can be explained by the etiological features of the disease. In the majority of hospitalized children with ARDs, relatively leukocytosis, lymphocytosis, and a slight increase in the level of ESR were observed during laboratory examinations, but the results were not statistically significant. During the analysis of the laboratory indicators in COVID-19 (PCR) positive patients, moderate leukocytosis, lymphocytosis, thrombocytopenia tendency, a slight increase in the level of CRP and EHS were observed. However, many of these laboratory findings are non-specific and similar to pneumonia. Xia W (2020), Henry BM (2020) and many other

researchers have studied the laboratory indicators in COVID-19 (PCR) positive children and showed that the laboratory results were normal [13, 14].

To recent time, data on the cytokine profile in children with respiratory disease are insufficient. Because cytokines not only cause activation of inflammation by enhancing immune responses, but also have a complex interaction with the coagulation system, recent studies have focused on the hyperproduction of the cytokine profile as a key factor in the severity of the respiratory diseases, especially in COVID-19. In our study, the analysis of cytokine levels showed that in both comparison groups, their concentration increased more sharply during COVID-19 than during ARDs. In our opinion, it is expected that pro-inflammatory cytokines increase during the acute period of the disease in the patients with respiratory diseases we observed. Because these diseases are inflammatory diseases. An acute inflammatory process indicates that all cytokines are actively produced to resist viral invasion. In comparison to children with ARDs, the prominent increase of pro-inflammatory cytokines in children with COVID-19 (PCR) positive pneumonia characterizes the severe course of the process. We think that the hyperproduction of proinflammatory cytokines during COVID-19 is related to the severity of the pandemic virus and is an inadequate or hyperergic response of the immune system to the antigen exposure.

In our study, the increase in the level of IL-1β, IL-6 coincided with the appearance of the first symptoms of the clinical course. The high levels of these pro-inflammatory cytokines correspond to the more severe clinical course of the disease. IL-1β, IL-6 activity in inflammatory processes is related to their tropism to basophils, endotheliocytes, neutrophils, and hepatocytes. An increase in body temperature, weakness, and loss of appetite were observed in both pathologies. It is known that IL-1β, Il-6 is one of the pyrogenic cytokines. Since IL-1β can cross the blood-brain barrier like IL-6, it affects the hypothalamus and pituitary centers, causing fever, loss of appetite, sleep disturbance, fatigue, etc.

IL-1β, IL-6, which causes an increase in the secretion of acute phase proteins in inflammatory diseases, also causes metabolic and hematological changes, increases the permeability of vascular walls and increases the expression of adhesion molecules. As a result, biologically active substances, prostaglandins, and inflammatory mediators from small molecule mediators cause exacerbation and activation of the inflammatory process. In our study, the increase of IL-1β, IL-6 is an expected result and coincide with the results of most researchers. Miromanova G. A., Smirnov I. E. and others showed the increase of IL-1β, IL-6 in patients with acute respiratory diseases [15, 16]. Hala K. S. et al., when examining the cytokine profile in children with SARS-CoV-2 infection, showed that the level of circulating IL-1β was increased in the early stage of the disease [17]. Ulhaq Syambani, Qian G.(2021), and many researchers noted that IL-6 was in the normal range or elevated between average concentration in COVID-19 (PCR) positive children, while Sun D. noted that the level of IL-6 increased [18-20]. The established characteristics of the production of pro-inflammatory cytokines in children with pneumonia caused by a new strain of the SARS-CoV-2 virus confirm the existing information about the formation of a specific immune response to the new type of the virus.

The concentration of IL-18 in children with positive COVID-19 PCR increased in contrast to ARDs patients. Increased production of IL-1β, IL-6, and IL-18 (due to the activation of the transcription factor NF-kB) is necessary for adequate anti-infective protection, which is accompanied by the expression of inflammatory cytokine genes. IL-18, like IL-1β, IL-6, plays an important role in the formation, regulation and activation of functional activity of acquired immunity. Consequently, IL-18 regulates the interrelationship between cellular and humoral immunity in respiratory diseases. The role of IL-18 in the pathogenesis of COVID-19 is reflected in the literature [21, 22]. During viral infections, IL-18 increases the activity of CD4+T- lymphocytes and NK cells, creates an interaction between macrophages and lymphocytes, and regulates T-helper's Th1 defense as well as Th1 and Th2 responses. Thus, IL-18 not only acts as a pro-inflammatory cytokine, but also contributes to lower antiviral defense as an immunosuppressive factor that helps shift immune responses from Th1 to Th2 type during inflammation. This is due to the dual role of IL-18 in inflammatory responses. It is quite possible that the hyperproduction of IL-18 in the early period of respiratory diseases contributes to the physiological activity of cell communication in the immune defense aimed at eliminating the pathogen. We think that this change observed in the level of IL-18 during ARDs is the result of its characteristic [16].

As a result of our research, it was determined that the increase in the level of cytokines in patients with respiratory tract diseases is considered a pathogenetic factor of exacerbation and aggravation of the inflammatory process in the bronchus and pulmonary system. However, further research is needed.

5. Conclusion

Thus, in addition to respiratory symptoms, in children with COVID-19 gastrointestinal symptoms, loss of smell and taste, muscle pain, unilateral and bilateral pneumonia on X-ray were alsom observed. Depending on the clinical course, proinflammatory cytokines IL-1β, IL-6, IL-18 in COVID-19 and IL-1β, IL-6 in respiratory diseases of other etiologies can be potential biomarkers for early diagnosis of the disease. Our research can help clinicians in properly managing clinical and laboratory data in children with COVID-19 and other respiratory diseases.

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