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CLINICAL AND LABORATORY CHARACTERISTICS OF THE MODERN COURSE OF INFECTIOUS MONONUCLEOSIS AND THE ALGORITHM FOR ESTABLISHING THE DIAGNOSIS

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Objective. *To evaluate the diagnostic significance of clinical manifestations and laboratory markers in patients with typical and atypical infectious mononucleosis (IM) and to develop a diagnostic algorithm based on the obtained results.*

Patients and methods. *A multicenter retrospective cohort study included 159 patients aged 16–65 years, divided into groups of typical IM (n=86), atypical IM (n=51), and acute respiratory viral infection (n=22). Clinical symptoms, ultrasound parameters of the liver and spleen, hemograms, biochemical indicators (alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP)), as well as polymerase chain reaction (PCR) and serological test results were analyzed. Statistical processing was performed using Python.*

Results. *Significant intergroup differences were identified. The highest diagnostic informativeness was demonstrated by virocytes (20 % in typical IM, 16 % in atypical IM, 1 % in controls), lymphocytosis, and increased ALT, AST, and LDH activity. ROC analysis confirmed the leading role of virocytes (AUC=1.0), as well as the significance of ALT (AUC=0.972), lymphocytes (AUC=0.970), and LDH (AUC=0.930). Based on threshold values of virocytes ≥3 %, lymphocytes ≥50 %, ALT ≥36* U/L*, and LDH ≥392* U/L*, a 12-point scale was developed with a sensitivity of 95.6 % and specificity of 100 %.*

Conclusions. *Virocytes are the most specific indicator of IM, while elevated ALT and LDH activity serve as important auxiliary criteria, with LDH enabling differentiation between typical and atypical courses. The developed scale optimizes IM diagnosis.*

Key words: *infectious mononucleosis; typical course; atypical course; virocytes; lymphocytosis; transaminases; LDH; diagnostic algorithm.*

Infectious mononucleosis (IM) belongs to the group of the most widespread viral diseases that cause differential-diagnostic difficulties for general practitioners, family physicians, and infectious disease specialists [1, 2]. It is known that more than 90 % of the world's population becomes infected with the Epstein–Barr virus during their lifetime. At the same time, a clinically apparent form of IM develops in far from all cases of primary infection [3, 4]. Recent studies indicate an increase in the incidence of IM among adolescents and young adults, with individuals aged 15–24 years remaining the most vulnerable age category [5]. The incidence of IM varies from 45 to 90 cases per 100,000 population per year in developed countries; however, the real figures may be higher due to undiagnosed cases with an atypical course [6, 7].

Diagnosis of IM is based on the classical triad of symptoms, which includes elevated body temperature, pharyngitis, and lymphadenopathy [1, 8]. However, real clinical practice demonstrates significant clinical heterogeneity in the course of the disease. According to the results of prospective observations, 75 % of young adults develop a typical variant of infectious mononucleosis with a full set of classical symptoms, 15 % have an atypical course with an incomplete clinical picture, and in 10 % of cases primary infection proceeds completely asymptomatically [3, 9]. It is the atypical forms of the disease that create the greatest difficulties for timely diagnosis and may lead to delayed establishment of the diagnosis, unjustified prescription of antibacterial agents, and the development of complications [10, 11].

A typical course of IM is characterized by the presence of the full aforementioned triad of symptoms and is usually accompanied by a pronounced clinical picture, which simplifies the initial diagnosis [8]. In contrast, atypical IM may manifest only individual components of the classical triad or may proceed with entirely uncharacteristic symptoms [10,12]. According to some authors, pharyngitis may be absent in almost 60 % of atypical cases, and lymphadenopathy is detected in only half of such patients [11]. The clinical picture of atypical forms of IM may include nonspecific manifestations such as nausea, skin manifestations (exanthems), diarrhea, or discomfort in the epigastric region,

which complicates timely diagnosis and leads to unnecessary diagnostic investigations [10, 13].

Some scientific studies indicate that atypical forms of IM may masquerade as other diseases, for example as bacterial tonsillitis, which in turn may result from the irrational prescription of antibacterial therapy [2, 11]. Moreover, the time from the onset of the first symptoms to verification of the diagnosis in an atypical course may be 60 % longer compared to the typical form, which is due to more prolonged diagnostic searches [11]. An important aspect is that in the atypical course of the disease, lymphadenopathy may be asymmetric or may involve atypical groups of lymph nodes, which further complicates the differential diagnosis with lymphoproliferative diseases [13–15].

Therefore, understanding the clinical features of the typical and atypical course of IM is fundamental for optimizing the diagnostic approach. The presence of atypical forms necessitates the development of clear diagnostic criteria and algorithms that would allow the disease to be identified in a timely manner even in the absence of a complete clinical picture [12, 15].

Thus, despite significant scientific advances in understanding the pathogenesis of IM, the problem of timely and accurate diagnosis of the disease, especially its atypical forms, remains relevant. The development of diagnostic algorithms based on a comprehensive assessment of clinical and laboratory indicators may contribute to improving the quality of diagnosis and reducing the time required to establish the diagnosis, which is important for optimizing treatment tactics and preventing disease complications.

The aim of the study was to determine the diagnostic value of clinical symptoms and laboratory markers in patients with typical and atypical infectious mononucleosis, as well as to develop a diagnostic algorithm based on the obtained data.

Patients and Methods

A multicenter retrospective cohort study was conducted from January 2022 to September 2025. The study included data from medical records of patients aged 16 to 65 years who were hospitalized with confirmed infectious mononucleosis caused by the Epstein–Barr virus. In addition, all enrolled IM patients had at least two of the three symptoms of the classical IM triad, namely elevated body temperature above 37.5 °C, clinical signs of pharyngitis, and lymphadenopathy of varying severity. Exclusion criteria included a history of immunosuppressive conditions (HIV, immunosuppressant use, oncological diseases), severe concomitant liver or kidney diseases, and pregnancy.

The control group consisted of patients with acute respiratory viral infection who were hospitalized during the same period with a clinical picture resembling IM, but in whom the diagnosis of IM was excluded based on negative serological test results and the absence of specific laboratory blood changes. In these patients, the number of virocytes in peripheral blood did not exceed 2 %, and EBV serological markers were not detected. Formation of the control group was necessary for a correct comparative analysis and for determining the specificity of the identified diagnostic markers. Data from the patients' medical records were analyzed, including findings of their clinical examination, duration of the disease, and the nature and severity of symptoms. The maximum body temperature within 24 hours before hospitalization, the presence of pharyngitis, and the size and localization of enlarged lymph nodes were considered. Particular attention was paid to the presence of palatal petechiae in the medical documentation, which some authors consider a highly specific sign of infectious mononucleosis. Abdominal ultrasound data (assessment of liver and spleen size) were also collected. Splenomegaly was defined as an increase in spleen length above 12 cm or thickness greater than 5 cm, while hepatomegaly was defined as an increase in the right lobe of the liver above 15 cm along the midclavicular line. The duration of hospitalization was calculated from the day of admission to the day of discharge. The time from the onset of the first symptoms to the establishment of the final diagnosis was recorded, as well as the fact of antibiotic therapy prescription and its duration. These data were important for analyzing clinical outcomes and assessing the efficiency of the diagnostic process. The results of a complete blood count with leukocyte differential, performed upon admission to the hospital, were analyzed. In addition, data from the medical records were analyzed for the results of biochemical blood tests, which included the determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) activity. The reference values were: ALT up to 41 U/L, AST up to 40 U/L, LDH from 135 to 225 U/L, and ALP from 40 to 150 U/L. The choice of these biochemical parameters was determined by their ability to reflect the degree of liver involvement and the overall severity of the infectious process. The results of polymerase chain reaction (PCR) or serological tests confirming or excluding (in the case of the control group) the diagnosis of IM were analyzed, as well as tests for the detection of heterophile antibodies by rapid methods (the Monospot test or Paul–Bunnell test, which are similar variants of immunochromatographic analysis allowing the detection of heterophile antibodies).

For the distribution of patients into groups, the final determination of IM was established based on a combination of clinical data, the presence of virocytes in peripheral blood, and positive serological test results. A typical course was defined by the presence of the classical triad of symptoms

(elevated body temperature, signs of pharyngitis, lymphadenopathy) combined with virocytes of 3 % or more and serological confirmation. An atypical course was defined in cases of serologically or PCR-confirmed IM with an incomplete clinical picture or virocytes of less than 3 percent. Such a classification made it possible to stratify patients according to clinical manifestations and to assess the diagnostic value of different criteria for each form of the disease.

Statistical data processing was performed using Python 3.9 and the libraries pandas 1.4.2, numpy 1.22.3, scipy 1.8.0, scikit-learn 1.0.2, statsmodels 0.13.2, and matplotlib 3.5.1 for visualization of the results. Checking the normality of distribution of quantitative variables was carried out using the Shapiro–Wilk test and analysis of Q–Q plots. Since most indicators did not correspond to a normal distribution, the data were presented as median with interquartile range, which is a more appropriate approach for describing non-normally distributed data. Comparison of quantitative indicators between the three groups (typical IM, atypical IM, control) was performed using the nonparametric Kruskal-Wallis test. When statistically significant differences were identified, pairwise comparisons were performed using the Mann–Whitney U-test with Bonferroni correction for multiple comparisons. This correction was necessary to control the type I error in multiple statistical tests. For comparison of two independent groups, the Mann-Whitney U-test was applied. Categorical variables were presented as absolute numbers and percentages. Comparison of frequencies between groups was carried out using Pearson's chi-square test. Differences were considered statistically significant at $p<0.05$.

To determine the diagnostic value of individual clinical and laboratory parameters, ROC analysis was performed with construction of the corresponding curves and calculation of the area under the curve. AUC values were interpreted according to widely accepted criteria. Optimal cutoff values for each parameter were determined using the Youden index method, which maximizes the sum of sensitivity and specificity. The Youden index was calculated using the formula J = sensitivity + specificity − 1. For each cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value were calculated with the corresponding 95 % confidence intervals using the Wilson method.

Univariate logistic regression analysis was conducted to determine the association of each clinical and laboratory parameter with the diagnosis of infectious mononucleosis. The results were presented as odds ratios with 95 % confidence intervals. Statistical significance was assessed using the Wald test. This stage of the analysis allowed identification of potential predictors of the diagnosis that could be included in the multivariate model.

Multivariate logistic regression analysis was performed using a stepwise selection method based on the Akaike information criterion to select the final model. All parameters that demonstrated a statistically significant association with the diagnosis in the univariate analysis were included in the initial model. The quality of the final model was assessed using the Hosmer–Lemeshow test.

For the analysis of factors associated with the length of hospitalization, Spearman correlation analysis was applied due to the non-normal distribution of the data.

Based on the results of the ROC analysis and logistic regression, a simple scoring system was developed for rapid assessment of the probability of infectious mononucleosis. The scale criteria included four laboratory parameters with the highest diagnostic value (AUC>0.90). Each parameter was assigned 3 points when exceeding the optimal cutoff value determined using the Youden index method. The theoretical score range was from 0 to 12. Validation of the scale was performed on the entire cohort of patients with construction of an ROC curve and determination of the optimal cutoff value for diagnosing IM. For each possible cutoff value of the scale, diagnostic characteristics–sensitivity, specificity, accuracy, positive predictive value, and negative predictive value–were calculated.

The study was approved by the Bioethics Committee of the medical institution. The study was conducted in accordance with the principles of the Declaration of Helsinki and the standards of Good Clinical Practice (GCP). Data confidentiality was ensured through anonymization of medical documentation, with each patient assigned a unique code and personal information stored separately from clinical data. Only researchers directly involved in the project had access to the database.

Research Results and their Discussion

The medical records of 159 patients aged 16 to 65 years who underwent inpatient treatment with suspected IM were examined and analyzed. Based on the analysis of clinical and laboratory data, the patients were divided into three groups. Typical IM was identified in 86 individuals, accounting for 54.1 % of the total sample; atypical IM was observed in 51 patients (32.1 %); and the control group with acute respiratory viral infection consisted of 22 individuals, representing 13.8 %.

The median age in the overall cohort was 22 years, with no statistically significant differences in age distribution between the groups. Women made up 49.7 % of the study population, and the sex ratio was approximately equal across all three groups, indicating the representativeness of the sample.

The clinical presentation of the disease demonstrated significant differences between the groups, which held important diagnostic value. The classic triad of symptoms was observed in all patients with a typical course of IM

without exception. In contrast, among patients with atypical IM, pharyngitis was diagnosed in only 39.2 % of cases, and lymphadenopathy was detected in 49.0 %. In the control group with ARVI, pharyngitis occurred in 72.7 % of patients; however, systemic lymphadenopathy was a rare finding, present in only two individuals (9.1 %). Splenomegaly, traditionally considered one of the pathognomonic symptoms of IM, was detected in 60.5 % of patients with a typical course. Interestingly, among those with atypical IM, splenic enlargement was somewhat less frequent–observed in 47.1 % of cases–although this difference did not reach statistical significance. None of the patients in the control group had splenomegaly on ultrasound examination, which supports the specificity of this feature for IM within the context of this study. Hepatomegaly proved to be a less specific sign, occurring with similar frequency across all groups (12.8 % in typical IM, 13.7 % in atypical IM, and 13.6 % in ARVI). A detailed distribution of symptoms is presented in Table 1.

Particular attention is drawn to the fact that palatal petechial enanthema, which some authors consider a highly specific sign of IM, was observed exclusively in patients with a typical course of the disease, occurring in 44.2 % of cases. None of the patients with atypical IM exhibited this clinical sign.

It is well known that hematological parameters have important diagnostic value in IM. In our study, they demonstrated clear patterns that allowed differentiation of IM from other respiratory infections. The total leukocyte count in peripheral blood was significantly higher in patients with IM compared to the control group. In typical IM, it was 11.2×10^9/L, and in atypical IM, 10.8×10^9/L, compared with the control group with ARVI. However, the most informative changes were qualitative alterations in the leukocyte formula. Thus, a marked increase in lymphocytes (60 % or higher) in patients with typical IM substantially exceeded the values in the control group (32 % to 42 % lymphocytes). Interestingly, in atypical IM, lymphocytosis was somewhat less pronounced, amounting to 57 %, although the difference from the typical form was not statistically significant. This indicates that lymphocytosis is a characteristic feature of IM regardless of the clinical form of the disease. At the same time, virocytes proved to be the most specific laboratory marker of IM, as confirmed by our study results. In typical IM, the median virocyte count was 20 %, and in atypical IM, 16 %, whereas in the control group, atypical forms of lymphocytes were practically absent, amounting to only 1 %. Statistical analysis confirmed the high discriminative capacity of this parameter across all three groups. It is noteworthy that even in patients with atypical IM, the relative number of virocytes differed significantly from the control values. Detailed laboratory parameters are presented in Table 2.

Biochemical indicators of liver function changed predictably in patients with infectious mononucleosis, which is consistent with widely recognized scientific data on hepatic involvement in this disease. Thus, ALT activity increased to 75 U/L (median) in typical IM, which was almost three times higher than the control values. In atypical IM, hepatocellular cytolysis was slightly less pronounced but still significantly different from normal, with a median ALT level of 67 U/L. A similar pattern was observed for AST and LDH activity. The LDH level was particularly indicative: in typical IM, it reached 590 U/L, almost twice the value in the control group, reflecting the intensity of the pathological process.

An elevated body temperature accompanied the clinical presentation in most patients; however, the nature of the fever response differed substantially between groups. In typical IM, the median body temperature reached 38.5 °C, whereas in atypical cases the fever was milder, at 37.8 °C. In the control group with ARVI, the temperature usually did not exceed subfebrile values, remaining around 37.5 °C. This difference is of important diagnostic value in the differential diagnosis of various forms of the disease.

A detailed comparison of the clinical and laboratory characteristics of the two forms of IM revealed several noteworthy features that may have practical significance. Although both forms are caused by the Epstein–Barr virus

Table 1

Frequency of clinical symptoms in the study groups

Symptom	Typical IM (n=86)	Atypical IM (n=51)	ARVI (n=22)	χ^2	p-value
Pharyngitis	86 (100.0 %)	20 (39.2 %)	16 (72.7 %)	68.82	<0.001
Lymphadenopathy	86 (100.0 %)	25 (49.0 %)	2 (9.1 %)	94.74	<0.001
Splenomegaly	52 (60.5 %)	24 (47.1 %)	0 (0.0 %)	25.69	<0.001
Hepatomegaly	11 (12.8 %)	7 (13.7 %)	3 (13.6 %)	3.29	0.193
Rash	24 (27.9 %)	16 (31.4 %)	1 (4.5 %)	8.79	0.012
Palatal petechiae	38 (44.2 %)	0 (0.0 %)	1 (4.5 %)	39.27	<0.001

and share similar pathogenetic mechanisms, the clinical presentation and certain laboratory parameters showed statistically significant differences, allowing differential diagnosis between them. The most prominent difference was the percentage of virocytes in peripheral blood. As mentioned earlier, in typical IM these cells accounted for an average of 20 % of the total leukocyte count, whereas in atypical IM they constituted only 16 %. This difference may seem modest, but it has important diagnostic value, particularly in patients with mild clinical symptoms in whom establishing the diagnosis can be challenging. The fever response also differed considerably: while in typical IM the temperature often reached febrile levels, in atypical cases it rarely exceeded 38 °C. This observation is consistent with the overall clinical picture, as the atypical form is characterized by less pronounced intoxication symptoms and a milder course, which complicates timely diagnosis in such patients. An interesting finding was the LDH level, which appeared to be the only biochemical marker capable of differentiating the two forms of the disease–something not reported in the available literature. In typical IM, the median LDH level reached 590 U/L, markedly higher than in atypical IM, where it was 480 U/L. Considering that LDH reflects the degree of tissue destruction, this may be associated with more pronounced systemic inflammation in the typical form. The percentage of lymphocytes was also slightly higher in typical IM (60 % vs. 57 %), although this difference was less significant compared with other parameters. Notably, aminotransferase levels did not show statistically significant differences between the two forms, potentially indicating a similar degree of hepatic involvement regardless of the clinical variant. This observation is of practical relevance, suggesting that liver function tests cannot be used for differential diagnosis between typical and atypical IM.

Further, to determine the diagnostic value of each individual laboratory parameter, we performed a ROC analysis, which allowed us to assess the ability of each model to distinguish patients with infectious mononucleosis from patients in the control group. The results were quite unexpected: several routine parameters demonstrated exceptional discriminatory power, confirming their value in the diagnostic process. For example, virocytes showed absolute diagnostic accuracy, with an area under the ROC curve equal to 1.0. The optimal cutoff value, determined using the Youden index method, was 3 %. At this cutoff, both sensitivity and specificity reached 100 %, which is a relatively rare result in clinical diagnostics. In fact, the presence of virocytes at 3 % or higher virtually guarantees a diagnosis of IM, making this parameter the most valuable diagnostic criterion. At the same time, the percentage of lymphocytes also demonstrated high diagnostic value, with an area under the curve (AUC) of 0.970. The optimal cutoff value was 50 %, at which sensitivity reached 87.6 % and specificity 100 % (the data are presented in Table 3 and visualized in Figure 1). This means that lymphocytosis above 50 % in a patient with an appropriate clinical picture virtually excludes alternative diagnoses and highly likely indicates IM.

Biochemical markers of liver involvement proved no less informative for the diagnosis of IM. ALT, with an AUC of 0.972 and a cutoff value of 36 U/L, provided a sensitivity of 92 % and a specificity of 100 %. Similar results were demonstrated by LDH, with an AUC of 0.930, an optimal cutoff value of 392 U/L, sensitivity of 81.8 %, and specificity of 95.5 %.

Table 2

Hematological and biochemical parameters in the study groups

Indicator	Typical IM (n=86)	Atypical IM (n=51)	ARVI (n=22)	p-value
Leukocytes, $\times 10^9$/L	11.2 (9.1;13.5)	10.8 (8.9;13.2)	7.8 (6.7;9.3)	<0.001
Lymphocytes, %	60 (57;66)	57 (52;65)	40 (32;42)	<0.001
Virocytes, %	20 (13;26)	16 (7;19)	1 (1;2)	<0.001
Neutrophils, %	29 (24;33)	32 (26;37)	52 (48;57)	<0.001
Monocytes, %	7 (5;9)	7 (5;9)	6 (4;8)	0.187
ALT, U/L	75 (52;125)	67 (45;93)	28 (22;33)	<0.001
AST, U/L	62 (45;95)	54 (38;82)	29 (24;34)	<0.001
LDH, U/L	590 (485;660)	480 (380;555)	320 (265;360)	<0.001
Alkaline phosphatase, U/L	98 (78;126)	92 (75;118)	89 (72;108)	0.215
ESR, mm/h	18 (12;25)	15 (10;22)	12 (8;17)	0.012

Note. Data are presented as median (interquartile range). p – value was calculated using the Kruskal-Wallis test for comparison of the three groups. ALT – alanine aminotransferase, AST – aspartate aminotransferase, LDH – lactate dehydrogenase, ESR – erythrocyte sedimentation rate.

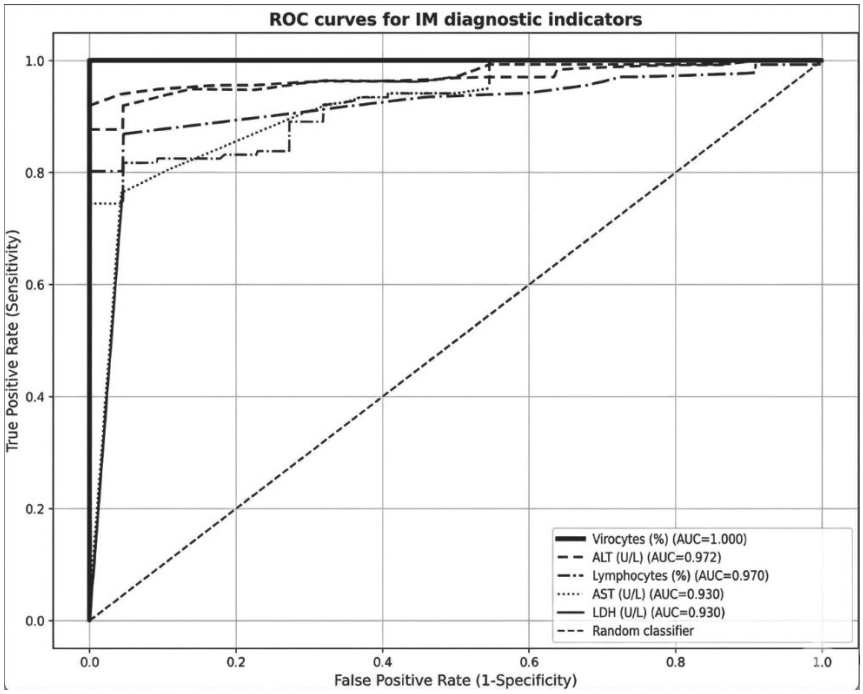

Fig. 1. ROC curves for laboratory biomarkers of infectious mononucleosis.

Table 3

Diagnostic value of laboratory biomarkers

Indicator	AUC	95 % CI	Threshold	Sensitivity	Specificity	Youden index
Virocytes (%)	1.000	1.000-1.000	≥3	100.0 %	100.0 %	1.000
ALT (U/L)	0.972	0.948-0.996	≥36	92.0 %	100.0 %	0.920
Lymphocytes (%)	0.970	0.945-0.995	≥50	87.6 %	100.0 %	0.876
LDH (U/L)	0.930	0.898-0.962	≥392	81.8 %	95.5 %	0.772
AST (U/L)	0.930	0.897-0.963	≥34	86.9 %	95.5 %	0.823
ESR (mm/h)	0.879	0.832-0.926	≥15	72.3 %	90.9 %	0.632
Leukocytes ($\times 10^9$/L)	0.810	0.749-0.871	≥9.5	75.2 %	81.8 %	0.570

Note. AUC – area under the ROC curve, CI – confidence interval. The threshold value (Threshold) was determined using the Youden index method (maximizing the sum of sensitivity and specificity).

In addition, the erythrocyte sedimentation rate, which is often criticized for its low specificity, demonstrated acceptable diagnostic value in our study, with an AUC of 0.879. At a threshold value of 15 mm/h, the sensitivity was 72.3 percent and the specificity 90.9 percent. This indicates that ESR may serve as a useful supplementary criterion, especially in settings with limited access to more specific laboratory tests, which is of practical importance for primary care physicians. Finally, the total leukocyte count proved to be the least informative (AUC 0.810), confirming the view that qualitative changes in the leukocyte formula have significantly greater diagnostic value compared with quantitative indicators. Therefore, in the diagnosis of IM, attention should be focused primarily on the alterations in the leukocyte formula rather than on the total leukocyte count.

Next, to determine the influence of individual parameters on the likelihood of establishing a diagnosis of IM, a univariate logistic regression analysis was performed, which made it possible to quantitatively assess this effect. The results confirmed the high predictive value of both clinical symptoms and laboratory biomarkers, which also has important practical significance. Thus, among the clinical signs, splenomegaly proved to be the strongest predictor, with an odds ratio of 10.2. This means that the presence of an enlarged spleen increases the likelihood of an IM diagnosis more than tenfold, making spleen palpation and ultrasound mandatory components of the diagnostic

process. Hepatomegaly was also closely associated with the diagnosis, although its predictive strength was lower, with an odds ratio of 3.3.

Laboratory parameters demonstrated strong associations with the diagnosis even when each component was analyzed separately. For example, each additional percent of virocytes increased the odds of diagnosing IM by a factor of 1.3. Considering that the difference between typical IM and the control group was about 19 %, the cumulative effect was quite significant for diagnosis. At the same time, an increase in body temperature by each degree was associated with an almost twofold increase in the odds of diagnosing IM. This explains why fever remains one of the key clinical diagnostic criteria, despite its low specificity and sensitivity. However, it should be remembered that the absence of hyperthermia does not exclude IM, especially in the atypical course of the disease. Lymphocytosis and elevated liver enzyme levels also showed strong associations with the diagnosis. An increase in lymphocytes by each 10 % raised the odds of diagnosing IM by approximately 1.28 times, while an increase in ALT by 10 U/L raised the odds by 1.22 times. These results support the inclusion of these parameters in diagnostic algorithms.

Given that we obtained several rather robust indicators that can be used for the diagnosis of IM, including atypical forms, we conducted a multivariable analysis to create an optimal set of diagnostic criteria for further development of a diagnostic scale. This analysis revealed that the independent predictors of the diagnosis remained virocytes, LDH level, body temperature, and the presence of splenomegaly. Other indicators lost statistical significance after adjustment for these four factors, indicating a certain degree of collinearity among the laboratory markers of inflammation.

Thus, based on the results of ROC analysis and logistic regression, a simple diagnostic scale for IM was developed. The main goal of creating the scale was to provide practicing physicians with a convenient tool for rapid assessment of the likelihood of infectious mononucleosis using routine laboratory parameters available in most healthcare facilities. The scale includes four parameters that demonstrated the highest diagnostic value and are widely accessible: virocytes, lymphocyte percentage, ALT level, and LDH. Each of these indicators contributed equally to the final score – 3 points for exceeding the corresponding threshold value – making the scale easy to remember and convenient for clinical use. The diagnostic scale itself is presented in Table 4. Theoretically, the possible score range of the scale is from 0 to 12, although in practice most patients score between 0 and 9 points.

Table 4

Structure and components of the diagnostic scale

Component	Threshold value	Points
Virocytes	≥3 %	3
Lymphocytes	≥50 %	3
ALT	≥36 U/L	3
LDH	≥392 U/L	3
Maximum score		**12**

Analysis of the distribution of scores revealed clear stratification of patients, confirming the diagnostic value of the scale. In the control group, the median score was 0 points, in atypical IM it was 8 points, and in typical IM it reached 10 points. The differences between all three groups were highly statistically significant, indicating the scale's ability to effectively differentiate various clinical conditions. The diagnostic characteristics of the scale were evaluated at different threshold values to identify the optimal cut-off score at which the presence of IM can be assumed (Table 5). It was found that the optimal balance between sensitivity and specificity was achieved at the threshold of 6 points. At this value, the sensitivity was 95.6 %, the specificity 100 %, and the overall diagnostic accuracy 96.2 %, which represents very high performance for a diagnostic test.

Table 5

Diagnostic characteristics of the proposed scale at different threshold values

Threshold	Sensitivity	Specificity	Accuracy	PPV	NPV
≥3	100.0 %	100.0 %	100.0 %	100.0 %	100.0 %
≥4	99.3 %	100.0 %	99.4 %	100.0 %	95.7 %
≥5	99.3 %	100.0 %	99.4 %	100.0 %	95.7 %
≥6	**95.6 %**	**100.0 %**	**96.2 %**	**100.0 %**	**78.6 %**
≥7	94.9 %	100.0 %	95.6 %	100.0 %	75.9 %
≥8	79.6 %	100.0 %	82.4 %	100.0 %	44.0 %
≥9	78.1 %	100.0 %	81.1 %	100.0 %	42.3 %

Note. PPV – positive predictive value, NPV – negative predictive value. The recommended threshold is highlighted in bold.

It is important to emphasize that at a threshold of 6 points, the positive predictive value (PPV) was 100 %, meaning that no patient without infectious mononucleosis scored 6 or more points. In contrast, the negative predictive value (NPV) was somewhat lower, at 78.6 %, indicating the presence of a certain number of false-negative results. This is entirely expected and clinically acceptable, as a low score on the scale does not definitively rule out the diagnosis but only indicates the need for further examination and dynamic monitoring.

Regarding additional diagnostic methods, serological confirmation of IM remains the gold standard, but the availability and informativeness of other tests vary significantly. In our study, the diagnostic performance of three of the most common methods was analyzed: the heterophile antibody test (Monospot), detection of VCA IgM antibodies to Epstein-Barr virus, and PCR for EBV DNA.

The Monospot test, which detects heterophile antibodies and is widely used due to its simplicity and rapid execution, demonstrated a sensitivity of 75.2 %. This means that approximately one-quarter of patients with confirmed infectious mononucleosis will have a negative result, which limits the diagnostic value of the test. Its specificity, however, was 100 %, meaning that a positive result almost always indicates IM. It is important to note the particularity of our sample–these were hospitalized patients already suspected of having IM and referred for hospitalization by other physicians–so at the outpatient stage, the sensitivity of diagnostic tests may be even lower. The positive predictive value reached 100 %, whereas the negative predictive value was much lower, only 39.3 %, making a negative Monospot result insufficient to rule out the diagnosis.

Detection of specific VCA IgM antibodies showed significantly better diagnostic performance compared to the heterophile test. The sensitivity of this method was 88.3 %, and specificity was 100 %, making VCA IgM the optimal choice for serological confirmation of the diagnosis, especially in doubtful cases or in atypical disease courses when the clinical picture is incomplete. The negative predictive value of 57.9 % indicates that a negative result substantially reduces the likelihood of IM but does not completely exclude it.

Analysis of the effectiveness of polymerase chain reaction (PCR) on patients' saliva samples revealed high sensitivity of the method – 89.8 %. However, it is important to remember that PCR detects viral DNA regardless of the phase of infection, whether during acute infection or latent carriage. Since most adults are EBV carriers following previous mononucleosis or asymptomatic infection, a positive PCR result cannot reliably confirm acute IM. This limits the method's utility for routine diagnostics, although it may be useful in specific situations, such as in immunosuppressed patients or those with severe atypical disease courses.

Considering all the above, a combined approach that integrates clinical assessment using the proposed scale with serological confirmation achieves optimal diagnostic accuracy. In patients with high scale scores (9 or more), a positive VCA IgM result confirms the diagnosis with approximately 100 % probability, whereas in cases with moderate scores (3 to 6), serology becomes the decisive factor for clinical decision-making compared to PCR. This approach allows for rational use of diagnostic resources.

Integration of the obtained results allowed the development of a practical diagnostic algorithm that structures the examination process for patients suspected of having IM. The algorithm is built on the principle of sequential screening with gradual narrowing of the differential diagnosis, optimizing the diagnostic process.

The first step involves clinical assessment for the presence of the classic triad of symptoms: elevated body temperature, pharyngitis, and lymphadenopathy. If the patient exhibits at least two of the three symptoms, a complete blood count with leukocyte formula and atypical lymphocyte (virocyte) assessment is recommended. In the absence of this triad, IM is unlikely, and alternative diagnoses should be considered, such as viral or bacterial tonsillitis or other viral infections.

The second step includes laboratory testing, which is crucial for diagnostic verification. The key parameter at this stage is the percentage of virocytes. If it is 3 % or higher, the likelihood of IM increases sharply, and the patient automatically proceeds to the third step of the algorithm. If the virocyte count is below 3 %, further evaluation of the so-called atypical laboratory profile is necessary, which includes assessing the percentage of lymphocytes, ALT levels, and the presence of splenomegaly. If at least two of these three criteria are positive (lymphocytes ≥50 %, ALT ≥36 U/L, presence of splenomegaly), the diagnosis of atypical IM remains probable and requires further confirmation.

The third step involves calculating the score using the proposed scale based on four laboratory parameters. Patients who score 6 points or more have a high or very high probability of IM. In these cases, a preliminary clinical diagnosis can be established and appropriate therapy initiated even before serological test results are available, allowing treatment to begin without delay. For a score of 3 points, mandatory serological confirmation is recommended, as the clinical-laboratory picture may correspond to either atypical IM or other viral infections.

The fourth step includes serological verification of the diagnosis, which is definitive in complex cases. For

patients with 6 points or more, serology serves a confirmatory function, whereas with 3 points, it becomes decisive for diagnosis. The optimal approach involves testing for VCA IgM and EBNA IgG. A combination of positive VCA IgM and negative EBNA IgG confirms an acute primary infection. The presence of both types of antibodies may indicate reactivation or a late phase of the disease. Overall, validation of the proposed algorithm is crucial, as it may demonstrate very high sensitivity, potentially reducing the average time to diagnosis to 2–3 days compared to 5–8 days with the traditional approach, which has important practical significance for optimizing patient management.

In addition to the issue of diagnosis, we analyzed the factors that influence the duration of hospitalization in patients with typical and atypical IM. The analysis revealed significant differences in the length of hospital stay between patients with the typical and atypical courses of infectious mononucleosis, which is important for inpatient care planning. The median duration of inpatient treatment in typical IM was 13 days, whereas in the atypical form patients were discharged much earlier, after 10 days from the moment of hospitalization. The control group with ARVI had the shortest hospital stay, 5 days, which reflects the milder course of these illnesses.

Spearman correlation analysis allowed us to identify factors associated with longer hospitalization and which can be used to predict the course of the disease. The strongest correlation was demonstrated by the lactate dehydrogenase level (r=0.82), confirming its value as a marker of disease severity and allowing this parameter to be used for patient stratification. Virocytes also showed a significant association with the duration of treatment (r=0.71), as did the ALT level (r=0.65). Body temperature at admission moderately correlated with the duration of hospitalization (r=0.51). Interestingly, the presence of a typical course of IM compared with the atypical form was also associated with a longer hospital stay (r=0.45), which likely reflects the overall greater severity of clinical manifestations in the typical form of the disease (table 6). This observation has practical value for predicting the length of hospitalization.

A noteworthy finding was the difference in the time to diagnosis between the two forms of IM. In the typical course, the median time from the onset of the first symptoms to diagnostic confirmation was 5 days, whereas in the atypical form this period increased to 8 days. This means that patients with atypical IM undergo the diagnostic process 60 % longer, leading to more frequent unjustified antibiotic therapy, additional diagnostic procedures, and delayed initiation of appropriate treatment, which may affect disease outcomes.

Table 6

Factors associated with the duration of hospitalization

Factor	Correlation coefficient (ρ)	p-value	Strength of association
LDH	0.82	<0.001	Strong
Virocytes	0.71	<0.001	Strong
ALT	0.65	<0.001	Moderate
Temperature	0.51	<0.001	Moderate
Typical IM	0.45	<0.001	Moderate
Splenomegaly	0.28	0.001	Weak
Lymphocytes (%)	0.22	0.005	Weak

Note. Spearman's correlation coefficient (ρ) was used due to the non-normal distribution of most variables.

The duration of empirically prescribed antibiotic therapy before the diagnosis of IM was established did not differ between the groups, amounting to 9 days in the typical course and 8 days in the atypical form. This indicates that regardless of the form of the disease, most patients receive antibiotics during the first week of illness until the true etiology becomes clear. Considering that antibacterial therapy in IM is not only unjustified but also potentially harmful (especially when ampicillin or amoxicillin are prescribed, as they may cause a characteristic rash), these findings highlight the importance of rapid and accurate early diagnosis.

Thus, considering all the obtained results, it can be stated that the developed diagnostic scale and clinical algorithm can significantly reduce the time to diagnosis, which is an important advantage from the perspective of clinical practice. Moreover, the use of the algorithm we propose allows standardization of the diagnostic approach and reduces the frequency of unjustified antibiotic prescriptions, which has both medical and economic significance for the healthcare system of our country, especially during the period of martial law.

Although infectious mononucleosis (IM) has been studied for decades, its diagnosis continues to pose certain challenges for physicians across various specialties. The classical triad of symptoms is predominantly characteristic of typical IM, whereas atypical forms lack one or more of the main clinical manifestations [5, 11]. According to different estimates, 15 to 25 % of primary Epstein-Barr virus infections present atypically; in our sample, such forms accounted for 32.1 % of all IM cases [4, 16]. These patients are most often prescribed antibiotics due to the misdiagnosis of bacterial tonsillitis or other infectious diseases.

In our study, we found that virocytes, as a diagnostic marker, demonstrated maximal discriminative ability with

an AUC of 1.0 at a threshold of 3 % or higher. Recent publications note that a virocyte count exceeding 10 % almost always indicates IM [1]. However, we observed that even at 3 %, this marker achieved 100 % sensitivity and specificity. A lymphocyte proportion of 50 % or higher provided a sensitivity of 87.6 % and specificity of 100 % in our sample, slightly outperforming Hogland's classical criteria at the same threshold [17]. Nevertheless, pronounced lymphocytosis can also occur in other viral infections, such as cytomegalovirus (CMV) infection or primary HIV [18]. Therefore, assessing this parameter alone, without considering virocytes and the patient's clinical data, may lead to diagnostic errors. ALT with a threshold of 36 U/L showed a sensitivity of 92 % and specificity of 100 % in our sample, making it a useful additional marker when IM is suspected. Mild elevations in liver enzymes occur in 80–90 % of IM patients due to transient hepatic involvement [19,20]. However, increased transaminase activity alone does not indicate a specific disease, as it reflects hepatocellular injury that may occur in viral hepatitis, toxic liver damage, and many other conditions. At the same time, LDH proved to be the only biochemical marker that significantly differentiated between typical and atypical IM courses. The median LDH was 590 U/L in typical IM compared to 480 U/L in atypical IM. This aspect is rarely discussed in the available literature, although LDH elevation in IM is mentioned as a nonspecific marker of tissue destruction [21]. Higher LDH values in typical IM may be related to a more robust immune response and greater systemic inflammation, but this remains speculative, since liver injury markers, ALT and AST, did not differ statistically between the two forms, indicating that hepatocyte involvement was roughly equivalent regardless of the clinical form of IM.

The diagnostic scale we developed, based on laboratory parameters selected using various statistical methods, allowed us to stratify patients according to disease risk and simplify the diagnostic process. Similar attempts to create such scales have been described in several publications, where authors aimed to reduce reliance on relatively expensive serological tests [22]. However, most of these studies focused on children and did not specifically address atypical forms of the disease in adults. Our scale, in contrast, utilizes routine laboratory markers that are available in any hospital. Furthermore, based on the obtained data and the scale, we also developed a diagnostic algorithm that involves stepwise patient assessment, starting with the evaluation of clinical symptoms and concluding with serological confirmation. This stepwise approach enables more efficient use of diagnostic resources and faster establishment of the diagnosis. Other authors also emphasize the need for standardized algorithms to improve the accuracy of IM diagnosis and reduce unjustified medication prescriptions [2,8]. Importantly, the algorithm specifically addresses patients with atypical IM, which are more challenging to diagnose.

It is also worth highlighting our work with machine learning. We applied a Random Forest algorithm to our dataset with the aim of stratifying patients into groups – typical IM, atypical IM, and ARVI-like illnesses. The algorithm achieved an overall accuracy of 91.7 % on our sample, which appears reasonably good. Interestingly, the feature importance analysis in the model highlighted the same parameters that showed the highest diagnostic value in our previous ROC analysis. This similarity between classical statistical results and machine learning outcomes supports the validity of our selected diagnostic criteria for the scale. However, the Random Forest model had notable limitations, especially in differentiating typical from atypical IM. Out of 15 cases of atypical IM, the model correctly identified only 11, while 4 were misclassified as typical IM. Despite the relatively high overall accuracy, the machine learning model did not demonstrate advantages over the traditional diagnostic scale, which is simpler to use and does not require specialized software. This is likely because, for the binary classification task (presence or absence of IM) based on well-selected laboratory markers, complex algorithms do not significantly improve accuracy compared to logistic regression or a simple scoring scale. Similar conclusions are reported in a review on the application of artificial intelligence in infectious disease diagnostics, emphasizing the importance of balancing model complexity with practical utility [23].

Furthermore, machine learning models require regular validation on independent datasets, which was not feasible in our setting. Therefore, in the case of the logistic regression model and the Random Forest algorithm, overfitting and/or memorization of specific characteristics of the patient sample could have occurred, which represents a limitation of our study. Moreover, the Random Forest model faced an additional limitation due to the relatively small training sample. While 111 patients for training and 48 for testing are sufficient for classical statistical analysis, these numbers may be insufficient for deep learning approaches to detect complex nonlinear relationships. Considering this, we did not include the results of the machine learning algorithms in the main part of this publication. Thus, these results should be regarded as preliminary and require validation in larger cohorts.

Regarding other potential limitations of the study, the primary one is its retrospective design, which imposes certain constraints on the interpretation of results. For instance, reliance on medical records did not allow for a systematic assessment of clinical parameters that may have

diagnostic value. We were unable to accurately measure the size of lymph nodes, liver, or spleen in centimeters, nor determine the precise duration of symptoms before presentation in all cases. Patients were included after hospitalization, which may introduce a bias toward more severe cases or cases where IM is easier to diagnose. Mild outpatient forms of IM that did not require hospitalization were not captured in our analysis, although it should be noted that such cases are common. Additionally, the control group was relatively small compared to the IM patient groups. Statistically, this did not pose major issues, but a larger control group would provide a more precise assessment of the specificity of diagnostic criteria.

In the future, prospective studies could validate the developed diagnostic algorithm in an independent cohort, assess its cost-effectiveness, and compare it with existing protocols. Based on such analysis, it may be appropriate to consider expanding the diagnostic scale with additional biomarkers to improve its accuracy in complex Cases with Atypical Presentations.

Conclusions

Atypical forms of infectious mononucleosis constitute a significant proportion of hospitalized patients. Among them, pharyngitis was observed in only 39.2 % of patients with atypical presentation, and lymphadenopathy in 49.0 %.

It was established that virocytes are the most specific laboratory marker of infectious mononucleosis, with relatively high sensitivity and specificity at a threshold value of 3 % or higher. This parameter reliably distinguishes patients with infectious mononucleosis from those with acute respiratory viral infections already at the stage of initial laboratory examination.

Elevated alanine aminotransferase (ALT) above 36 U/L and lactate dehydrogenase (LDH) above 392 U/L are informative additional diagnostic criteria for infectious mononucleosis, with sensitivities of 92 % and 81.8 %, respectively. LDH was the only biochemical marker that reliably differed between typical and atypical disease courses.

The developed diagnostic scale based on four laboratory parameters provides effective stratification of patients according to the risk of infectious mononucleosis. Patients with a total score of 6 or higher have a high likelihood of disease, whereas those with lower scores can be considered as unlikely cases, allowing optimization of diagnostic resources and reduction of time to final diagnosis.

The proposed stepwise diagnostic algorithm enables structured patient evaluation for suspected infectious mononucleosis, starting from clinical assessment and ending with serological confirmation. The algorithm identifies patients with an atypical laboratory profile who require additional diagnostic attention.

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КЛІНІЧНА ТА ЛАБОРАТОРНА ХАРАКТЕРИСТИКА СУЧАСНОГО ПЕРЕБІГУ ІНФЕКЦІЙНОГО МОНОНУКЛЕОЗУ ТА АЛГОРИТМ ВСТАНОВЛЕННЯ ДІАГНОЗУ

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РЕЗЮМЕ. Мета роботи *– оцінити діагностичну значущість клінічних проявів і лабораторних маркерів у хворих на типовий та атиповий інфекційний мононуклеоз (ІМ) і сформувати діагностичний алгоритм на підставі отриманих результатів.*

Пацієнти і методи. *До багатоцентрового ретроспективного когортного дослідження включено 159 пацієнтів віком 16–65 років, поділених на групи типового ІМ (n=86), атипового ІМ (n=51) та гострої респіраторної вірусної інфекції (n=22). Здійснено аналіз клінічних симптомів, ультразвукових параметрів печінки і селезінки, гемограм, біохімічних показників (аланінамінотрансферази (АЛТ), аспартатамінотрансферази (АСТ), лактатдегідрогенази (ЛДГ) та лужної фосфатази (ЛФ)), а також результатів полімеразної ланцюгової реакції (ПЛР) і серологічних тестів. Статистичну обробку здійснено із застосуванням Python.*

Результати досліджень. *Виявлено суттєві міжгрупові відмінності. Найвищу діагностичну інформативність продемонстрували віроцити (20 % при типовому ІМ, 16 % – при атиповому, 1 % – у контролі), лімфоцитоз і підвищення активності АЛТ, АСТ і ЛДГ. ROC-аналіз підтвердив провідну роль віроцитів (AUC=1,0), а також значущість АЛТ (AUC=0,972), лімфоцитів (AUC=0,970) і ЛДГ (AUC=0,930). На підставі порогових значень віроцитів ≥3 %, лімфоцитів ≥50 %, АЛТ ≥36 од./л і ЛДГ ≥392 од./л сформовано 12-бальну шкалу з чутливістю 95,6 % та специфічністю 100 %.*

Висновки. *Віроцити є найбільш специфічним маркером ІМ, тоді як підвищена активність АЛТ та ЛДГ виступають важливими допоміжними критеріями, причому ЛДГ дозволяє диференціювати типовий і атиповий перебіг. Розроблена шкала оптимізує діагностику ІМ.*

Ключові слова: *інфекційний мононуклеоз, типовий перебіг, атиповий перебіг; віроцити; лімфоцитоз; трансферази; ЛДГ; діагностичний алгоритм.*

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