http://doi.org/10.35784/iapgos.9055 *received: 22.01.2026 | revised: 18.02.2026 | accepted: 05.06.2026 | available online: 30.06.2026*

EVALUATION OF INFORMATIONAL DIAGNOSTIC CRITERIA AND SEVERITY BIOMARKERS USING A DISCRIMINATION MODEL IN PATIENTS WITH COVID-19

Gryhoriy Gradil[1], Oleg Avrunin[2], Kateryna Yurko[1], Nataliia Shushlyapina[1], Yuliia Kalashnyk-Vakulenko[1], Mariia Shostatska[3], Aigul Iskakova[4]

[1]Kharkiv National Medical University of the Ministry of Health of Ukraine, Kharkiv, Ukraine, [2]Kharkiv National University of Radio Electronics, Kharkiv, Ukraine, [3]Vinnytsia Academician D. K. Zabolotnyi Professional Medical College, Vinnytsia, Ukraine, [4]Kazakh National Research Technical University named after K.I. Satpayev, Almaty, Kazakhstan

Abstract*. The paper examines the features of viral pneumonias that in the future may be caused by highly pathogenic viruses (HPCoVs) (SARS-CoV-2, MERS-CoV, SARS-CoV), H5N1, H5N7 and influenza A (H1N1) pdm. Rapidly progressive viral pneumonia that develops in these diseases can lead to a fatal complication – acute respiratory distress syndrome (ARDS). Confirmation and refutation of the diagnosis of ARDS today is a difficult task that requires the development and improvement of diagnostic methods. To compare the diagnostic effectiveness of the methods, the possibility of using criteria and parametric recognition models was considered. The discrimination model was built on the basis of the quadratic normalized Euclidean distance between the vectors of mean values by state of quantities. The perspective of the work is to improve methods for assessing diagnostic criteria and severity biomarkers using a discrimination model based on quadratic notched Euclidean distance, which will allow improving the detection of ARDS – a fatal complication of respiratory system infection with highly pathogenic viruses.*

Keywords: ARDS, pneumonia viral, COVID-19, biomarkers, human health, medical diagnostic

OCENA INFORMACYJNYCH KRYTERIÓW DIAGNOSTYCZNYCH I BIOMARKERÓW CIĘŻKOŚCI PRZEBIEGU CHOROBY Z WYKORZYSTANIEM MODELU DYSKRYMINACYJNEGO U PACJENTÓW Z COVID-19

Streszczenie. *W niniejszym artykule przeanalizowano cechy wirusowych zapaleń płuc, które w przyszłości mogą być wywoływane przez wysoce zjadliwe wirusy (HPCoV) (SARS-CoV-2, MERS-CoV, SARS-CoV), H5N1, H5N7 oraz wirusa grypy A(H1N1)pdm. Szybko postępujące wirusowe zapalenie płuc, które rozwija się w przebiegu tych chorób, może prowadzić do śmiertelnego powikłania – zespołu ostrej niewydolności oddechowej (ARDS). Potwierdzenie lub wykluczenie diagnozy ARDS jest obecnie trudnym zadaniem, wymagającym opracowania i udoskonalenia metod diagnostycznych. W celu porównania skuteczności diagnostycznej metod rozważono możliwość zastosowania kryteriów i parametrycznych modeli rozpoznawczych. Model dyskryminacyjny zbudowano w oparciu o kwadratową znormalizowaną odległość euklidesową między wektorami średnich wartości stanów wielkości. Perspektywą pracy jest udoskonalenie metod oceny kryteriów diagnostycznych i biomarkerów ciężkości choroby przy użyciu modelu dyskryminacyjnego zbudowanego w oparciu o kwadratową znormalizowaną odległość euklidesową, co pozwoli na poprawę wykrywalności ARDS – śmiertelnego powikłania zakażeń układu oddechowego wywołanych przez wysoce zjadliwe wirusy.*

Słowa kluczowe: ARDS, wirusowe zapalenie płuc, COVID-19, biomarkery, zdrowie ludzkie, diagnostyka medyczna

Introduction

After the SARS-CoV-2/COVID-19 pandemic, the possibility of the next threat is predicted, which may be caused by highly pathogenic viruses (HPCoVs) (SARS-CoV-2, MERS-CoV, and SARS-CoV), H5N1, H5N7. The World Health Organization has adopted the conditional name X – disease for theoretically possible pathogens that can cause epidemics or pandemics with extremely high mortality. Infectious diseases COVID-19 and pandemic influenza A(H1N1)pdm09, which are prone to global spread and recurrence, also remain relevant. These diseases often develop rapidly progressive viral pneumonia, which can lead to a fatal complication – acute respiratory distress syndrome (ARDS). Confirmation and refutation of the diagnosis of ARDS today is a complex task, which dictates the need to develop and improve diagnostic methods and determine the diagnostic value of indicators, including discriminant analysis**.** Study design. A literature review on the problem under study was conducted in PubMed and Google Scholar with a search for articles devoted to the use of diagnostic criteria and biomarkers of severity in patients with ARDS complicating viral pneumonia in COVID-19 /SARS-CoV-2 and pandemic influenza within the limits of clinical sense. To compare the diagnostic effectiveness of the methods, the possibility of using criteria and models of parametric recognition (discrimination) was considered. References from individual studies and previous systematic reviews on the topic were searched manually. **The purpose of the work**. Improving the diagnosis of ARDS complicating viral pneumonia in patients with COVID-19/SARS-CoV-2 and pandemic influenza A(H1N1)pdm09: assessment of the diagnostic efficacy of oxygenation impairment indicators, radiological signs, and biomarkers using a discrimination model based on quadratic, unweighted Euclidean distance.

1. Analysis of literature

In the article [23] authors note that acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome associated with multiple pathophysiological abnormalities that manifests secondary to multiple etiological factors [23]. Lyons P. G. et al. [17] draw attention to the peculiarities of viral pneumonias – "SARS-CoV-2 pneumonia and influenza pneumonia differ markedly in terms of hospitalization trajectories, radiography, and outcome prognoses, with SARS-CoV-2 disease being more severe in all parameters evaluated". Studies have shown that there are some similarities in the mode of transmission and pathogenesis of influenza and COVID-19. Luo J.et al. [16] point out the widely recognized pathogenic mechanisms of influenza viruses that can cause extensive pulmonary oedema, pneumonia, alveolar haemorrhage, and contribute to the formation of ARDS or multiple organ failure, and note that there are still many unclear aspects in the pathogenesis of influenza and SARS-CoV-2, especially in the mechanism of tissue damage repair. The severe course of COVID-19 and pandemic influenza also leads to the development of ARDS. Meyer N. J. et al. [19], note that: "…The COVID-19 pandemic has caused an increase in ARDS and revealed the problems associated with this syndrome, in particular the unacceptably high mortality rate and the lack of effective pharmacotherapy". The role of radiological imaging in detecting pulmonary complications in the early stages of viral pneumonia, radiological characteristics of patients with SARS-CoV-2/COVID-19 coronavirus infection and pandemic influenza, and the difficulties of differentiating viral pneumonia are presented in the following works [5, 11–14]. Today, there is an increasing number of studies on the possibilities of using data obtained during CT radiological imaging to create systems for assessing the severity of viral pneumonia

and its complications of ARDS using artificial intelligence, machine learning, or tools based on deep learning and software. With a high frequency ARDS complicates the course of coronavirus infections, pandemic influenza, and avian influenza (H5N1). Hagens L. A. et al. [9] note that "the accuracy of diagnosing acute respiratory distress syndrome (ARDS) is associated with the risk of bias. There is a lack of validated diagnostic tests in an objective setting, which emphasizes the need for high-quality diagnostic studies in ARDS". Machnicki S. et al. [18, p. 653] in a review of published data on CT scans of patients with COVID-19 note that artificial intelligence is likely to play an increasing role in the assessment of CT images of a number of problems associated with COVID-19. Wang Y. et al. [27] emphasize that "Since the accuracy of ARDS diagnosis based on clinical syndrome alone has been questioned, countless studies have focused on identifying ARDS biomarkers". Hsu A. T. et al. [10] note that matrix metalloproteinases (MMPs) released by primed neutrophils into the circulation play a significant role in the pathophysiology of ARDS and increased plasma MMP-9 activity correlates with subsequent reductions in PaO2/FiO2 in patients who develop ARDS. Davey A. et al. [6] indicate that "inflammatory damage to the alveolar epithelium and endothelial capillary membrane is a central event in the pathogenesis of acute lung injury (ALI)/ARI and involves degradation of the basement membrane. Matrix metalloproteinases (MMPs) are involved in a variety of pulmonary pathologies and are capable of degrading all components of the extracellular matrix, including the basement membrane and key non-matrix mediators of lung injury, such as chemokines and cell surface receptors". The difficulty of predicting the onset of acute lung injury by assessing only clinical methods, which are useful but imperfect, is indicated by Agrawal A. et al. [1]. Joffre J. et al. [12] emphasize that at the time of presentation to the emergency department, patients with COVID-19 patients had elevated serum endothelial biomarkers (IL-6, IL-8, VEGF) that correlated with the severity of their disease. Fremont R. D. et al. [7, p. 2] suggested "that a panel of multiple biomarkers that reflect inflammation, lung epithelial and endothelial damage, fibrosis, and abnormalities in coagulation and fibrinolysis would have better sensitivity and specificity for the diagnosis of APL/ARDS than any single biomarker". Wang C. et al. [26] note that typical laboratory findings on admission to the hospital of COVID-19 patients are lymphopenia and bilateral opacities or induration on the KChest CT. According to the authors of the work [22], the assessment of severity of chest CT correlates well with laboratory parameters and can help in predicting the outcome of the disease with COVID-19. At the same time, the analysis of radiographic images is extremely difficult to automate, which is associated with the projection of a multitude of anatomical details onto each element of the formed image [20]. The absence of changes in chest CT cannot exclude COVID-19, especially in patients with recent symptoms. The final diagnosis must be confirmed by a positive PCR test, which is considered the "gold" standard. As noted, today there is an increasing number of studies on the possibilities of using data obtained from CT radiological visualization to create systems for assessing the severity of the disease using artificial intelligence, machine learning or tools based on deep learning and software. "A special place in this list is occupied by the intellectual analysis of medical data (Medical Data Mining – MDM), which sets as its main goal the diagnosis of patient conditions and the development of specific recommendations for treatment using the Data Mining apparatus primarily classification, clustering, prediction, association, identification and definition of changes (paths and faults detection). It should be noted that in most real situations that arise in MDM, it is impossible to use the already developed results of classical intellectual data analysis. This is explained by the high level of a priori and current uncertainty, which is inherent in the tasks of medical diagnostics" [2]. At the same time, in many real situations, the choice of options has to be made under the condition of a priori uncertainty, when, based on the available data, it is impossible to specify in advance which of the possible options must be chosen in order to ensure the achievement of the given goal [20]. Meyer N. J. et al. [19] rightly note that "no diagnostic test confirms or refutes the diagnosis of ARDS". The effectiveness of solving the tasks of monitoring the state of objects with random characteristics largely depends on the correct selection of the most informative set of features sensitive to changes in the properties of the object. Such control is implemented in the form of testing, the result of which is evaluated by reliability – the probability of making the right decision. The task is complicated by the fact that due to the uncertainty of the properties of the object, the selection of informative features becomes problematic, especially in cases of insufficient metrological support of information processes in the structure of the control system, which is often observed in medical diagnostics. Determining the optimal set of information features according to the criterion of maximum reliability is a classic task of statistical synthesis under conditions of a priori uncertainty [3, 21]. In addition, the signs can be ranked by control reliability indicators or by the probability of erroneous decisions. The possibility of using criteria and models of parametric recognition (discrimination) to compare the diagnostic effectiveness methods for assessing external respiration disorders compared to the conditional norm is considered below [3, 21, 28]. Despite the abundance of diagnostic data and their analysis for the detection of complicated viral pneumonia in COVID-19, this study is the first to attempt to summarize the results and identify the most significant indicators in diagnosing this pathology. The results of identifying the indicators that have the greatest influence on diagnostic decision-making when establishing a diagnosis of complicated viral pneumonia in COVID-19 are presented.

2. Materials and methods

We searched for articles on the use of diagnostic criteria and severity biomarkers in patients with ARDS complicating viral pneumonia in COVID-19 /SARS-CoV-2 and pandemic influenza, analysing the data presented in them for the period 2010–2023, including meta-analyses [15, 27] systematic reviews of the literature [9, 18], reference values [4, 8, 25]. To some extent, this allows for comparison with the already described changes in ARDS indicators in severe viral infections, despite the lack of an own control group. Diagnostic indicators and biomarkers of ARDS were compared with reference values according to the literature, which in this case are not a control group in the classical sense, but are a comparative reference. To compare the diagnostic effectiveness of the methods, the possibility of using criteria and parametric recognition (discrimination) models was considered. The study utilized statistically reliable diagnostic data from open sources indicating the presence of complicated viral pneumonia in COVID-19 and a control group. This is evident from the indicator values in Table 1.

The discrimination model was built on the basis of the quadratic normalized Euclidean distance between the vectors of mean values by the states of the quantities according to the formula

$$\delta^2 = \sum_{i=1}^{n} \left(\frac{m_i^{(0)} - m_i^{(1)}}{\sigma_i} \right)^2 \quad (1)$$

where $m_i^{(0)}$ and $m_i{}^{(1)}$ are the mean values; $\sigma_i^{(0)}$ and are the mean square deviations for different states (normal and pathological) of each *i*-th indicator from their total number *n*. Expression (1) assumes mutual independence of the vector components according to the linear discrimination model (1, 2).

The probability of a decision-making error regarding the state of the control object is determined by the value of the Laplace probability integral [3, 21].

$$P_{er} = 1 - \Phi(\delta/2) \quad (2)$$

Table 1. Diagnostic criteria and biomarkers of severity of ARDS complicating viral pneumonia in patients with COVID-19

	Indicator	COVID-19, ARDS	Reference value
1	Response to oxygen therapy	Saturation remains below 90%. No improvement in oxygen therapy via face mask (SpO2), need for CPAP.	An increase in SpO_2 after the start of oxygen therapy is the main marker of improvement in the patient's condition.
2	Respiratory rate	30–60 /min (range)	12–24 /min (range)
3	Serum ferritin. Ferritin levels are an important marker of inflammation and disease prognosis, and a sharp increase is associated with worsening clinical condition.	Peak ferritin levels in COVID-19 can reach 10,000 ng/mL and above in extreme cases such as cytokine storm and severe disease, including multiorgan failure and sepsis. Elevation in adult males above 300 ng/mL; in adult females above 120 ng/mL Range – males: 300–5000 ng/mL (maximum 10,000 ng/mL) Range – females: 120–5000 ng/mL (maximum 10,000 ng/mL)	In adult men: 20–300 ng/mL (95% CI 20–300 µg/L). In adult women: 20–120 ng/mL (95% CI 20–120 µg/L) (In moderate and severe forms of COVID-19, ferritin levels can vary from 1000 to 5000 ng/mL)
4	PaO2/FiO2	Oxygenation impairment (hypoxemia): Mild: 200 mm Hg < PaO2/FiO2 ≤ 300 with PEEP or CPAP ≥ 5 cm H2O Moderate: 100 mm Hg < PaO2/FiO2 ≤ 200 with PEEP or CPAP ≥ 5 cm H2O Severe: PaO2/FiO2 ≤ 100 with PEEP or CPAP ≥ 5 cm H2O	PaO2/FiO2 = 300–500 mmHg
5	Presence of radiological signs	>10%	<10% (The actual presence on CT of complete bilateral filling of the frontal projection of the lungs with 'ground glass' characterizes 100% of the lesion)
6	Peripheral oxygen saturation (SpO2)	SpO2 ≤ 93%	SpO2 95–100% (range) (Average may decrease but usually remains above 90%)
7	IL-6 (pg/ml) in blood serum	Diagnostic criterion – increase > 7.0 pg/ml ≤ 10,000 pg/ml, this is the maximum Range 7.0–10,000 pg/ml	Normal range 0– 7.0 pg/ml
8	Lymphopenia (absolute or relative percentage of lymphocytes in the blood)	Lymphocyte content – absolute lymphopenia – < $1.0*10^9$/l, or relative percentage in the blood < 18%	M: 18–40%, F: 18–40% (absolute and relative percentage) in the blood normally (1.0–4.5)–($10–10^9$)/l
9	Serum D-dimer*	In COVID-19, peak D-dimer levels can be significantly higher than 10 µg. Diagnostic criterion is an increase of more than 0.55 µg FEU/mL Range: 0.55–100 µg FEU/mL	Reference value for a healthy male 0–0.55 µg FEU/ml
10	C-reactive protein in serum	Peak C-reactive protein levels: In extremely severe cases, such as cytokine storm, sepsis, or severe trauma, CRP levels can significantly exceed 200 mg/L and reach 500–1000 mg/L. Elevation of C-reactive protein is 5 times the upper reference value. Range 5–1000 mg/L.	Reference value 0–5 mg/L (in adults should be less than 5 mg/L) (Normal C-reactive protein levels: In healthy people, serum C-reactive protein levels are usually very low. In patients with acute respiratory distress syndrome (ARDS) or severe COVID-19, CRP levels can be very high, sometimes exceeding 300 mg/L)
11	IL 10 (pg/ml) in blood serum	Increase more than 0.31 pg/ml Maximum low – to zero level, Maximum high – more than 1,000 pg/ml. Range 0.31–100 pg/ml (if we take the maximum, then ≤1,000 pg/ml)	Reference value 0.31 pg/ml (Under normal conditions, the level of IL-10 in the blood is usually not high, and in most cases in the serum of healthy people it can be within very low values, sometimes close to zero)
12	VEGF, pg/ml in serum	Elevation greater than 126.9 pg/mL. Range 126.9–1,000 pg/mL. *Mild COVID-19: VEGF levels may remain in the range of 50–100 pg/mL, possibly with a slight increase compared to normal. *Moderate COVID-19: VEGF levels may increase to 100–200 pg/mL in the context of inflammation and hypoxia. *Severe COVID-19: In severe cases (e.g., ARDS, sepsis, or cytokine storm), VEGF levels may increase significantly and reach 500–1,000 pg/mL, and in emergency cases – even higher.	Median – Min – Max Control: 126.9 – 80.4 – 178.6
13	MMP 9 (ng/mL) in serum	More than 411 (range 305–535) ng/mL	MMP 9 (ng/mL) in serum controls 333 (221–493) [5]

The probability of error is smaller, the more δ, i.e. the more the dispersion-normalized square of the distance between the mean vectors. Therefore, the values δ, or δ^2 according to equations (1) and (2) allow quantitatively comparing both single informative diagnostic indicators and sets of indicators in terms of informativeness (discriminatory ability) [3, 21].

At the same time, for each group of patients, statistical indicators were found: average values $m_i^{(0)}$ and $m_i{}^{(1)}$ and dispersion $\sigma_i^{(0)}$ and $\sigma_i{}^{(1)}$ for various pathological conditions and the conditional norm (from the control group). Moreover, for the calculation according to formula (1) the maximum standard deviation was chosen

$$\sigma_i = max(\sigma_i{}^{(0)}, \sigma_i{}^{(1)}) \quad (3)$$

The application of a linear discrimination model based on the normalized Euclidean distance for this distribution of results across relatively compactly grouped clusters allowed us to clearly identify the main features of complicated viral pneumonia in COVID-19 without resorting to more complex methods or neural network approaches.

To determine the diagnostic value of COVID-19 indicators, a discriminant analysis was performed by determining the normalized Euclidean distance [20, 22] with the addition of the following diagnostic criteria X_i ($i = \overline{1,13}$): X_1 – response to oxygen therapy; X_2 – respiratory rate; X_3 – serum ferritin; X_4 – oxygenation disorders PaO2/FiO2; X_5 – radiological signs; X_6 – peripheral oxygen saturation (SpO2); X_7 – IL-6 (pg/ml) in blood serum; X_8 – lymphopenia; X_9 – D-dimer in serum; X_{10} – C-reactive protein in serum; X_{11} – IL 10 (pg/ml) in blood serum; X_{12} – VEGF, pg/mol in blood serum; X_{13} – MMP 9 (ng/mL) in blood serum. Input diagnostic indicators for patients with reliably detected COVID-19 and comparative benchmarks (reference values) for calculation according to formulas (1)–(3) are located in Table 1. The given radiological indicator (5) characterizes the characteristic changes in the X-ray picture of the lungs relative to the typical sign for viral pneumonias in COVID-19 in the form of 'ground glass'. The actual presence of complete bilateral filling of the X-ray frontal projection of the lungs with 'ground glass' characterizes 100% of the lesion. The average value for COVID pneumonia according to our data

was 60% with a deviation of 28%. The reference values were less than 10 percent filling of the X-ray picture (5%±4.8%) with such a sign typical for viral pneumonias in COVID-19. Output data for calculating normalized Euclidean distances δ separately for each indicator and their contribution with sequential addition $\Sigma\delta$ are given in Table 2. The indicators in Tables 1 and 2 are listed in order of decreasing normalized Euclidean distance to clearly demonstrate the diagnostic significance of each of them and their cumulative contribution to the discrimination model.

Table 2. Output data for calculating normalized Euclidean distances δ separately for each indicator and their contribution with sequential addition Σδ

Indicator serial number	Indicator *X*	δ	$\Sigma\delta$
1	Response to oxygen therapy	1.72	1.72
2	Respiratory rate	1.64	2.38
3	Ferritin in blood serum.	1.51	2.81
4	Oxygenation disorders PaO2/FiO2	1.49	3.18
5	Radiological signs	1.44	3.49
6	Peripheral oxygen saturation (SpO2)	1.27	3.72
7	IL-6 (pg/ml) in blood serum	1.22	3.91
8	Lymphopenia	1.17	4.08
9	Serum D-dimer	1.0	4.20
10	C-reactive protein in serum	0.96	4.31
11	IL 10 (pg/ml) in blood serum	0.90	4.40
12	VEGF, pg/ml in blood serum	0.83	4.48
13	MMP 9 (ng/mL) in blood serum	0.78	4.55

3. Results and discussion

Figure 1 shows the increase in the normalized Euclidean distance according to formula (1) when adding diagnostic indicators to the discrimination model. Figure 2 shows the decrease in the probability of diagnostic decision error, calculated according to formula (2). From the analysis of these graphs, it is determined that the greatest diagnostic significance in determining COVID-19 is the response to oxygen therapy. In addition, of the 6 most significant indicators, the use of which reduces the probability of diagnostic error to 0.07, 4 belong to respiratory indicators (Response to oxygen therapy, Respiratory rate, Oxygenation disorders PaO2/FiO2, Peripheral oxygen saturation (SpO2)), the 5th indicator in terms of the largest contribution to the discrimination model is the presence of radiological changes that characterize viral pneumonia in COVID-19, and only one of these 6 indicators, namely, the 4th (Serum ferritin), refers to laboratory blood test data.

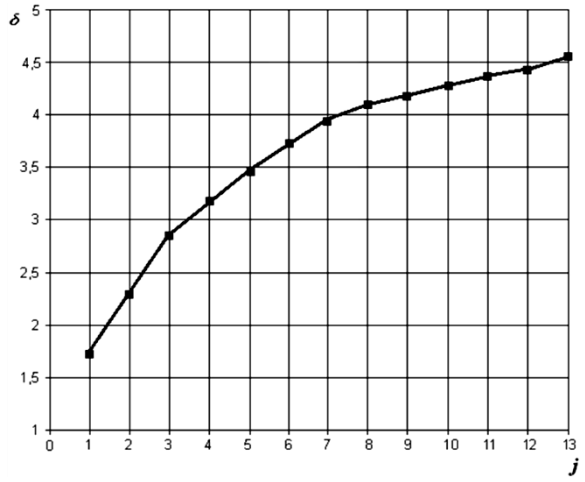


Fig. 1. Increase in normalized Euclidean distance when adding diagnostic indicators to the COVID-19 and control group discrimination model (indicators by numbers, respectively: X_1 – response to oxygen therapy; X_2 – respiratory rate; X_3 – serum ferritin; X_4 – oxygenation disorders PaO2/FiO2; X_5 – radiological signs; X_6 – peripheral oxygen saturation (SpO2); X_7 IL-6 (pg/ml) in blood serum; X_8 – lymphopenia; X_9 – D-dimer in serum; X_{10} – C-reactive protein in serum; X_{11},– IL 10 (pg/ml) in blood serum; X_{12} – VEGF, pg/ml in blood serum; X_{13} – MMP 9 (ng/mL) in blood serum)

Additionally, the diagnostic error is reduced to 0.04 when determining COVID-19 IL-6 (pg/ml) in serum, Lymphopenia, D-dimer in serum and C-reactive protein in serum. It should be noted that the latter indicators, such as IL 10 (pg/ml) in in serum, VEGF, pg/mL in serum and MMP 9 (ng/mL) in serum according to our data do not add significant information to the discrimination model and reduce the probability of making an incorrect diagnostic decision by only 0.02 in total. This is evidenced by the areas of horizontal direction of the graphs of the normalized Euclidean distance and the probability of error of the diagnostic decision in Figures 1 and 2, respectively.

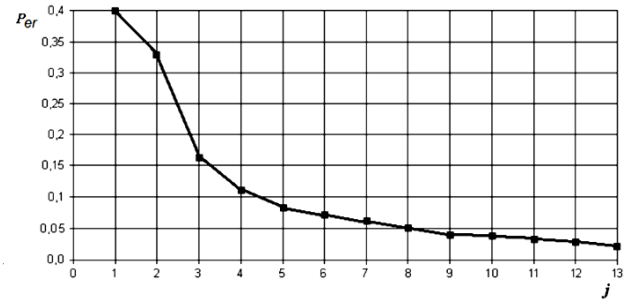


Fig. 2. Reduction of the probability error of making a diagnostic decision when adding diagnostic indicators to the COVID-19 and control group discrimination model (indicators by numbers, respectively: X_1 – response to oxygen therapy; X_2– respiratory rate; X_3 – serum ferritin; X_4 – oxygenation disorderPaO2/FiO2; X_5 – radiological signs; X_6 – peripheral oxygen saturation (SpO2); X_7 IL-6 (pg/ml) in blood serum; X_8 – lymphopenia; X_9 – D-dimer in blood serum; X_{10} – C-reactive protein in blood serum; X_{11},– IL 10 (pg/ml) in blood serum; X_{12} – VEGF, pg/ml in blood serum; X_{13} – MMP 9 (ng/mL) in blood serum)

4. Discussion

With high frequency, ARDS complicates the course of lung damage in infectious diseases caused by highly pathogenic viruses (HPCoVs) (SARS-CoV-2, MERS-CoV, and SARS-CoV), H5N1, and pandemic influenza A(H1N1)pdm09. As Meyer N. J. et al. [19] point out, "Although ARDS has a codified clinical definition, known as the Berlin definition, with stages that assess the risk of mortality, there is no single test to identify or exclude the diagnosis". "Despite progress in our understanding of the pathobiology of ARDS, the mechanisms underlying its pathogenesis are still unknown". Hagens L. A. [9] note that "the accuracy of ARDS diagnosis is associated with the risk of bias. There is a lack of validated diagnostic tests in an objective setting, which emphasizes the need for high-quality diagnostic studies in ARDS". Meyer N. J. et al. [19] rightly note that "no diagnostic test confirms or refutes the diagnosis of ARDS". In this study, using a discrimination model based on the quadratic Euclidean distance, we attempted to evaluate the effectiveness of diagnosing ARDS complicating viral pneumonia in patients with COVID-19/SARS-CoV-2 and pandemic influenza A(H1N1)pdm09. Studies have shown that there are some similarities in the mode of transmission and pathogenesis of influenza and COVID-19 [16]. There are two major problems that lead to the fact that seemingly similar studies of biomarkers in intensive care give different results. One of the problems is the traditional non-reproducibility due to false-positive selection of biomarkers or unreliable statistical models [24]. According to our studies of individual diagnostic criteria and biomarkers in terms of the contribution to the discrimination model, four of the six most significant indicators characterize the parameters of external respiration. In terms of the contribution to the discrimination model, the 5th indicator is the presence of radiological changes characterizing lung damage in COVID-19, and only one biomarker out of these 6 indicators (Serum Ferritin). Our results show that the above diagnostic criteria and the serum ferritin biomarker may be markers of ARDS in viral pneumonias arising against the background of these infections. Given some

similarities in the mode of transmission and pathogenesis of pandemic influenza and COVID-19, the high probability of ARDS complications in these diseases, we assume that to some extent our assessment of diagnostic criteria and severity biomarkers may be relevant for influenza A(H1N1)pdm09. This study has limitations. Diagnostic indicators and biomarkers of ARDS were compared with reference values according to the literature, which in this case are not a control group in the classical sense, but are a comparative reference. Reference values of biomarkers, indicators of oxygenation disorders, and the presence of radiological signs were used as control references. The data presented may vary depending on the population and methods, which is also a limitation of this approach.

5. Conclusions

1. The use of a certain set of information signs according to the criterion of maximum reliability in the analysis of signs of ARDS complicating viral pneumonia allows improving the diagnostic process.

2. A comprehensive analysis of indicators of oxygenation disorders, biomarkers, and radiographic data using a discrimination model based on the normalized Euclidean distance in patients with COVID-19 and pandemic influenza can reduce the likelihood of error in making a diagnostic decision.

3. Of the six most significant indicators, four characterize the parameters of external respiration (Response to oxygen therapy, Respiratory rate, Oxygenation disorders PaO2/FiO2, Peripheral oxygen saturation (SpO2)) and can be markers of ARDS in viral pneumonia in patients with COVID-19. The 5th indicator in terms of the largest contribution to the discrimination model is the presence of radiological changes that characterize viral pneumonia in COVID-19, and only one of these 6 indicators, namely, the 4th (Serum ferritin), refers to the data of laboratory blood tests. Other indicators can contribute relatively high informativeness only in the absence of these first six indicators.

4. It was found that the main markers of complicated viral pneumonia in COVID-19 are indicators associated with functional impairments of external respiration. These indicators provide the evidence base for diagnosing this type of complicated viral pneumonia and characterize its dynamic course.

5. Improving the selection of informative features, reducing the error of the probability of making a diagnostic decision when adding diagnostic indicators to the discrimination model affects the reduction of the diagnostic error of ARDS in viral pneumonia.

6. Prospects for further development

Improving the assessment of diagnostic criteria and severity biomarkers using a discrimination model based on quadratic, unweighted Euclidean distance will improve the detection of ARDS, a fatal complication of respiratory tract infections caused by highly pathogenic viruses (HPCoVs) (SARS-CoV-2, MERS-CoV, and SARS-CoV), pandemic influenza A(H1N1)pdm09, and influenza H5N1, H5N7. The main limitations of the discrimination model may be the complex, non-compact, and overlapping distributions of indicator values for complicated viral pneumonia in COVID-19 and the control group, which will require further elaboration of the proposed approach.

Disclosures

The authors declare no conflicts of interest.

References

[1] Agrawal, A., Matthay, M. A., Kangelaris, K. N., Stein, J., Chu, J. C., Imp, B. M., Cortez, A., Abbott, J., Liu, K. D., & Calfee, C. S. (2013). Plasma Angiopoietin-2 Predicts the Onset of Acute Lung Injury in Critically Ill Patients. *American Journal of Respiratory and Critical Care Medicine*, *187*(7), 736–742. https://doi.org/10.1164/rccm.201208-1460OC

[2] Avrunin, G. (2017). Principles of computer planning in the functional nasal surgery. *Przegląd Elektrotechniczny*, *1*(3), 142–145. https://doi.org/10.15199/48.2017.03.32

[3] Avrunin, O. G., Nosova, Y. V., Abdelhamid, I. Y., Pavlov, S. V., Shushliapina, N. O., Wójcik, W., Kisała, P., & Kalizhanova, A. (2021). Possibilities of Automated Diagnostics of Odontogenic Sinusitis According to the Computer Tomography Data. *Sensors*, *21*(4), 1198. https://doi.org/10.3390/s21041198

[4] Beliy, A. N., Krasnoselskiy, M. V., Mitryaeva, N. A., Grebenik, L. V., & Radchenko, A. A. (2016). The clinical significance of vegf in the serum of patients with secondary edematous breast cancer. *Ukrainian Journal of Radiology*, *XXIV*(4), 24–28.

[5] Busi Rizzi, E., Schininà, V., Ferraro, F., Rovighi, L., Cristoforo, M., Chiappetta, D., Lisena, F., Lauria, F., & Bibbolino, C. (2010). Radiological findings of pneumonia in patients with swine-origin influenza A virus (H1N1). *La Radiologia Medica*, *115*(4), 507–515. https://doi.org/10.1007/s11547-010-0553-9

[6] Davey, A., McAuley, D. F., & O'Kane, C. M. (2011). Matrix metalloproteinases in acute lung injury: Mediators of injury and drivers of repair. *European Respiratory Journal*, *38*(4), 959–970. https://doi.org/10.1183/09031936.00032111

[7] Fremont, R. D., Koyama, T., Calfee, C. S., Wu, W., Dossett, L. A., Bossert, F. R., Mitchell, D., Wickersham, N., Bernard, G. R., Matthay, M. A., May, A. K., & Ware, L. B. (2010). Acute Lung Injury in Patients With Traumatic Injuries: Utility of a Panel of Biomarkers for Diagnosis and Pathogenesis. *Journal of Trauma: Injury, Infection & Critical Care*, *68*(5), 1121–1127. https://doi.org/10.1097/TA.0b013e3181c40728

[8] Gelzo, M., Cacciapuoti, S., Pinchera, B., De Rosa, A., Cernera, G., Scialò, F., Comegna, M., Mormile, M., Fabbrocini, G., Parrella, R., Corso, G., Gentile, I., & Castaldo, G. (2022). Matrix metalloproteinases (MMP) 3 and 9 as biomarkers of severity in COVID-19 patients. *Scientific Reports*, *12*(1), 1212. https://doi.org/10.1038/s41598-021-04677-8

[9] Hagens, L. A., Heijnen, N. F. L., Smit, M. R., Schultz, M. J., Bergmans, D. C. J. J., Schnabel, R. M., & Bos, L. D. J. (2021). Systematic review of diagnostic methods for acute respiratory distress syndrome. *ERJ Open Research*, *7*(1), 00504–02020. https://doi.org/10.1183/23120541.00504-2020

[10] Hsu, A. T., Barrett, C. D., DeBusk, G. M., Ellson, C. D., Gautam, S., Talmor, D. S., Gallagher, D. C., & Yaffe, M. B. (2015). Kinetics and Role of Plasma Matrix Metalloproteinase-9 Expression in Acute Lung Injury and the Acute Respiratory Distress Syndrome. *Shock*, *44*(2), 128–136. https://doi.org/10.1097/SHK.0000000000000386

[11] Ishiguro, T., Kobayashi, Y., Uozumi, R., Takata, N., Takaku, Y., Kagiyama, N., Kanauchi, T., Shimizu, Y., & Takayanagi, N. (2019). Viral Pneumonia Requiring Differentiation from Acute and Progressive Diffuse Interstitial Lung Diseases. *Internal Medicine*, *58*(24), 3509–3519. https://doi.org/10.2169/internalmedicine.2696-19

[12] Joffre, J., Rodriguez, L., Matthay, Z. A., Lloyd, E., Fields, A. T., Bainton, R. J., Kurien, P., Sil, A., Calfee, C. S., Woodruff, P. G., Erle, D. J., Hendrickson, C., Krummel, M. F., Langelier, C. R., Matthay, M. A., Kornblith, L. Z., & Hellman, J. (2022). COVID-19–associated Lung Microvascular Endotheliopathy: A "From the Bench" Perspective. *American Journal of Respiratory and Critical Care Medicine*, *206*(8), 961–972. https://doi.org/10.1164/rccm.202107-1774OC

[13] Kang, M., Hong, K. S., Chikontwe, P., Luna, M., Jang, J. G., Park, J., Shin, K.-C., Park, S. H., & Ahn, J. H. (2021). Quantitative Assessment of Chest CT Patterns in COVID-19 and Bacterial Pneumonia Patients: A Deep Learning Perspective. *Journal of Korean Medical Science*, *36*(5), e46. https://doi.org/10.3346/jkms.2021.36.e46

[14] Kitsiouli, E., Tenopoulou, M., Papadopoulos, S., & Lekka, M. E. (2021). Phospholipases A2 as biomarkers in acute respiratory distress syndrome. *Biomedical Journal*, *44*(6), 663–670. https://doi.org/10.1016/j.bj.2021.08.005

[15] Kouhsari, E., Azizian, K., Sholeh, M., Shayestehpour, M., Hashemian, M., Karamollahi, S., Yaghoubi, S., & Sadeghiifard, N. (2021). Clinical, epidemiological, laboratory, and radiological characteristics of novel Coronavirus (2019-nCoV) in retrospective studies: A systemic review and meta-analysis. *Indian Journal of Medical Microbiology*, *39*(1), 104–115. https://doi.org/10.1016/j.ijmmb.2020.10.004

[16] Luo, J., Zhang, Z., Zhao, S., & Gao, R. (2023). A Comparison of Etiology, Pathogenesis, Vaccinal and Antiviral Drug Development between Influenza and COVID-19. *International Journal of Molecular Sciences*, *24*(7), 6369. https://doi.org/10.3390/ijms24076369

[17] Lyons, P. G., Bhavani, S. V., Mody, A., Bewley, A., Dittman, K., Doyle, A., Windham, S. L., Patel, T. M., Raju, B. N., Keller, M., Churpek, M. M., Calfee, C. S., Michelson, A. P., Kannampallil, T., Geng, E. H., & Sinha, P. (2022). Hospital trajectories and early predictors of clinical outcomes differ between SARS-CoV-2 and influenza pneumonia. *eBioMedicine*, *85*, 104295. https://doi.org/10.1016/j.ebiom.2022.104295

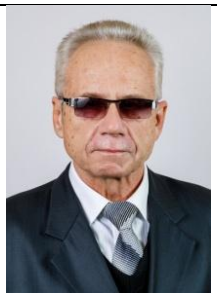
[18] Machnicki, S., Patel, D., Singh, A., Talwar, A., Mina, B., Oks, M., Makkar, P., Naidich, D., Mehta, A., Hill, N. S., Brown, K. K., & Raoof, S. (2021). The Usefulness of Chest CT Imaging in Patients With Suspected or Diagnosed COVID-19. *Chest*, *160*(2), 652–670. https://doi.org/10.1016/j.chest.2021.04.004

[19] Meyer, N. J., Gattinoni, L., & Calfee, C. S. (2021). Acute respiratory distress syndrome. *The Lancet*, *398*(10300), 622–637. https://doi.org/10.1016/S0140-6736(21)00439-6
[20] Saied, H. F. I., Al_Omari, A. K., & Avrunin, O. G. (2011). An Attempt of the Determination of Aerodynamic Characteristics of Nasal Airways. In R. S. Choraś (Ed.), *Image Processing and Communications Challenges 3* (Vol. 102, pp. 311–322). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-23154-4_35
[21] Selivanova, K. G., Avrunin, O. G., Zlepko, S. M., Romanyuk, S. O., Zabolotna, N. I., Kotyra, A., Komada, P., & Smailova, S. (2016). *Quality improvement of diagnosis of the electromyography data based on statistical characteristics of the measured signals* (R. S. Romaniuk, Ed.; p. 100312R). https://doi.org/10.1117/12.2248953
[22] Sharma, S., Aggarwal, A., Sharma, R. K., Patras, E., & Singhal, A. (2022). Correlation of chest CT severity score with clinical parameters in COVID-19 pulmonary disease in a tertiary care hospital in Delhi during the pandemic period. *Egyptian Journal of Radiology and Nuclear Medicine*, *53*(1), 166. https://doi.org/10.1186/s43055-022-00832-x
[23] Sinha, P., & Bos, L. D. (2021). Pathophysiology of the Acute Respiratory Distress Syndrome. *Critical Care Clinics*, *37*(4), 795–815. https://doi.org/10.1016/j.ccc.2021.05.005
[24] Sweeney, T. E., & Khatri, P. (2017). Generalizable Biomarkers in Critical Care: Toward Precision Medicine. *Critical Care Medicine*, *45*(6), 934–939. https://doi.org/10.1097/CCM.0000000000002402
[25] The ARDS Definition Task Force. (2012). Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*, *307*(23). https://doi.org/10.1001/jama.2012.5669
[26] Wang, C., Horby, P. W., Hayden, F. G., & Gao, G. F. (2020). A novel coronavirus outbreak of global health concern. *The Lancet*, *395*(10223), 470–473. https://doi.org/10.1016/S0140-6736(20)30185-9
[27] Wang, Y., Wang, H., Zhang, C., Zhang, C., Yang, H., Gao, R., & Tong, Z. (2019). Lung fluid biomarkers for acute respiratory distress syndrome: A systematic review and meta-analysis. *Critical Care*, *23*(1), 43. https://doi.org/10.1186/s13054-019-2336-6
[28] Wójcik, W., Pavlov, S., & Kalimoldayev, M. (Eds). (2019). *Information Technology in Medical Diagnostics II* (1st edn). CRC Press. https://doi.org/10.1201/9780429057618

Ph.D. Gryhoriy I. Gradil
email: hi.hradil@knnu.edu.ua

Candidate of Medical Sciences, associate professor of the Department of Infectious Diseases, Pediatric Infectious Diseases and Phthisiology, Kharkiv National Medical University; of the Ministry of Health of Ukraine
Scientific directions: viral infections of the respiratory system, immunology, immunohistochemistry.

https://orcid.org/0000-0001-5655-6188



Prof. Oleg G. Avrunin
e-mail: oleh.avrunin@nure.ua

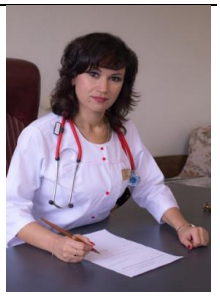
Doctor of Technical Sciences, professor, Head of the Department of Biomedical Engineering, Kharkiv National University of Radio Electronics.
Scientific directions: devices for functional diagnostics, computer vision, digital image processing

https://orcid.org/0000-0002-6312-687X

Prof. Kateryna V. Yurko
e-mail: kv.yurko@knmu.edu.ua

Doctor of Medical Sciences, professor, Head of the Department of Infectious Diseases, Pediatric Infectious Diseases and Phthisiology of the Kharkiv National Medical University of the Ministry of Health of Ukraine.
Scientific directions: parenteral hepatitis, HIV-infection, acute respiratory viral infections.

https://orcid.org/0000-0002-1226-5431



Ph.D. Nataliia O. Shushlyapina
e-mail: no.shushliapina@knmu.edu.ua

Candidate of Medical Sciences, associate professor of the Department of Otorhinolaryngology, Kharkiv National Medical University, Ministry of Health of Ukraine.
Scientific directions: functional rhinosurgery, endoscopic surgery, diagnostic of respiratore-olfactory diseases.

https://orcid.org/0000-0002-6347-3150

Ph.D. Yuliia M. Kalashnyk-Vakulenko
e-mail: ym.kalashnyk@knmu.edu.ua

Candidate of Medical Sciences, associate professor of the Department of Otorhinolaryngology, Kharkiv National Medical University, Ministry of Health of Ukraine.
Research interests: endoscopic surgery, diagnostic of respiratory diseases

https://orcid.org/0000-0002-7733-3503

Ph.D. Mariia Shostatska
e-mail: mariashostatska@gmail.com

Doctor of Philosophy (Ph.D.) in medicine, Deputy Director for Educational Work, Vinnytsia Academician D. K. Zabolotnyi Professional Medical College. Vinnytsia.
Research interests: endoscopic surgery, diagnostics, information technology in medicine.

https://orcid.org/0000-0002-1835-8348

Ph.D. Aigul Iskakova
e-mail: a.iskakova@satbayev.university

Ph.D., associate professor, Kazakh National Research Technical University named after K.I. Satpayev, Institute of Automation and Information Technologies, Department of Automation and Control.
Research interests: information technology in medicine.

https://orcid.org/0000-0001-8043-819X