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Predictive value of the Elixhauser comorbidity index in assessing the risk of coronavirus disease (COVID-19) mortality in patients with pneumonia

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim. To determine the spectrum of comorbid pathology and to find out the prognostic value of the Elixhauser Comorbidity Index (ECI) in assessing the risk of death from coronavirus disease (COVID-19) in patients with pneumonia.

Material and methods. The study included 123 patients with COVID-19 with pneumonia who were examined and treated according to the Order of the Ministry of Health of Ukraine of 28.03.2020 No. 722. Depending on the disease outcome, the patients were divided into groups: 77 patients who recovered and 46 patients who died. The ECI was calculated for all the patients. Statistical processing of the data was performed using Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. In patients with COVID-19 and pneumonia, comorbid conditions were most often represented by chronic cardiovascular disease (63.4 %), obesity (28.5 %), endocrine pathology (26.0 %) and discirculatory encephalopathy (23.6 %). Among patients with a fatal outcome, coronary heart disease with cardiac arrhythmias, obesity, endocrine diseases, primarily diabetes mellitus, and discirculatory encephalopathy were more common ($p < 0.05$) as compared to patients who recovered. Among the comorbidities integrated into the ECI, the most commonly diagnosed comorbidities in COVID-19 patients with pneumonia were hypertension (58.5 %), congestive heart failure (33.3 %), obesity (28.5 %), neurodegenerative disorders (23.6 %), and diabetes, both without (13.8 %) and with chronic complications (7.7 %). The following ECI components were more common in patients with COVID-19 pneumonia who died as a result of COVID-19 than in patients who recovered: congestive heart failure ($p = 0.008$), cardiac arrhythmias ($p = 0.001$), neurodegenerative disorders ($p = 0.0003$), diabetes mellitus ($p = 0.004$) including diabetes without chronic complications ($p = 0.01$), and obesity ($p = 0.04$). The ECI score in patients with a fatal outcome was 2.2 times higher ($p < 0.05$) than that in patients with COVID-19 pneumonia who recovered. The ECI >7 was predictive of the likelihood of COVID-19 death in patients with pneumonia (AUC = 0.656, $p = 0.002$).

Conclusions. The frequency of chronic comorbidities in patients with COVID-19 and pneumonia has been determined taking into account the ECI components. The prognostic significance of the ECI score >7 in assessing the risk of fatal outcome has been established.

Keywords: coronavirus disease, COVID-19, viral infection, pneumonia, comorbidity, Elixhauser comorbidity index, diagnosis, prognosis.

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Прогностичне значення індексу коморбідності Елікскхаузера в оцінюванні ризику летального наслідку коронавірусної хвороби (COVID-19) у пацієнтів із пневмонією

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Мета роботи – визначити спектр коморбідної патології та з'ясувати прогностичне значення індексу коморбідності Елікскхаузера (ECI) в оцінюванні ризику летального наслідку коронавірусної хвороби (COVID-19) у пацієнтів із пневмонією.

Матеріали і методи. До дослідження залучено 123 хворих на COVID-19 із пневмонією, яких обстежили та призначили лікування відповідно до Наказу МОЗ України від 28.03.2020 р. № 722. Залежно від наслідку хвороби пацієнтів поділили на групи: 77 осіб, які одужали, та 46 хворих, котрі померли. В усіх хворих обрахували індекс коморбідності Елікскхаузера. Статистично дані опрацювали в програмі Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. У хворих на COVID-19 із пневмонією як коморбідні стани найчастіше виявляли хронічну серцево-судинну патологію (63,4 %), ожиріння (28,5 %), ендокринну патологію (26,0 %) та дисциркуляторну енцефалопатію (23,6 %). У пацієнтів із летальним наслідком хвороби частіше ($p < 0,05$), ніж у хворих, котрі одужали, діагностували ішемічну хворобу серця з серцевою аритмією, ожиріння, ендокринні захворювання, насамперед діабет, дисциркуляторну енцефалопатію. Серед коморбідних станів, які враховує ECI, у хворих на COVID-19 і пневмонію найчастіше виявляли гіпертензію (58,5 %), застійну серцеву недостатність (33,3 %), ожиріння (28,5 %), нейродегенеративні розлади (23,6 %), а також діабет – і без хронічних ускладнень (13,8 %), і з ними (7,7 %). У хворих на COVID-19 із пневмонією, які померли внаслідок COVID-19, частіше, ніж у пацієнтів, котрі одужали, виявляли такі компоненти ECI: застійну серцеву недостатність ($p = 0,008$), серцеві аритмії ($p = 0,001$), нейродегенеративні розлади ($p = 0,0003$), діабет ($p = 0,004$), зокрема діабет без хронічних ускладнень ($p = 0,01$), ожиріння ($p = 0,04$). Показник ECI у пацієнтів із летальним наслідком в 2,2 раза вищий ($p < 0,05$), ніж у хворих на COVID-19 і пневмонію, котрі одужали. Прогностичне значення щодо оцінювання імовірності летального наслідку COVID-19 у хворих із пневмонією мав ECI >7 (AUC = 0,656, $p = 0,002$).

Висновки. Визначено частоту хронічних коморбідних станів у хворих на COVID-19 із пневмонією, беручи до уваги компоненти ECI. Встановлено прогностичну значущість показника ECI >7 під час оцінювання ризику летального наслідку хвороби.

Ключові слова: коронавірусна хвороба, COVID-19, вірусна інфекція, пневмонія, коморбідність, індекс коморбідності Елікскхаузера, діагностика, прогноз.

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Starting with the first wave of the coronavirus disease (COVID-19) pandemic, many studies have discussed risk factors that predicted the severity of the infection and adverse outcomes. The risk factors for COVID-19 mortality that researchers most often highlighted were patient age over 65, male gender, lower socioeconomic status, and various comorbidities [1,2,3,4]. At the same time, their combination predicted poorer treatment outcomes and, accordingly, a higher risk of death. However, the burden of chronic comorbidities in these studies was assessed by simply counting the number of conditions that could affect the course of COVID-19 with a certain probability [5,6]. Meanwhile, the results of such studies by different authors have been quite controversial regarding the role of various chronic diseases in predicting clinical outcomes of COVID-19 [1,7,8].

Today, an integral assessment of the comorbidity impact on the risk of potential complications and death is a promising area for improving the efficiency of predicting the course of various diseases. The Elixhauser Comorbidity Index (ECI) is adapted for use with the International Classification of Diseases, 10th Revision and is most often used in clinical trials to assess the mortality risk [9,10,11]. Integral comorbidity indices, in particular the ECI, are not specialized for use with a specific underlying patient pathology. Therefore, it is necessary to conduct a number of studies to determine their prognostic value in different pathologies, for example, to determine the high risk of surgical bleeding [12], readmission in patients with chronic obstructive pulmonary disease [13], to assess the risk of in-hospital and one-year mortality and length of hospital stay in patients with cardiovascular disease [14], etc.

During the COVID-19 pandemic, it became clear that the burden of comorbidities is a significant predictor of critical illness in hospitalized patients. Therefore, over time, the literature has published the results of studies to determine the information content of existing comorbidity indices and compare the effectiveness of their use in clinical practice. One of the first publications [15], which was a systematic review and meta-analysis determining the feasibility of using the Charlson Comorbidity Index in COVID-19, conducted before 15 July 2020, has demonstrated the informativeness of this index. It has been shown that a Charlson Comorbidity Index of ≥3 indicated an increased risk of developing a fatal outcome of COVID-19, and a one-point increase in this index resulted in a 16 % increase in risk [15].

A study [16] analyzed all cases of hospital admissions for COVID-19 in 8 public hospitals in Catalonia (Spain) for the period from 15 June to 8 December 2020 using three integral indices, namely the Charlson index, the ECI and the Queralt index. It has been demonstrated that each of these indices had a certain informativeness in assessing the risk of developing critical COVID-19, including the presence of indications for transfer to the intensive care unit, the need for invasive mechanical ventilation, or death in hospital [16]. At the same time, the information content of existing integrative prognostic indices for certain categories of patients with COVID-19 is being evaluated. For example, when assessing the prognostic significance of the Charlson index and the ECI, a study [17] additionally took into account a smoking history, and a study [18] also considered the ethnic component when applying the above indices.

Thus, research is needed to determine the informative value of comorbidity indices for certain categories of patients with COVID-19.

Aim

To determine the spectrum of comorbid pathology and to find out the prognostic value of the Elixhauser Comorbidity Index in assessing the risk of death from COVID-19 in patients with pneumonia.

Material and methods

The study included 123 patients with COVID-19 and pneumonia who were examined and treated according to the Order of the Ministry of Health of Ukraine dated 28.03.2020 No. 722 "Organisation of medical care for patients with COVID-19". The diagnosis of COVID-19 in all the patients was confirmed by the detection of RNA-SARS-CoV-2 in nasopharyngeal mucus by polymerase chain reaction. Pneumonia was confirmed by imaging methods (chest X-ray or computed tomography). All the patients were admitted to the Municipal Non-Profit Enterprise "Regional Infectious Disease Clinical Hospital" of the Zaporizhzhia Regional Council. The patients were included in the study with informed consent. Depending on the disease outcome, the patients were divided into groups: 77 patients who recovered and 46 patients who died. The ECI was calculated for all the patients [19,20].

Statistical data processing was performed using the software Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). For the differential applying of parametric or non-parametric methods of statistical data analysis, the distribution normality for the data on studied parameters was determined using the Shapiro–Wilk test. To define differences between qualitative variables in independent groups, the non-parametric method of the χ^2 criterion was used. The parametric Student's t-test was applied to determine differences in ECI between the studied groups. The results of the quantitative ECI index were presented in the form of the mean value and the standard error of the mean value M ± m. To establish the diagnostic value of the ECI in predicting the risk of developing a fatal outcome of COVID-19 with pneumonia, a ROC analysis was performed to determine the cut-off point. Differences at $p < 0.05$ were considered significant.

Results

When analysing the list of chronic comorbidities in patients with COVID-19 and pneumonia, a wide range of comorbid conditions was identified. Chronic cardiovascular disease (63.4 %) was the most commonly reported condition, with hypertension (58.5 %) and coronary heart disease (52.0 %) predominance. It should be noted that among patients who died as a result of COVID-19, coronary heart disease was more common than that in patients who recovered (73.9 % vs. 38.9 %, $\chi^2 = 14.10$, $p = 0.0002$) as well as the presence of cardiac arrhythmia in the form of permanent atrial fibrillation (26.1 % vs. 5.2 %, $\chi^2 = 11.11$, $p = 0.001$). Almost one in three patients with COVID-19 pneumonia was obese (28.5 %), and the frequency of this comorbidity was statistically sig-

nificantly higher in patients who died compared to the group of patients who recovered (39.1 % vs. 22.1 %, χ^2 = 4.11, p = 0.04). One in four patients with COVID-19 pneumonia had endocrine pathology (26.0 %), and among patients who died, comorbid endocrine diseases were more common (41.3 % vs. 16.9 %, χ^2 = 8.92, p = 0.003), primarily diabetes mellitus (34.8 % vs. 13.5 %, χ^2 = 8.21, p = 0.004). Almost one in four patients had comorbid discirculatory encephalopathy (23.6 %), which was also more common in patients who died (41.3 % vs. 13.0 %, χ^2 = 12.82, p = 0.0003) *(Table 1)*.

In the next part of our work, we analysed the frequency of comorbid conditions integrated into the ECI in COVID-19 patients with pneumonia and compared the frequency of their detection depending on the lethal disease outcome. The most common comorbidities in COVID-19 patients with pneumonia were the following components of the ECI: hypertension (58.5 %), congestive heart failure (33.3 %), obesity (28.5 %), neurodegenerative disorders (23.6 %), and diabetes mellitus both without chronic complications (13.8 %) and with chronic complications (7.7 %). Comparison of the chronic comorbidity incidence in patients with COVID-19 pneumonia with different disease outcomes has shown that patients who died as a result of COVID-19 were more likely to have comorbid congestive heart failure (χ^2 = 6.95, p = 0.008), cardiac arrhythmias (χ^2 = 11.11, p = 0.001), neurodegenerative disorders (χ^2 = 12.82, p = 0.0003), diabetes mellitus (χ^2 = 8.21, p = 0.004), including diabetes without chronic complications (χ^2 = 6.28, p = 0.01), and obesity (χ^2 = 4.11, p = 0.04) than patients who recovered *(Table 2)*.

According to our study results, the ECI score was 5.07 ± 0.50 points in patients with COVID-19 and pneumonia. Comparison of the ECI score depending on the COVID-19 outcome has shown a statistically significantly higher level in the group of patients who died compared to the group of recovered patients: 7.72 ± 1.03 points versus 3.48 ± 0.48 points (2.2 times, p < 0.05) *(Fig. 1A)*. To determine the threshold level of the ECI in patients with COVID-19 pneumonia for predicting the probable lethal disease outcome, a ROC analysis was performed to determine the cut-off point. Based on the ROC analysis results, the diagnostic value of the ECI in patients with COVID-19 pneumonia has been established. The ECI score >7 indicated a high probability of mortality (AUC = 0.656, p = 0.002) (sensitivity – 50.0 %, specificity – 81.7 %) *(Fig. 1B)*.

Discussion

Many studies have been focused on the prognostic value of the chronic comorbidity burden in patients with COVID-19, which could significantly affect the course and outcome of COVID-19 [5,6,21]. However, the results of studies by different authors are quite controversial regarding the role of various chronic diseases in predicting clinical outcomes of COVID-19 [1,7,8].

In our study, when clarifying the spectrum of comorbidities in patients with COVID-19 and pneumonia, it has been found that chronic cardiovascular disease, obesity, endocrine pathology and discirculatory encephalopathy were most common. Among patients with a fatal outcome, coronary heart disease with cardiac arrhythmia, obesity, endocrine diseases, especially diabetes mellitus, and

Table 1. List of comorbid conditions in COVID-19 patients with pneumonia and comparison of their frequency depending on the disease outcome, abs. (%)

Indicator, units of measure	COVID-19 patients with pneumonia, n = 123	COVID-19 patients with pneumonia	
		recovered, n = 77	died, n = 46
Cardiovascular pathology:	78 (63.4)	44 (57.1)	34 (73.9)
– coronary heart disease	64 (52.0)	30 (38.9)	34 (73.9)*
– permanent form of atrial fibrillation	16 (13.0)	4 (5.2)	12 (26.1)*
– stage II–III hypertension	72 (58.5)	44 (57.1)	28 (60.9)
– post-infarction cardiosclerosis	8 (6.5)	3 (3.9)	5 (10.9)
– ischemic stroke in a history	8 (6.5)	4 (5.2)	4 (8.7)
Discirculatory encephalopathy	29 (23.6)	10 (13.0)	19 (41.3)*
Chronic obstructive pulmonary disease:	9 (7.3)	4 (5.2)	5 (10.9)
– chronic obstructive pulmonary disease	5 (4.1)	2 (2.6)	3 (6.5)
– bronchial asthma	3 (2.4)	2 (2.6)	1 (2.2)
– pulmonary sarcoidosis	1 (0.8)	–	1 (2.2)
– pulmonary circulatory disorders "pulmonary heart"	1 (0.8)	–	1 (2.2)
Endocrine diseases:	32 (26.0)	13 (16.9)	19 (41.3)*
– diabetes mellitus	26 (21.1)	10 (13.0)	16 (34.8)*
– autoimmune thyroiditis	6 (4.9)	3 (3.9)	3 (6.5)
Stage II–III chronic kidney disease	7 (5.7)	3 (3.9)	4 (8.7)
Obesity	35 (28.5)	17 (22.1)	18 (39.1)*
Diseases of the gastrointestinal tract:	10 (8.1)	8 (10.4)	2 (4.3)
– peptic ulcer without bleeding	2 (1.6)	2 (2.6)	–
– liver diseases	8 (6.5)	6 (7.8)	2 (4.3)
Oncopathology in remission	2 (1.6)	1 (1.3)	1 (2.2)
Rheumatoid arthritis	6 (4.9)	2 (2.6)	4 (8.7)
Obliterating endarteritis	1 (0.8)	–	1 (2.2)
Haemophilia	1 (0.8)	–	1 (2.2)

*: significant differences compared to patients with COVID-19 pneumonia who recovered (p < 0.01).

Table 2. Comparison between the incidence of comorbid conditions integrated into the ECI calculation in patients with COVID-19 pneumonia depending on the disease outcome, abs. (%)

Indicator, units of measure	COVID-19 patients with pneumonia, n = 123	COVID-19 patients with pneumonia	
		recovered, n = 77	died, n = 46
Congestive heart failure	41 (33.3)	19 (24.7)	22 (47.8)*
Cardiac arrhythmias	16 (13.0)	4 (5.2)	12 (26.1)*
Pulmonary circulation disorders	1 (0.8)	–	1 (2.2)
Peripheral vascular disorders	1 (0.8)	–	1 (2.2)
Hypertension	72 (58.5)	44 (57.1)	28 (60.9)
Neurodegenerative disorders	29 (23.6)	10 (13.0)	19 (41.3)*
Chronic lung diseases	9 (7.3)	4 (5.2)	5 (10.9)
No diabetes mellitus	97 (78.9)	67 (87.0)	30 (65.2)*
Diabetes mellitus without chronic complications	17 (13.8)	6 (7.8)	11 (23.9)*
Diabetes mellitus with chronic complications	9 (7.3)	4 (5.2)	5 (10.9)
Hypothyroidism	6 (4.9)	3 (3.9)	3 (6.5)
Renal failure	7 (5.7)	3 (3.9)	4 (8.7)
Liver diseases	8 (6.5)	6 (7.8)	2 (4.3)
Ulcer disease without bleeding	2 (1.6)	2 (2.6)	–
Solid tumor without metastases	2 (1.6)	1 (1.3)	1 (2.2)
Rheumatoid arthritis / collagenosis	6 (4.9)	2 (2.6)	4 (8.7)
Coagulopathy	1 (0.8)	–	1 (2.2)
Obesity	35 (28.5)	17 (22.1)	18 (39.1)*

*: significant differences compared to patients with COVID-19 pneumonia who recovered (p < 0.01).

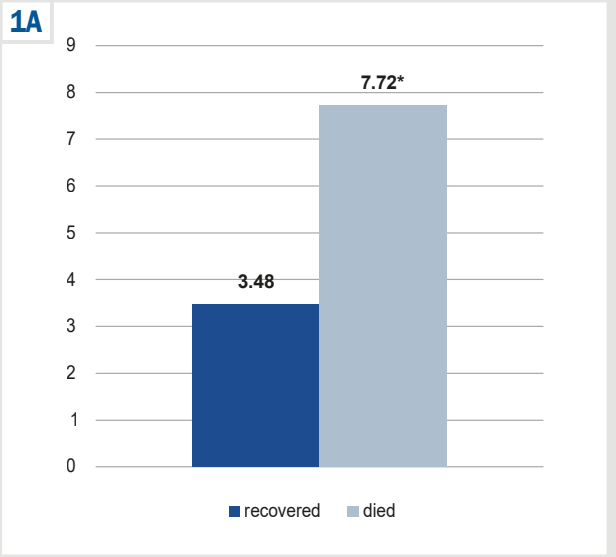

Fig. 1. Comparison of the ECI score in patients with COVID-19 pneumonia depending on the disease outcome (**A**) and the threshold ECI score for the mortality risk assessment (**B**).
*: significant differences compared to patients with COVID-19 pneumonia who recovered ($p < 0.01$).

discirculatory encephalopathy were documented more often ($p < 0.05$) as compared to patients who recovered. However, when compared with the results of other studies, it is noteworthy that some of them have demonstrated the greatest significance of certain comorbidities. For example, a study has shown that the presence of diabetes mellitus was statistically significantly associated with the risk of death from COVID-19 [7].

However, the results of a meta-analysis [8] have only identified a list of certain comorbid conditions, including cardiovascular disease, hypertension, diabetes mellitus, congestive heart failure, chronic kidney disease, and oncology, which posed a greater risk of mortality in patients with COVID-19 compared to those without these comorbidities.

In view of the above, the results of studies on integrated comorbidity indices for the assessment of chronic comorbidity burden and the risk of critical course and death from COVID-19 deserve special attention today. The calculation of comorbidity indexes involves the sum of scores based on the risk weight of each comorbidity [22,23]. Considering the weighted value given to each comorbidity ultimately provides more meaningful information, as the weight assigned to each comorbidity reflects the higher, lower, or neutral impact of the respective comorbidity on the risk of death for a particular patient [10]. For example, the ECI was developed based on the International Classification of Diseases algorithms with a corresponding weighting factor for each selected comorbid condition. The assignment of appropriate weighting factors to certain comorbidities made it possible to describe the burden of a particular comorbidity and increase the efficiency of using this model [19,20,24,25].

In our study, we have determined the informative value of the ECI in assessing the risk of death from COVID-19 in patients with pneumonia. It should be noted that in the spectrum of comorbidities integrated into the ECI, patients with COVID-19 pneumonia most often had hypertension (58.5 %), congestive heart failure (33.3 %), obesity (28.5 %), neurodegenerative disorders (23.6 %), and diabetes mellitus both without chronic complications (13.8 %) and with chronic complications (7.7 %). Patients with COVID-19 pneumonia who died from this pathology were more likely to have the following ECI components ($p < 0.05$) than those who recovered: congestive heart failure, cardiac arrhythmias, neurodegenerative disorders, diabetes mellitus, including diabetes without chronic complications, and obesity. In patients with COVID-19 and fatal pneumonia, the ECI score was 2.2 times higher ($p < 0.05$) than that in patients who recovered. Based on the ROC analysis results, we have established a threshold ECI level of >7 (AUC = 0.656, p = 0.002). That is, if this ECI value is exceeded in a particular patient, the risk of death should be considered significant.

The COVID-19 pandemic has posed unprecedented challenges to healthcare systems around the world [26]. New evidence suggests that patients' chronic diseases and certain genetic factors play a crucial role in predicting the severity of COVID-19, that is why this research area is the most relevant. A study [26] based on a sample of more than 500,000 individuals from three biobanks has found a significant association of severe COVID-19 with obesity, metabolic disorders, and cardiovascular disease, which, on the one hand, has confirmed the already known risk factors and, on the other hand, expanded the understanding of the relationship between existing clinical phenotypes and COVID-19 outcomes. At the same time, more recent studies have provided increasing evidence that the presentation of concomitant chronic pathology not only in the form of specific diagnoses, but also in the form of comorbidity indices (Charlson or Elixhauser), insured the greatest improvement in prognostic models [27,28].

Conclusions

1. In patients with COVID-19 and pneumonia, comorbid conditions are most often represented by chronic cardiovascular disease (63.4 %), obesity (28.5 %), endocrine patho-

logy (26.0 %) and discirculatory encephalopathy (23.6 %). Among patients with a fatal outcome, coronary heart disease (p = 0.0002) with cardiac arrhythmia (p = 0.001), obesity (p = 0.04), endocrine diseases (p = 0.003), primarily diabetes mellitus (p = 0.004), and discirculatory encephalopathy (p = 0.0003) were more common as compared to patients who recovered.

2. Among the comorbidities integrated into the Elixhauser Comorbidity Index, patients with COVID-19 and pneumonia most often have hypertension (58.5%), congestive heart failure (33.3 %), obesity (28.5 %), neurodegenerative disorders (23.6 %), and diabetes mellitus both without chronic complications (13.8 %) and with chronic complications (7.7 %). Patients with COVID-19 pneumonia who died from COVID-19 were more likely to have the following components of the Elixhauser Comorbidity Index as compared to patients who recovered: congestive heart failure (p = 0.008), cardiac arrhythmias (p = 0.001), neurodegenerative disorders (p = 0.0003), diabetes mellitus (p = 0.004), including diabetes without chronic complications (p = 0.01), and obesity (p = 0.04).

3. The Elixhauser Comorbidity Index in patients with a fatal outcome is 2.2 times higher (p < 0.05) than that in patients with COVID-19 and pneumonia who recovered. The Elixhauser Comorbidity Index >7 (AUC = 0.656, p = 0.002) is predictive of the probability of mortality from COVID-19 in patients with pneumonia.

Prospects for further research. In our opinion, prospects for further research are to determine the prognostic value of ECI among different age groups of patients with COVID-19.

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