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Original article

An evidence-based model for predicting adverse outcome in COVID-19 patients with comorbid pathology

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Abstract

The COVID-19 pandemic has placed an unprecedented burden on health care systems, highlighting the critical need for intensive care and respiratory support. The severe course of COVID-19, complicated by multi-organ failure, often results in prolonged hospitalisation in intensive care units. A thorough understanding of risk and protective factors is necessary to optimise treatment strategies and protect the healthcare system from overload.

Objective: To study risk factors associated with the prevalence and severity of COVID-19 in the adult population to improve patient stratification and optimize therapy.

Methods: This study is a retrospective, cohort study. We retrospectively analysed 511 medical records from 3696 patients with confirmed SARS-CoV-2 infection who were observed in the City Infectious Diseases Hospital of Shymkent, Kazakhstan in the period from January to October 2021. Patients were divided into 2 groups: main group (n=327) - with comorbidities, control group (n=184) - without comorbidities.

Results. The analysis revealed a set of demographic, clinical (symptoms, complications), immunological (cytokine storm), haematological (leukocyte and platelet levels), biochemical (factor VIII, protein C) and radiological (changes in lung tissue) factors that can be used to predict the course of COVID-19. The association of comorbidities (hypertension, diabetes) with increased risk of severe course of the disease was confirmed. Hypoxia plays a key role in the development of multi-organ failure.

Inflammatory markers (C-reactive protein, ferritin, D-dimer) and pro-inflammatory cytokines (IL-6, IL-1) are predictors of unfavourable outcomes. Identification and validation of risk factors and prognostic markers in COVID-19 is crucial for patient stratification, timely identification of high-risk groups and development of individualised treatment strategies.

Conclusions. Age, gender, presence of comorbidities, immunological and laboratory markers play an important role in determining the severity of COVID-19. Further studies are needed to validate these risk factors and develop clinical guidelines to improve outcomes in patients with COVID-19.

Key words: COVID-19, predictors, SARS-CoV-2, severity, comorbidity.

1. Introduction

COVID-19 coronavirus infection has been associated with high rates of ICU hospitalisations and the need for respiratory support in patients with certain comorbidities. Polyorgan failure in COVID-19 could occur due to progression of respiratory failure. In such cases, patients were transferred to intensive care units, where the fight for their life continued for an average of a week. A comprehensive study of the risks and protective factors against COVID-19 helps in the development of measures to slow transmission and protect health systems. These measures should include diagnosis, isolation and treatment of all COVID-19 cases, including mild to moderate disease. Current scientific research describes various patient factors that may be useful to clinicians in predicting COVID-19 severity and mortality. These factors include: Demographic. Older age is considered a key predictor of mortality. There is also evidence that male gender is associated with a more severe course of COVID-19. Clinical. The proportion of the main clinical symptoms of infection has been determined, and the incidence of complications in severe forms of COVID-19 has been analysed.

The dynamics of cytokine status in patients with severe forms of COVID-19 was studied, and the diagnostic significance of each cytokine studied was determined. haematological. The diagnostic significance of the main laboratory markers of peripheral blood: levels of leukocytes, platelets, relative and absolute number of neutrophils, lymphocytes was determined. Biochemical. High levels of factor VIII and low protein C activity have been described in some critical patients. Radiological. ST segment elevation in COVID-19 is associated with a poor prognosis despite variability in clinical manifestations [1]. The risk of severe course of the disease and unfavourable outcomes in patients of older age groups. It is associated with a decline in the functions of the immune system, occurring with age, a decrease in physiological reserves, polymorbidity. Patients with comorbidities such as arterial hypertension or diabetes mellitus statistically carry the disease in a more severe form. Hypoxia is the pathological process that underlies the development of

multi-organ failure in COVID-19. All structural and metabolic damage is a direct or indirect consequence of hypoxia. Changes in laboratory parameters depend on the stage of infection. For example, a decrease in the level of lymphocytes, the main cells of the immune system, is one of the main signs in COVID-19. CT findings may include COVID-19-specific lung changes such as frosted glass-like thickening, areas of consolidation, reticular changes, and others. In addition to the major risk factors for COVID-19 severity and mortality, laboratory values and levels of pro-inflammatory cytokines that may indicate worsening clinical outcomes include: inflammatory markers. Elevated levels of C-reactive protein, ferritin, D-dimer, fibrinogen, lactate dehydrogenase, and COE. Coagulation. Increased levels prothrombin time and activated partial thromboplastin time. Elevated levels proinflammatory cytokines. These include IL-6, IL-1, tumour necrosis factor α and interferon gamma [2,3,4].

Objective: To study risk factors associated with the prevalence and severity of COVID-19 in the adult population to improve patient stratification and optimize therapy.

2. Materials and Methods

This study is a retrospective cohort study. We retrospectively analysed 511 case histories from 3696 patients with confirmed SARS-CoV-2 infection who were observed in the city infectious disease hospital of Shymkent, Kazakhstan in the period from January to October 2021. Patients were divided into 2 groups: main group (n=327) - with comorbidities, control group (n=184) - without comorbidities.

- 1) The observed group of cardiovascular system (CVS) comorbidities included: coronary heart disease (CHD), arterial hypertension (AH);
- 2) in the group of concomitant endocrine diseases (ED) obesity of 2 degrees and more, diabetes mellitus (DM) type I and II;
- 3) in the group of concomitant malignant neoplasms (MN) skin cancer, haemoblastosis, neuroblastosis, gastric cancer, breast cancer;
- 4) in the group of associated other diseases (OD) chronic kidney disease (CKD), HIV infection, chronic gastritis, hepatitis, chronic pancreatitis, iron deficiency anaemia.
- 5) in the group of associated autoimmune diseases systemic lupus erythematosus, rheumatoid arthritis.

Data collection. We analysed data from electronic medical records: social status, demographic characteristics, comorbidities, risk factors for exposure (including contact with a known COVID-19 case, recent history of travel to COVID-19-disadvantaged countries),

presence of symptoms several days before onset, vital signs at first clinical presentation (respiratory rate, blood pressure, temperature and pulse rate), respiratory symptoms, gastrointestinal symptoms, detection of pneumonia on physical examination.

Inclusion criteria: Age over 18 years; history of: positive PCR assay for SARS-CoV-2, evidence of one or more comorbidities; treatment of the patient in hospital.

Exclusion criteria: age below 18 years; pregnant women, absence of PCR data.

Methods. Logistic regression method was used to build a predictive model of the probability of a certain outcome. Nijelkerk's R2 coefficient served as a measure of certainty; it indicates the part of the variance explained by logistic regression. To assess the diagnostic significance of quantitative traits in further predicting a certain outcome, the ROC curve analysis method was used. The separating value of the quantitative trait at the cut-off point was categorised by the highest value of the Youden index. A predictive model was developed to determine the probability of an outcome that depended on the laboratory data index. Categorical data were displayed with exact values and percentages. Comparison of percentages in the analysis of four-field contingency tables was performed on the basis of Pearson's chi-square test (for expected values greater than 10), Fisher's exact test (for expected values less than 10).

Comparison of percentages in the analysis of multi-field contingency tables was performed using Pearson's chi-square criterion. We analysed the indicator 'patient status: 1-working, 2-not working' as a function of the indicator 'group 1-counter, 2-osn', significant differences (p < 0.001) were found (based on the method: Pearson's chi-square).

3. Results

As a result of the analysis of the indicators 'sex: 1-wife, 2-husband' depending on the indicator 'group 1-contr, 2-osn'. According to the presented table, when analysing the indicator 'sex: 1-woman, 2-male' depending on the indicator 'group 1-counter, 2-osn', significant differences were found (p<0.001). Significance was found when comparing the control and main group by place of residence (p=0.003). The odds of living in the village were 2.368 times higher in the control group compared to the main group, the differences in odds were statistically significant (95% CI: 1.320 - 4.248).

 \ast - predictor influence is statistically significant (p<0.05)

This regression model obtained is statistically significant (p<0.001). Based on the value of the Nijelkerk coefficient of determination, the model explains 45.8% of the observed variance of the outcome.

When the indicator 'platelets' was analysed, the odds of fatal outcome increased when above 320 by a factor of 4.974. When the 'albumin' indicator was

analysed, the odds of mortality increased at a reading of 2 by a factor of 40.069. When the indicator 'creatinine 1-(62-115 μmol/l), 2-(above 115 μmol/l)' was analysed, the odds of mortality increased with a reading above 115 by a factor of 2.246. When assessing the indicator 'LDH:1-(240-480 U/L.), 2-(above 480 U/L.)', the odds of mortality increased with a value above 480 by a factor of 6.473. Analysis of 'troponin: 1-(0.2 - 0.5 ng/ml), 2-(above 0.5 ng/ml)' increased the odds of mortality above 0.5 by a factor of 3.195. By analysing the indicator 'red blood cells: 1-(3.5-4.00), 2-(3.0-3.5), 3-(2.9-2.5), 4-(<2.5)', the odds of mortality were increased at 2.9-2.5 by 43.886 times, and at less than 2.5 by 16.471 times. In the analysis of 'leucopenia: 1-(1.5 x 109/L), 2-(0.5-1 x 109/L), 3-(less than 0.5 x 109/L), 4-no', the odds of mortality were increased at less than 0.5 by a factor of 32.521 (Table 3).

Table 1 - Demographic data

Indicator	Categories	Main group	Control group	р
maliant atalan	works	92 (50,0)	93 (28,5)	< 0,001*
patient status –	not working	92 (50,0)	233 (71,5)	
	City	168 (91,3)	266 (81,6)	0,003*
place of residence –	Village	16 (8,7)	60 (18,4)	
J	Women	71 (38,6)	195 (59,8)	< 0,001*
gender –	Men	113 (61,4)	131 (40,2)	
* - differences are statisticall	ly significant (p < 0.05)			

Table 2 - Analysis of the age indicator of patients

Indicator	Categories	Main group	Control group	p
	нет	1 (0,5)	0 (0,0)	< 0,001*
age of patients at the time of	18-34	53 (28,8)	20 (6,1)	
the examination	35-59	128 (69,6)	162 (49,7)	
	60 и более	2 (1,1)	144 (44,2)	
* - differences are statistically sign	nificant (n < 0.05)			

Table 3 - Characteristics of the relationship between model predictors and the probability of identifying the outcome

Indicators	Unadjusted		Adjusted	
	COR; 95% ДИ	p	AOR; 95% ДИ	p
platelets	3,000; 1,204 – 7,471	0,018*	4,974; 1,551 – 15,959	0,007*
albumin	13,452; 1,198 – 150,958	0,035*	40,069; 3,384 – 474,850	0,003*
creatinine	9,167; 5,409 – 15,534	< 0,001*	2,246; 1,112 – 4,536	0,024*
LDH	11,097; 6,673 – 18,449	< 0,001*	6,473; 3,146 – 13,316	< 0,001*
troponin	9,609; 5,812 – 15,895	< 0,001*	3,195; 1,619 – 6,309	0,001*
erythrocytes	33,381; 3,959 – 281,463	0,001*	43,886; 4,116 – 467,781	0,002*
leucopenia	5,143; 0,617 – 42,863	0,130	32,521; 3,168 – 333,953	0,003*

Our group analysed the indicator 'D-dimer: 1-(up to $0.5 \mu g/ml$), 2-(above $0.5 \mu g/ml$) ' as a function of the indicator "group 1-contr, 2-osn". The odds of indicator 2 in the indicator 2 group were 3.370 times higher compared to the indicator 1 group, the odds differences were statistically significant (95% CI: 2.310 -4.918). We analysed the indicator of 'CRP: 1-(0-1 mg/L.), 2-(above 1 mg/L.)' according to the indicator group 1counter, 2-axis. According to the obtained data, we found

statistically significant differences (p < 0.001) when evaluating the indicator 'CRP: 1-(0-1 mg/litre), 2-(above 1 mg/litre)' depending on the indicator 'group 1-counter, 2osn' (method used: Pearson's Chi-square). When evaluating the indicator 'ferritin: " depending on the indicator "group 1-contr, 2-osn', we found statistically significant differences (p< 0.001) (method used: Pearson's Chi-square) (Table 4).

Table 4 - Analysis of laboratory data indicators

Indicator	Categories	Control group	Main group	p
D-dimer	up to 0.5	173 (94,0)	230 (70,6)	< 0,001*
	above 0.5	11 (6,0)	96 (29,4)	
CRP _	0-1	118 (64,1)	113 (34,7)	< 0,001*
	above 1	66 (35,9)	213 (65,3)	
Ferritin	norm	167 (90,8)	174 (53,4)	< 0,001*
	increase	17 (9,2)	152 (46,6)	

predictor influence is statistically significant (p < 0.05)

When assessing the dependence of the probability of lethal outcome on the value of the logistic

function P using ROC-analysis, the following curve was obtained (Figure 1).

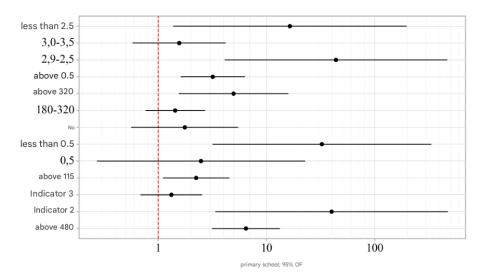


Figure 1 - Estimates of odds ratios with 95% CI for the studied predictors of Outcome

The area under the ROC curve was 0.875 ± 0.024 with 95% CI: 0.828 - 0.923.

This resulting model was statistically significant (p < 0.001) (Figure 2).

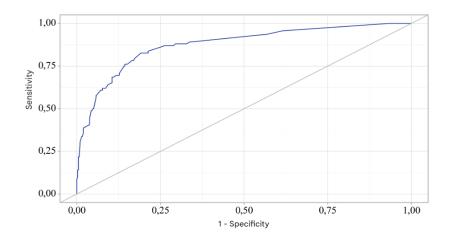


Figure 2 - ROC-curve characterising the dependence of the Exodus probability on the value of the logistic function P

The threshold value of the logistic function P at the cut-off point, which corresponded to the highest value of the Youden index, was 0.147. The prediction of lethal outcome when the value of the logistic function P is higher than or equal to this value. The sensitivity and

specificity of the model were 82.6% and 80.9%, respectively (Figure 3).

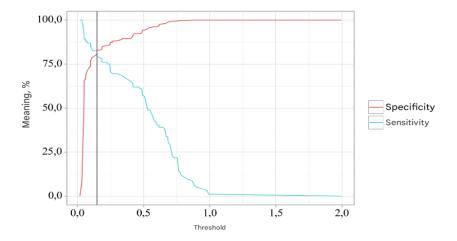


Figure 3 - Sensitivity and specificity analysis of the model depending on the threshold values of the logistic function P

4. Discussion

The study investigated parameters that could predict unfavourable outcome in patients with COVID-19, such as: demographic characteristics. Patient's severity, body mass index, oxygen saturation, percentage of pulmonary tissue lesions on computed tomography were considered. Co-morbidities. Arterial hypertension, ischaemic heart disease, stroke, atrial fibrillation, obesity, diabetes mellitus, bronchial asthma, chronic obstructive pulmonary disease and others were assessed. According to the results of this study, patients' demographic and social characteristics such as age, gender, place of residence, underlying diseases, and analysis laboratory data (e.g., low albumin and leukocyte levels, elevated LDH levels) were associated with COVID-19 disease outcomes in patients with comorbidities. Some demographic and social factors reported by foreign publications are associated with a higher incidence of severe clinical course of COVID-19 [5-8]. Among which, older age is a major predictor of mortality and is thus considered a key factor in the proposed clinical severity risk scales [9]. Another study that reported an increased focus on age and gender also found a greater impact on COVID-19 outcomes [10]. A history of comorbidities such as cardiovascular disease, chronic kidney disease, chronic lung disease (especially COPD), diabetes mellitus, hypertension, immunosuppression, obesity and anaemia

predispose patients to a poor outcome in COVID-19 [11-15]. In this study in patients having cancer status were predisposed with high probability of fatal outcome. Among the comorbidities, oncopathology is the major comorbidity that is associated with poor outcomes COVID-19 [16,17]. The reason for this hypothesis is the fact that, fatal outcome from COVID-19 in patients having oncological status is associated with male gender, previous comorbidities and age more than 55 years [18]. The article states that after cancer patients, in patients diagnosed with diabetes mellitus COVID-19 was very severe. Worldwide, the prevalence of diabetes mellitus among people with COVID-19 is very high. The Centers for Disease Control and Prevention (CDC) in the US reported that diabetes mellitus is a common comorbidity, with a prevalence of about 10% among 122.653 people with COVID-19 [19]. One study indicated that the prevalence of diabetes was about 17% among 1,043 COVID-19 patients with comorbidities [20]. A metaanalysis comprising 18 studies (n=14.558) from China, the USA and Italy found an increased severity of disease course in people with diabetes compared with those without [21]. The largest nationwide study, conducted in England (n=61.414.470), found 3.5 and twice the odds of COVID-19-related in-hospital death in people with DM1 and DM2, respectively [22]. One study confirmed anaemia in 35.5% of 222 hospitalised patients, while another study confirmed anaemia in 61% of 206 patients with COVID-19, showing a high prevalence of anaemia among patients with COVID-19 [23-25]. In our study, patients diagnosed with anaemia had poor clinical condition, thus showing poor survival rate and prolonged stay in health care facility, the data are consistent with the foreign data cited [26]. Information from foreign countries confirmed the relevance of different biochemical tests as independent or having as part of their correlates to determine the severity, poor prognosis or mortality associated with COVID-19 [27]. Clinical laboratory tests comprising biochemical, and haematological, inflammatory coagulation parameters have been considered to recognise severe or critical forms of COVID-19. Also, these parameters provided valuable clinical information to effectively monitor the clinical course of COVID-19. According to our study, D-dimer was associated with the worst prognosis of COVID-19. Elevated D-dimer levels in patients with COVID-19 are a marker for the presence of disseminated intravascular coagulopathy and severe disease course, which prompted clinicians to hypothesise that elevated D-dimer concentrations are indicative of comorbid disease. Existing venous thromboembolism, leading to ventilation-perfusion mismatch [28]. A study of 343 patients with COVID-19 showed that 12 of 67 patients with D-dimer levels ≥2.0 µg/mL on admission died compared with 1 of 267 patients whose D-dimer levels were <2.0 µg/mL (P< 0.001; hazard ratio 51.5; 95% CI 12.9-206.7), showing a very high mortality rate among patients with COVID-19 [29]. According to our study, elevated lactate dehydrogenase (LDH) level was statistically significant and associated with greater disease severity, which is consistent with other data from foreign studies [30,31]. Our results suggest a high association of lowered white blood cell count with the diagnosis of COVID-19. In the above study, out of 1099 cases, leucopenia was observed in 33.7% of patients on admission and was more severe in severe cases [32]. In the present study, high cardiac troponin levels were noted in patients with severe COVID-19 disease. It is hypothesised that biochemical markers of cardiac dysfunction are associated with the severity of COVID-19 disease [33]. Cardiac complications associated with COVID-19 are directly related to elevations in both troponin and brain natriuretic peptide (BNP) levels. A meta-analysis including 17.794 patients showed that patients with high troponin I levels were more likely to have an unfavourable prognosis (OR=5.22, 95% CI=2.73-7.31, P<0.001) and that high troponin I levels (>13.75 ng/L) combined with elevated AST levels (>28 units/L) or advanced age (>60 years) were strong predictors of poor outcome [34].

5. Conclusion

Factors like age, comorbidities, immune response, laboratory markers and measures of organ dysfunction may individually or collectively predict worse outcomes in COVID-19 disease. Establishing the factors that dispose COVID-19 complications is critical to guide clinical care, improve patient outcomes, and allocate limited resources. 'Patients with COVID-19 who have comorbid conditions such as arterial hypertension, obesity, chronic lung disease, diabetes mellitus, and cardiovascular disease statistically have a worse disease burden. These people usually have the worst prognosis compared to patients without comorbidities. They should take all necessary precautions to avoid SARS

CoV-2 infection. Thus, abnormal laboratory findings are important early predictors of COVID-19 severity and inhospital mortality. Also, pre-existing chronic diseases especially arterial hypertension, diabetes mellitus, anaemia, oncology are an indicator of high risk of mortality. Therefore, in such cases, urgent interventions should be applied. Professional actions to improve patient management can reduce the likelihood of unfavourable patient outcomes.

Conflicts of interest: None to declare

Institutional Review Board Statement: Not applicable.

Author contributions. M.Z.A. – concept and design; data access, statistical analysis, manuscript drafting, and supervision. G.N.A. – manuscript drafting and critical revision for important intellectual content. G.G.S., T.D.,

and I.S.S. – critical revision for important intellectual content; data acquisition, analysis, and interpretation; manuscript drafting. All authors have read and agreed to the published version of the manuscript.

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Қосымша аурулары бар науқастардағы COVID-19 инфекциясын қолайсыз нәтижесін болжаудың дәлелді моделі

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Түйіндеме

СОVID-19 пандемиясы денсаулық сақтау жүйелері үшін бұрын-соңды болмаған ауыртпалыққа айналды, бұл қарқынды терапия мен тыныс алуды қолдаудың шұғыл қажеттілігін атап өтті. Ағзаның көптеген мүшелері мен жүйелерінің жеткіліксіздігімен асқынған ауыр COVID-19 ағымы көбінесе жансақтау бөлімшелеріне ұзақ мерзімді ауруханаға жатқызуға әкеледі. Емдеу стратегиясын оңтайландыру және денсаулық сақтау жүйесін шамадан тыс жүктемеден қорғау үшін қауіп факторлары мен қорғаныс туралы терең түсінік қажет.

Зерттеудің мақсаты: науқастардың стратификациясын жақсарту және терапияны оңтайландыру үшін ересек популяцияда COVID-19 таралуы мен ауырлығына байланысты қауіп факторларын зерттеу.

Әдістері. Бұл зерттеу ретроспективті, когортты болып табылады. 2021 жылдың қаңтар-қазан айлары аралығында Шымкент қаласының (Қазақстан) Қалалық жұқпалы аурулар ауруханасында байқалған SARS-CoV-2 инфекциясы расталған 3696 пациенттің 511 ауру тарихы ретроспективті талданды. Науқастар 2 топқа бөлінді: негізгі топ (n=327) - қатар жүретін аурулары бар, бақылау тобы (n=184) - қатар жүретін аурулары жоқ.

Нәтижелері. Талдау COVID-19 ағымын болжау үшін пайдаланылуы мүмкін демографиялық, клиникалық (тән белгілер, асқынулар), иммунологиялық (цитокиндік дауыл), гематологиялық (лейкоциттер, тромбоциттер деңгейі), биохимиялық (VIII фактор, C-реактивті ақуыз) және рентгенологиялық (өкпе тінінің өзгеруі) факторлардың жиынтығын анықтады. Қатар жүретін аурулардың (артериялық гипертензия, қант

диабеті) аурудың ауыр ағымының жоғары қаупімен байланысы расталды. Гипоксия көптеген органдардың жеткіліксіздігінің дамуында шешуші рөл атқарады. Қабыну маркерлері (С-реактивті ақуыз, ферритин, D-димер) және қабынуға қарсы цитокиндер (ІС-6, ІС-1) қолайсыз нәтижелердің болжаушылары болып табылады.

Қорытынды. COVID-19 ауырлығын анықтауда науқастың жасы, жынысы, қосымша аурулардың болуы, иммунологиялық және зертханалық маркерлер маңызды рөл атқарады. Осы қауіп факторларын растау және COVID-19 ауыртатын науқастардың нәтижелерін жақсарту үшін клиникалық нұсқауларды әзірлеу үшін қосымша зерттеулер қажет.

Түйін сөздер: COVID-19, болжаушы факторлар, SARS-CoV-2, ауырлық дәрежесі, қосымша патология.

Доказательная модель прогнозирования неблагоприятного исхода у больных COVID-19 с коморбидной патологией

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Резюме

Пандемия COVID-19 стала беспрецедентным бременем для систем здравоохранения, подчеркнув острую необходимость в интенсивной терапии и респираторной поддержке. Тяжелое течение COVID-19, осложненное полиорганной недостаточностью, часто приводит к длительной госпитализации в отделения интенсивной терапии. Для оптимизации стратегии лечения и защиты системы здравоохранения от перегрузки необходимо глубокое понимание факторов риска и защиты.

Цель исследования: изучить факторы риска, связанные с распространенностью и тяжестью течения COVID-19 среди взрослого населения, для улучшения стратификации пациентов и оптимизации терапии.

Методы. Данное исследование является ретроспективным, когортным. Ретроспективно проанализировано 511 историй болезни 3696 пациентов с подтвержденной SARS-CoV-2 инфекцией, наблюдавшихся в городской инфекционной больнице г. Шымкента (Казахстан) в период с января по октябрь 2021 года. Пациенты были разделены на 2 группы: основная группа (n=327) - с сопутствующими заболеваниями, контрольная группа (n=184) - без сопутствующих заболеваний.

Результаты. Анализ выявил набор демографических, клинических (характерные симптомы, осложнения), иммунологических (цитокиновый шторм), гематологических (уровень лейкоцитов и тромбоцитов), биохимических (фактор VIII, С-реактивный белок) и рентгенологических (изменения в легочной ткани) факторов, которые могут быть использованы для прогнозирования течения COVID-19. Подтверждена связь сопутствующих заболеваний (артериальная гипертензия, сахарный диабет) с повышенным риском тяжелого течения заболевания. Гипоксия играет ключевую роль в развитии полиорганной недостаточности. Маркеры воспаления (С-реактивный белок, ферритин, D-димер) и провоспалительные цитокины (IL-6, IL-1) являются предикторами неблагоприятных исходов.

Выводы. Возраст, пол, наличие сопутствующих заболеваний, иммунологические и лабораторные маркеры играют важную роль в определении тяжести COVID-19. Необходимы дальнейшие исследования для подтверждения этих факторов риска и разработки клинических рекомендаций для улучшения результатов лечения пациентов с COVID-19.

Ключевые слова: COVID-19, предикторы, SARS-CoV-2, тяжесть, сопутствующая патология.