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PREDICTIVE VALUE OF HEMOGRAM INDICES IN THE EVALUATION OF THE 30-DAY MORTALITY RISKS IN COVID-19 DEPENDING ON GENDER

Lyudmila G. Turgunova[1], https://orcid.org/0000-0002-6962-4247

Irina V. Mekhantseva[1], https://orcid.org/0000-0001-6601-8172

Yelena M. Laryushina[1], https://orcid.org/0000-0002-9590-690X

Assel R. Alina[1], https://orcid.org/0000-0002-3229-1506

Anar A. Turmukhambetova[2], https://orcid.org/0000-0002-4668-3295

[1] Karaganda Medical University, Department of Internal Medicine, Karaganda, Kazakhstan;
[2] Karaganda Medical University, Department of Strategic Development and Science, Karaganda, Kazakhstan.

Abstract

The aim. SARS-CoV-2 infection can have a profound effect on the functioning of the immune system. Differences in the prognostic significance of hemogram indices raise the question of existing gender immunological differences. The study aims to compare the significance of the hematological indices for the evaluation of the 30-day mortality risk in men and women.

Materials and methods. A retrospective observational study included 1419 patients with a positive PCR nasopharyngeal swab for COVID-19 hospitalized between 1 May 2021 and 30 August 2021 at Karaganda clinical hospital, Kazakhstan. Laboratory tests performed upon admission included a complete blood count to obtain NLR, NPR, PLR, and SII. A receiver operating characteristic curve was performed to analyze the efficiency of the prognosis of the 30-day mortality. Using univariate and multivariate Cox regression was analyzed the association of neutrophil indices with mortality.

Results. In total, 95 people (8.5%) died in 30 days, the mortality rate among men was 1,9 times higher than among women. The value of SII and TLR in predicting mortality in women was AUC 0.714 and 0.624 respectively. In men, NLR had the highest AUC of 0.736.

Conclusion. Elevated NLR, NPR, and SII have significant predictive value in COVID-19 mortality, especially NPR in females and NLR in males.

Key words: *COVID-19, mortality, gender, hemogram indices, neutrophil-lymphocyte index.*

Резюме

ПРОГНОСТИЧЕСКАЯ ЦЕННОСТЬ ИНДЕКСОВ ГЕМОГРАММЫ В РИСКЕ РАЗВИТИЯ 30-ДНЕВНОЙ СМЕРТНОСТИ ПРИ COVID-19 В ЗАВИСИМОСТИ ОТ ПОЛА

Людмила Г. Тургунова[1], https://orcid.org/0000-0002-6962-4247

Ирина В. Механцева[1], https://orcid.org/0000-0001-6601-8172

Елена М. Ларюшина[1], https://orcid.org/0000-0002-9590-690X

Асель Р. Алина[1], https://orcid.org/0000-0002-3229-1506

Анар А. Турмухамбетова[2], https://orcid.org/0000-0002-4668-3295

[1] НАО «Медицинский университет Караганды», Кафедра внутренних болезней, г. Караганда, Республика Казахстан;
[2] НАО «Медицинский университет Караганды», г. Караганда, Республика Казахстан.

Цель. Инфекция SARS-CoV-2 может оказывать сильное влияние на функционирование иммунной системы. Различия показателей прогностической значимости гемограмм ставят вопрос о существующих гендерных иммунологических различиях. Целью исследования является сравнение значимости гематологических показателей для оценки риска 30-дневной смертности у мужчин и женщин.

Материалы и методы. Мы провели ретроспективное обсервационное исследование, которое включало 1419 пациентов с положительным ПЦР-мазком из носоглотки на COVID-19, госпитализированных в период с 1 мая 2021 г. по 30 августа 2021 в Областную клиническую больницу г. Караганды. Лабораторные тесты, проведенные при поступлении, включали полный анализ крови для получения NLR, NPR, PLR и SII. Кривая ROC была построена для анализа эффективности прогноза 30-дневной смертности. С помощью одномерной и многомерной регрессии Кокса была проанализирована ассоциация нейтрофильных индексов со смертностью.

Результаты. По результатам проведенного исследования за 30-дневный период умерло 95 человек (8,5%), смертность среди мужчин была в 1,9 раза выше, чем среди женщин. Мы обнаружили повышенные значения NLR,

NPR и SII у пациентов с фатальным исходом COVID-19 независимо от пола. Тем не менее, мы впервые сравнили прогностическую значимость индексов воспаления, основанные на подсчете клеток крови, такие как NLR, NPR, TLR и SII, для смертности у мужчин и женщин. В частности, в нашем исследовании значения AUC как NLR, так и NPR были самыми высокими среди оцениваемых комбинированных индексов для прогнозирования смертности (0,785 и 0,798) у женщин и NLR – у мужчин (0,736).

Заключение. Данные маркеры могут быть полезными для прогнозирования смертности, у женщин особенно NPR, у мужчин - NLR.

Ключевые слова: *COVID-19, пол, смертность, гематологические индексы, нейтрофильно-лимфоцитарный индекс.*

Түйіндеме

COVID-19 КЕЗІНДЕ ЖЫНЫСЫНА БАЙЛАНЫСТЫ 30 КҮНДІК ӨЛІМ ДАМУЫ ҚАУПІНДЕГІ ГЕМОГРАММА ИНДЕКСТЕРІНІҢ БОЛЖАМДЫ МӘНІ

Людмила Г. Тургунова[1], https://orcid.org/0000-0002-6962-4247

Ирина В. Механцева[1], https://orcid.org/0000-0001-6601-8172

Елена М. Ларюшина[1], https://orcid.org/0000-0002-9590-690X

Асель Р. Алина[1], https://orcid.org/0000-0002-3229-1506

Анар А. Турмухамбетова[2], https://orcid.org/0000-0002-4668-3295

1 "Қарағанды медицина университеті" КЕАҚ, Ішкі аурулар кафедрасы, Қарағанды қ., Қазақстан Республикасы;
2 "Қарағанды медицина университеті" КЕАҚ, Стратегиялық даму және ғылым факультеті, Қарағанды қ., Қазақстан Республикасы.

Зерттеу мақсаты: SARS-CoV-2 инфекциясы иммундық жүйенің жұмысына қатты әсер етуі мүмкін. Гемограммалардың болжамды маңыздылығы көрсеткіштерінің айырмашылықтары белгілі гендерлік иммунологиялық ерекшеліктер туралы сұрақ туғызады. Зерттеудің мақсаты ерлер мен әйелдердің 30 күндік өлім қаупін бағалау үшін гематологиялық көрсеткіштердің маңыздылығын салыстыру болып табылады.

Материалдар мен әдістер: Біз 2021 жылғы 1 мамыр мен 2021 жылғы 30 тамыз аралығында Қарағанды қаласының Облыстық клиникалық ауруханасына жатқызылған COVID-19-ға оң мұрын-жұтқыншақ ПТР-жағындысы бар 1419 пациентті қамтитын ретроспективті обсервациялық зерттеуін жүргіздік. Қабылдау кезінде жүргізілген зертханалық зерттеулер NLR, NPR, PLR және SII алу үшін толық қан анализін қамтыды. ROC қисығы 30 күндік өлім болжамының тиімділігін талдау үшін салынды. Бір өлшемді және көп өлшемді Кокс регрессиясы арқылы нейтрофильді индекстердің өліммен байланысы талданды.

Нәтижелері және талқылауы: Зерттеу нәтижелері бойынша 30 күндік кезеңде 95 адам қайтыс болды (8,5%), ерлер арасындағы өлім әйелдерге қарағанда 1,9 есе жоғары болды. Біз жынысына қарамастан өліммен аяқталған COVID-19 пациенттерінде NLR, NPR және SII мәндерінің жоғарылағанын анықтадық. Дегенмен, біз алғаш рет ерлер мен әйелдердің өлімі үшін NLR, NPR, TLR және SII сияқты қан жасушаларын санауға негізделген қабыну индекстерінің болжамдық маңыздылығын салыстырдық. Атап айтқанда, біздің зерттеуімізде NLR және NPR тәрізді AUC мәндері әйелдерде (0,785 және 0,798) және NLR – ерлерде (0,736) өлімді болжау үшін бағаланған біріктірілген индекстер арасында ең жоғары болды.

Қорытынды: Бұл маркерлер әйелдерде, әсіресе NPR, ерлерде – NLR өлімді болжау үшін пайдалы болуы мүмкін.

Түйінді сөздер: *COVID-19, жыныс, өлім, гематологиялық индекстер, нейтрофилді-лимфоцитарлық индекс.*

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Introduction

COVID-19, which had spread rapidly from China around the world in 2019, had infected more than 410,000,000 people by early 2022 and caused 5,810,880 deaths worldwide, creating a global crisis worse than all previous epidemics and pandemics [27]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause a wide variety of symptoms ranging from mild manifestations to severe pneumonia with acute respiratory failure, respiratory distress syndrome, and death [28].

The mortality rate for COVID-19 according to a meta-analysis was 17.1%, ranging from 11,5% in the general population of hospitalized patients to 40.5% among critically ill patients [14]. Mortality rates were higher among men than women, 4.7–13.8% and 2.8–10.2%, respectively [18,29]. Of the total number of deaths, males accounted for 65%–70.5% [4,6]. However, most studies did not consider gender as a decisive factor in data analysis, despite its clear implications for mortality from COVID-19.

SARS-CoV-2 infection can have a profound effect on the functioning of the immune system, leading to severe dysregulation and depletion of immune cells [15]. Inflammatory syndrome, one of the mechanisms of dysregulation of the body's immune response to COVID-19, is characterized by an increase in pro-inflammatory markers and the potential development of life-threatening multiple organ failure and mortality [16]. The research shows differences in the levels of mediators in men and women depending on the severity of the disease. In males, especially in severe cases, a high level of pro-inflammatory markers was noted. In female patients, compared with males, a favorable phenotype was revealed in the form of an increased level of the anti-inflammatory marker interleukin-10 (IL-10). IL-10 is involved in inflammation resolution and tissue repair in inflammatory diseases [21].

The neutrophil-to-lymphocyte ratio (NLR), which appears to be more sensitive than isolated absolute neutrophil or lymphocyte counts in both bacterial and viral pneumonia, is a known marker of the systemic inflammatory response. Since the beginning of the pandemic, numerous studies have shown the significance of NLR in predicting the severity of COVID-19, the risk of intubation, need for the intensive care, and mortality [5]. The results of a meta-analysis showed that there is no consensus on the optimal threshold of the NLR index. The wide variation means that optimal thresholds may differ in different populations, as NLR has previously been found to depend on ethnicity, age, and gender [23].

In addition to NLR, hemogram indices including platelet levels have shown some promise. This is due to the fact that several studies have described the prognostic value of thrombocytopenia, which is associated with a more severe course of the disease and deterioration in the function of external respiration, and supposedly it can be used to predict not only 28-day mortality but also long-term mortality after 6 months [30]. Platelet-lymphocyte ratio (PLR) has been described as a possible predictor for the severity of COVID-19, but not mortality [24]. The least studied hemogram-derived ratio is the Systemic immune-inflammation index (SII), which is defined as platelet count×NLR, and NPR (neutrophil-to-platelet ratio). Two studies have found that SII can predict COVID-19 mortality the same as NLR, but the best prognostic marker was not determined in these studies [5,7]; in another study, SII was superior to NLR, Monocyte-to-lymphocyte ratio (MLR) and PLR in predicting mortality [10]. Currently, there are no studies investigating the predictive value of hemogram-derived indices on the risk of mortality in men and women with COVID-19.

Our study aimed to investigate the significance of NLR, TLR, NPR, and SII in predicting 30-day mortality in patients with COVID-19 depending on gender.

Materials and methods. Our retrospective study included 1419 patients (608 men and 811 women) who were hospitalized from May to August 2021 with COVID-19 associated pneumonia in the infectious diseases center of the Karaganda regional clinical hospital and the clinic of the Karaganda Medical University. *The study included* all patients with COVID-19 who were hospitalized between May and August 2021. Inclusion Criteria: Adults over 18 years of age, PCR-positive for COVID-19 nasopharyngeal swab. *Exclusion criteria:* children under the age of 18, pregnant or lactating women. Demographic data, comorbidities, blood pressure (BP), heart rate, and oxygen saturation were collected for all patients from electronic medical records. Laboratory tests performed upon admission included complete blood count and biochemical parameters (alanine aminotransferase, aspartate aminotransferase, bilirubin, and creatinine). Charlson comorbidity index were calculated for all patients. The percentage of lung tissue damage was estimated according to the results of chest computed tomography (CT). All tests were carried out within the first two days of admission to the hospital. The observation period was 30 days from the date of admission. The primary endpoint was death (we determined mortality from all causes and from specific causes); the life status of the patients discharged before the censoring date was ascertained using phone calls made by two physicians on October 20, 2021. Of the 1419 patients, 300 patients were excluded: 98 had no results of the actual biochemical test, 169 patients did not have a chest CT scan, and 33 lacked a full leukocyte count. In the end, a total of 1119 patients (646 women and 473 men) were included in the analysis. The study was approved by the ethical committee of the Karaganda Medical University dated April 14, 2021, №18.

Statistical analyses were performed using SPSS 21.0. The Kolmogorov-Smirnov test was performed to check the variables for normal distribution. In descriptive statistics, for quantitative comparisons, the Mann-Whitney U-test for independent groups was used; categorical data were analyzed using Pearson's $\chi 2$ test. The receiver operating characteristic (ROC) curve was performed to analyze the efficiency of the prognosis of the 30-day mortality. We exploited Youden Index values to identify the optimal cut-off values. Using univariate and multivariate Cox regression, the association of NLR, PLR, NPR, and SII levels with mortality within 30 days of hospitalization was analyzed and independent predictors and hazard ratios (HR) were established at a 95% confidence interval (CI) for each factor. Covariates with $p<0.05$ or ones changing the main effect estimate by ≥10% were included in the multivariate analysis. The critical significance level (p-level) when testing statistical hypotheses were taken as 0.05.

Results

In the present study, we analyzed data from 646 women and 473 men with COVID-19-associated lung disease. In total, 95 people (8.5%) died in 30 days, of which 81 people died in the hospital (7.2% mortality). The 30-day mortality rate among men was 1,9 times higher than among women: 11.8% (55 patients) versus 6.2% (40 patients), respectively (z=3.22; p=0.001) *(Figure 1A)*. The structure of mortality was: mortality from cardiopulmonary insufficiency (79%) and cerebral edema (19%).

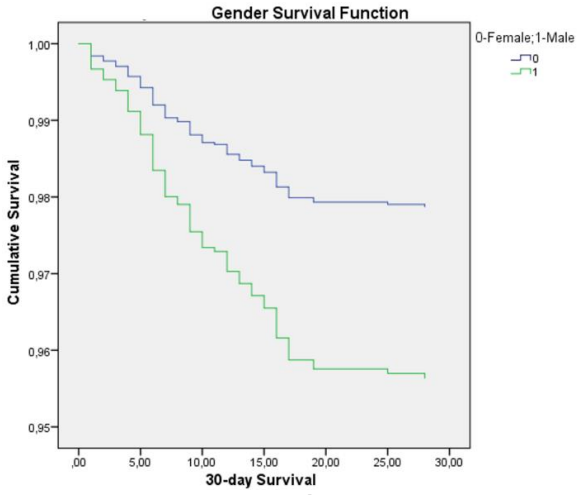
The clinical characteristics and laboratory parameters of patients are presented in *Table 1*. As can be seen from the table, women included in our research were generally older than men: among them, patients aged 65 years and older accounted for 39.6%, while among men – 31.9%. When comparing outcomes by age, female survivors were older than male survivors, 60.5 (51.0–70.0) years and 56.0 (41.0–66.0) respectively (p=0.0001). There was no statistically significant difference in age among female and male non-survivors (67.0 (59–77.5) and 70 (62–78) respectively (p = 0.409)).

Table 1.

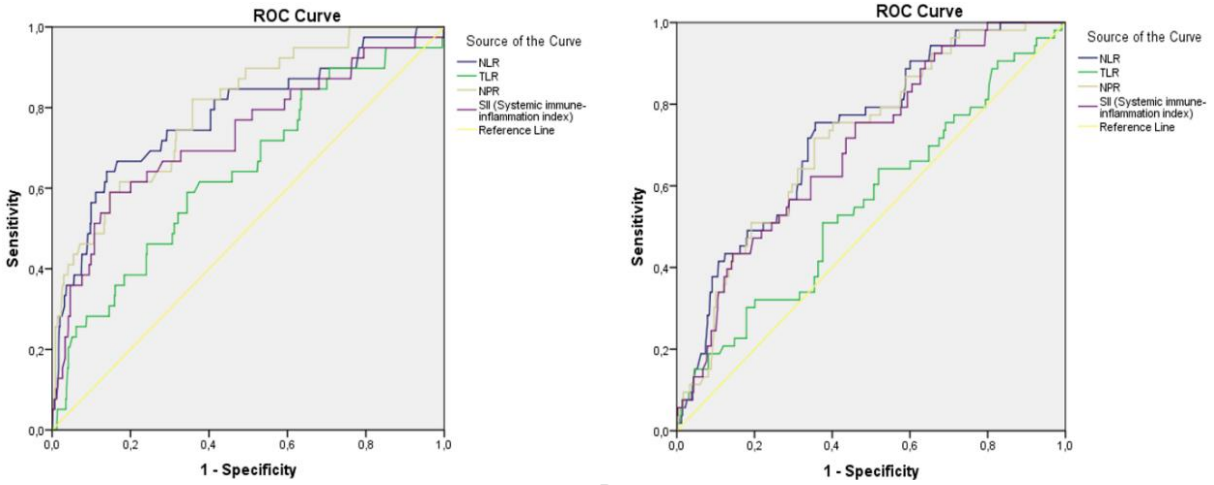
Clinical characteristics and Laboratory parameters of patients depending on gender.

Variables	All patients (n=1119)	Males (n=473)	Females (n=646)	P-level
	Me (Q_{25}-Q_{75})	Me (Q_{25}-Q_{75})	Me (Q_{25}-Q_{75})	
Age, years	60 (48-69)	58 (43-68)	61 (51-70)	0.0001
Younger than 65 (%) 65 years and older (%)	712 (63.7) 407 (36.3)	322 (68,1) 151 (31.9)	390 (60,4) 256 (39.6)	0.004
Comorbidities (%)				
Arterial hypertension	581 (51.9)	228 (48.2)	353 (54.6)	0.033
Chronic heart failure	383 (34.2)	140 (29.6)	243 (37.6)	0.005
Functional class of Chronic heart failure 1 2 3	 259 (23.1) 81 (7.2) 43 (3.8)	 86 (18.2) 36 (7.6) 18 (3.8)	 173 (26.8) 45 (7.0) 25 (3.9)	0,009
Chronic obstructive pulmonary disease	20 (1.8)	14 (3,0)	6 (0,9)	0.011
Chronic kidney disease	62 (5.5)	32 (6.8)	30 (4.6)	0.125
Diabetes mellitus	184 (16.4)	66 (14.0)	118 (18.3)	0.055
Myocardial infarction	38 (3.4)	26 (5.5)	12 (1.9)	0.001
Comorbidity index 0-1 2-3 4	646 (57.7) 286 (25.6) 187 (16.7)	288 (60.9) 98 (20.7) 87 (18.4)	358 (55.4) 188 (29.1) 100 (15.5)	0.283
Clinical data				
Systolic blood pressure., mmHg	120 (120-130)	120 (120-129)	120 (110-130)	0.146
Diastolic blood pressure, mmHg	80 (70-80)	80 (70-80)	80 (70-80)	0.140
Heart rate, beats/min	80 (77-89)	82 (78-90)	80 (76-88)	0.002
Saturation O_2, %	95 (92-97)	95 (91-96)	95 (92-97)	0.055
Lung tissue damage, %	28 (16-50)	28 (17-50)	28 (16-48)	0.815
Computed tomography (%) CT 1 CT 2 CT 3 CT 4	537 (48) 330 (29.5) 174 (15.5) 78 (7)	232 (49) 128 (27.1) 82 (17.3) 31 (6.6)	305 (47.2) 202 (31.3) 92 (14.2) 47 (7.3)	0.294
Aspartate aminotransferase, IU/l	28.0 (23.0-43.0)	30.1 (24.5-48.0)	27.0 (23.0-38.0)	0.0001
Alanine aminotransferase, IU/l	29 (20-37)	30 (20-43)	27 (19-34)	0.0001
Creatinine, μmol/l	86.4 (74.2-98.0)	92.0 (79.5-105.5)	83.0 (71-92)	0.0001
Glucose, mmol/l	6.2 (5.1–7.8)	6.00 (5.10–7.30)	6.47 (5.20–8.37)	0.004
NLR	2.82 (1.78-4.38)	3.19 (2.01-4.93)	2.59 (1.61-4.06)	0.0001
TLR	159.1 (113.3–215.9)	156.6 (111.8-224.8)	160.3 (114.5-209.4)	0.852
NPR	14.27 (8.91–23.72)	16.43 (10.40-27.21)	12.68 (8.12-21.28)	0.0001
SII (Systemic immune-inflammation index)	552.5 (314.7–953.9)	573.71 (328.00-1045.33)	533.08 (300.17-875.82)	0.027

The Charlson comorbidity index equal to 1 or higher was identified in 52.1% of patients: 55% of women and 48.2% of men. The Charlson comorbidity index of 1 or higher was more common in surviving females compared to males – 49.1% and 39.6% respectively (p=0.0001); in non-surviving groups, the comorbidity index of 1 or higher was present in 80.8% of females and 77.1% of males (p=0.934). Gender-dependent differences in the structure of concomitant pathology were revealed in our study: the incidence of COPD and MI was significantly higher in males, while AH and CHF were more common in females. In women, 1 functional class of CHF prevailed (26.8% compared with 18.2% in men); the frequency of decompensated CHF was 3.9% and 3.8%, in women and men respectively.



A



B

Figure 1. (A) Gender-based survival graph. (B) ROC curves for NLR, TLR, NPR, and SII for predicting the mortality of COVID-19 among females (a) and males (b).

In the groups of non-survivors, males compared to females had higher levels of creatinine (p = 0.026), while AST and ALT levels did not differ (p=0.142; p=0.530).

The values of NLR, NPR, and SII were significantly higher in men compared to women, and PLR did not differ between groups (174.6 in men compared to 192.4 in women; p = 0.136). When comparing NLR, NPR, SII, and PLR between groups of female and male survivors, the following statistical differences were found: in the group of female survivors NLR and NPR were 2.52 (1.55–3.89) and 12.3 (7.9–20.0) respectively, this being significantly lower than the same indices in male survivors – 3.00 (1.87–4.62); p= 0.0001) and 15.6 (10.0–25.3); p=0.0001), respectively. There was no considerable difference in PLR and SII between the groups of surviving females (159.1 (113.3–205.3) and 514.45 (298.38–809.18) respectively) and males (155.0 (112.0–223.0); p= 0.974 and 554.00 (320.29–958.47) p=0.067). Between the groups of non-surviving women and men, all hematological indices did not show substantial differences: NLR (p=0.392), NPR (p=0.479), TLR (p=0.136,) and SII (p=0.350).

ROC analysis was performed in both groups to assess the effectiveness of hematological indices in predicting patient mortality *(Figure 1B).*

The extent of lung tissue damage according to CT data did not differ between groups, the percentage of lung tissue damage was less than 50% for the majority of patients in both groups (78.5% of women and 76.1% of men). Among the surviving females and males, the average percentage of lung tissue damage was 26% (15-40) and 25% (15-44) (p = 0.815) respectively; among non-survivors, it extended up to 70% (46-80) and 70% (40-85) (p=0.803). The number of patients in need of invasive ventilation, their oxygen saturation, blood pressure, and the respiratory rate did not differ between the groups. The history of receiving antibacterial drugs and anticoagulants before hospitalization had no significant differences.

Laboratory parameters are shown in Table 1. The data demonstrate that males compared to females had higher levels of transaminases, creatinine, and glucose.

In the group of surviving women, compared with surviving men, the levels of transaminases (p=0.0001) and creatinine (p=0.0001) were significantly lower.

As can be seen from *Table 3*, in females, all indices were statistically significant but differed from each other in terms of predicting efficacy. When the cut-off was chosen for NLR was >5.17 and for NPR >15.26, the given results showed the highest comparable AUCs of 0.785 (95% CI 0.702-0.869) and 0.798 (95% CI 0.727-0.870) respectively. NLR had higher specificity than NPR, but lower sensitivity. The value of SII and PLR in predicting mortality in women was inferior to NLR and NPR: AUC 0.714 (95% CI 0.678–0.749) and 0.624 (0.528–0.720) respectively. In men, hematological parameters were less effective in predicting mortality than in women. PLR had no statistical importance (p=0.381), while NLR had the highest AUC of 0.736 (95% CI 0.671–0.801) compared to NPR and SII.

The results of the unadjusted odds ratio for the variables *(Table 2)* showed that in both groups, an increase in NLR, NPR, and SII was associated with the development of 30-day mortality, while PLR showed a statistically significant relation only in females. Age, the presence of arterial hypertension (AH), chronic heart failure (CHF), diabetes mellitus (DM), and chronic kidney disease (CKD) were factors that significantly increased the risk of mortality in both groups. In men, the higher mortality risks were also connected to myocardial infarction (MI) and chronic obstructive pulmonary disease (COPD).

Table 2.

Results of univariate analysis of indicators with the risk of 30-day mortality in women and men.

Variables	Females		Males	
	cOdds Ratio (95% CI)	P-level	cOdds Ratio (95% CI)	P-level
Age	1.032 (1.008–1.056)	0.008	1.074 (1.049–1.099)	0.0001
Temperature	0.999 (0.972-1.027)	0.967	1.726 (1.217–2.447)	0.002
SBP	1.000 (0.971-1.030)	0.984	1.005 (0.979-1.031)	0.711
Diastolic blood pressure	0.979 (0.938-1.022)	0.328	0.980 (0.943–1.019)	0.317
Heart rate	1.039 (1.015–1,065)	0.002	1.052 (1.027–1.077)	0.0001
Saturation O2	0.911 (0.890–0.932)	0.0001	0.941 (0.920–0.962)	0.0001
Arterial hypertension	4.213 (1.835–9.673)	0.001	4.513 (2.313-8.805)	0.0001
Chronic heart failure	3.329 (1.703–6.510)	0.0001	6.925 (3.748–12.795)	0.0001
Chronic obstructive pulmonary disease	0.000	0.999	3.200 (0.968–10.577)	0.057
Diabetes mellitus	2.599 (1.313–5.147)	0.006	3.019 (1.572–5.799)	0.001
Myocardial infarction	3.137 (0.664-14.826)	0.149	3.773 (1.556–9.151)	0.003
Chronic kidney disease	16.682 (7.357–37.827)	0.0001	7.588 (3.517–16.369)	0.0001
Aspartate aminotransferase	1.001 (1.000–1.002)	0.027	1.007 (1.001–1.013)	0.033
Alanine aminotransferase	1.009 (1.000–1.018)	0.045	0.998 (0.988–1.007)	0.636
Creatinine	1.012 (1.006–1.019)	0.0001	1.003 (1.001–1.005)	0.0001
Extent of lung tissue damage	1.055 (1.039–1.070)	0.0001	1.048 (1.035–1.061)	0.0001

Table 3.

The value of hematological indices on admission in predicting 30-day mortality in patients with COVID-19 pneumonia.

Females					
Variables	Cut-off	AUC (95% CI)	Sensitivity	Specificity	P-level
NLR	>5.17	0.785 (0,702-0.869)	75.0	70.5	0.000
TLR	>184.8	0.624 (0.528-0.720)	57.5	65.7	0.008
NPR	>15.26	0.798 (0.727-0.870)	82.1	0.642	0.000
SII	>1211.3	0.714 (0.678–0.749)	57.5	85.3	0.000
Males					
Variables	Cut-off	AUC (95% CI)	Sensitivity	Specificity	P-level
NLR	>3.58	0.736 (0.671-0.801	76.4	64.4	0.000
TLR	>179.9	0.536 (0.450–0.623)	49.1	62.4	0.381
NPR	>19.24	0.714 (0.649-0.782)	71.7	64.6	0.000
SII	>1277.2	0.714 (0.617–0.812)	41.8	85.6	0.000

The results of multivariate Cox regression assessing the relation of hematological indices with mortality are shown in *Table 4*. Model 1 adjusted the hazard ratio (HR) of hematological indices for age, heart rate, presence of AH, DM, CHF, CKD, and aspartate aminotransferase (AST) level; in males, model 1 additionally included previous MI and the presence of COPD.

As a result of this adjustment, NLR, NPR, PLR, and SII retained a statistically significant correlation with the risk of mortality in women, while in males only NLR, NPR, and SII still showed significance. Model 2 corrected the HR of hematological parameters for oxygen saturation, and model 3 – was for the extent of lung tissue damage. This adjustment resulted in the loss of a statistically significant correlation with mortality of NLR (HR = 1.024; 95% CI, 0.993–1.056, p = 0.137), PLR (HR = 1.000; 95% CI, 0.998–1.002, p = 0.913) and SII (HR = 1.000; 95% CI, 1.000-1.000, p = 0.461) in women and NPR in men (HR = 1.006; 95% CI 0.998-1.014, p = 0.144).

Further adjustment for oxygen saturation and the percentage of lung tissue involvement did not affect the relationship between the NPR and mortality in females in the fully adjusted model. In males, NLR had the highest predictive value after correction (HR=1.070; 95% CI 1.016–1.126, p=0.010). SII also retained predictive value in men, but with a negligible HR value (HR = 1.000 95% CI, 1.000–1.000, p = 0.007).

Discussion

In the present study, we were the first to compare the significance of the hematological indices NLR, PLR, NPR, and SII for the valuation of the 30-day mortality risk in men and women. As a result of our study, we found that NLR is a strong predictor of the prognosis for COVID-19 mortality in men at a cut-off of 3.58, AUC 0.736 (95% CI (0.671–0.801).

The studies have shown different cut-off points and predictive capabilities of NLR: optimal cut-off NLR values ranged from 3.3 to 11.75, with 64–100% sensitivity and 63.6–90.6% specificity (AUC: 0.72-0.945) [11]. This wide range of variations indicates that absolute NLR values measured across populations are unlikely to be comparable and cut-off values may vary in different populations.

Previously, the values of NLR and PLR in the population were reported to depend on age, sex, and race [3]. A study by Yuwei Liu, Xuebei Du, and Jing Chen [12] showed that each unit increase of NLR caused changes in the adjusted OR ratio for male mortality by 1.10 (P=0.016) and female mortality by 1.00 (P=0.972), but the difference for interaction was not statistically significant (P=0.240). We found no difference in NLR levels between non-surviving females and males (p = 0.392). In our study, in a

multivariate model, after adjustment for all cofounders, NLR retained predictive value for mortality risk only in men; in women, the statistically significant relationship between NLR and mortality was lost.

Table 4.

Hazard ratios of the indexes under investigation obtained by Cox regression analysis in males and females.

Females				
	NLR	NPR	TLR	SII
Unadjusted HR (95% CI) P-value	1,091 (1,068-1,115) 0,0001	1,009 (1,007-1,011) 0,0001	1,002 (1,001-1,004) 0,007	1,000 (1.000-1.000) 0,0001
Model 1 HR (95% CI) P-value	1.057 (1.028-1.087) 0.0001	1.009 (1.006-1.012) 0.0001	1.002 (1.000-1.003) 0.046	1.000 (1.000-1.000) 0.005
Model 2 HR (95% CI) P-value	1.035 (1.003-1.067) 0.030	1.010 (1.006-1.013) 0.0001	1.001 (0,999-1.003) 0.433	1.000 (1.000-1.000) 0.148
Model 3 HR (95% CI) P-value	1.024 (0.993-1.056) 0.137	1.008 (1.005-1.012) 0.0001	1.000 (0.998-1.002) 0.913	1.000 (1.000-1.000) 0.461
Males				
	NLR	NPR	TLR	SII
Unadjusted HR (95% CI) P-value	1,113 (1.071-1.157) 0.0001	1,014 (1.008-1.020) 0.0001	1.002 (1.000-1.004) 0.095	1,000 (1.000-1.000) 0,001
Model 1 HR (95% CI) P-value	1.088(1.039-1.140) 0.0001	1.008 (1.001-1.016) 0.025	- 	1.000 (1.000-1.000) 0.002
Model 2 HR (95% CI) P-value	1.089 (1.039-1.141) 0,0001	1.011 (1.003-1.018) 0.005	- 	1.000 (1.000-1.000) 0.002
Model 3 HR (95% CI) P-value	1.070 (1.016-1.126) 0,010	1.006 (0,998-1.014) 0.144	- 	1.000 (1.000-1.000) 0.007

Model 1 – age, heart rate, presence of Arterial hypertension, Diabetes mellitus, Chronic heart failure, Chronic kidney disease, Aspartate aminotransferase level (Myocardial infarction, Chronic obstructive pulmonary disease in males), NLR (or NPR or PLR or SII); Model 2: Model 1 + Oxygen Saturation (SaO_2). Model 3: Model 2 + extent of lung tissue damage.

Tahir Belice and al. showed that higher NLR levels were more common among deceased patients and higher in men compared to women regardless of age [2]. The authors suggest that the higher neutrophil-to-lymphocyte ratio in older men diagnosed with COVID-19 may explain the increased mortality in this group. Differences in the prognostic significance of NLR raise the question of existing gender immunological differences due to sex hormones, the X chromosome, and other factors [19].

NPR, which is a novel marker of the neutrophil-to-platelet ratio, has demonstrated a possibility to predict mortality with the optimal cut-off value >15.26 in women (AUC = 0.798) better than in men with a cut-off >19.24 (AUC = 0.714). After adjustment for such cofounders as oxygen saturation, and percentage of lung tissue damage, the correlation of NPR with the risk of mortality in men was lost (p=0.144), however, in women in the full model, NPR retained its association with the fatal outcome (p=0.0001).

NPR and NLR in a predictive model (adjusted for age, gender, oxygen saturation, C-reactive protein level and the rate of NLR and NPR changes during the first week after admission) demonstrated the same results for identifying patients at risk of fatal outcomes with the accuracy of model prediction, including NLR (AUC=0.873) and NPR (AUC=0.875) [13]. In another study, an analysis of the predictive value of NPR, NLR, PLR, and SII for assessing the risk of transfer to the intensive care unit showed that after correction with cofounders (body temperature, heart rate, blood pressure, oxygen saturation, glucose, transaminase, D-dimer, Lactate dehydrogenase), all indices lost their association with intensive care unit (ICU) hospitalization, except NPR, which still possessed a borderline value in the model (p = 0.055) [25].

In our study, PLR did not demonstrate the ability to predict mortality in males; in females, PLR showed little ability (AUC 0.624) to predict mortality in univariate analysis (p=0.046) but not in multivariate one (p=0.913). This is consistent with the results of most studies in which PLR can be used to predict disease severity but fails to predict mortality [26].

Studies examining the predictive value of SII for assessing the mortality risk in patients with COVID-19 are few. Studies by other authors have shown that lower survival is associated with high levels of NLR (AUC 0.697), PLR (AUC 0.572), and SII (AUC 0.628). After correction involving cofounders, only SII retained its correlation with survival rates (HR = 1.0001; 95% CI, 1.0000–1.0001, p = 0.029). When distributing study groups depending on the cut-off level (>1.835), the authors did not find any gender-related differences (p=0.16) [24]. In our study, the SII prediction accuracy for mortality in men and women was comparable (AUC 0.714). SII after correction with

cofounders, including oxygen saturation and percentage of lung tissue damage, retained its predictive value for a fatal outcome only in males with a small relative risk value (HR = 1.000 95% CI, 1.000-1.000, p = 0.014), while in females association between SII and mortality in the full model did not reach statistical significance (p=0.461).

In line with the previous studies, we observed elevated NLR, NPR, and SII values in patients with fatal COVID-19 outcomes regardless of gender. However, we were the first to compare the predictive value of blood cell count-based inflammation indices, such as NLR, NPR, PLR, and SII for mortality risk evaluation in males and females. In our study, the AUC values of both NLR (0.785) and NPR (0.798) for women and only NLR (0.736) for men were the highest among the estimated combined indices for predicting mortality. Our data suggest that in both men and women PLR and SII are inferior to NLR and, in women, also to NPR, in the predictive ability to identify patients with high mortality risk.

The results of a meta-analysis showed that males have a 5 % higher (13% in comparison to 8%) risk of mortality [17]. These data are consistent with the results of our study, in which mortality among men was 1,9 times higher than among women (z=3.22; p=0.001).

The known gender differences in innate and adaptive immunity, the influence of genetics, sex hormones, microbiome, and features of ACE-2 expression [8] previously have been already considered as mechanisms for a different response to COVID-19 infection in males and females. Gender-dependent differences in the leukocyte response to COVID-19 acute respiratory tract infection have been also established before [16]. The innate immune response appears to be more active in male patients, as evidenced by higher numbers of inflammatory neutrophils and monocytes circulating in the blood. Neutrophils, the most abundant circulating white blood cells, are an important component of the immune system. Experimentally excessively elevated amounts of neutrophils in coronavirus-infected rats proved to correlate with inflammation of the lung tissue, epithelial cell permeability, and hemorrhagic lesions [9]. In addition, compared to females, male rat neutrophils showed significantly higher recruitment of CXCL-1, which engages neutrophils to kill microbes as well as to activate protease and reactive oxygen species [3,22]. Thus, extensive lung tissue damage in male rats with a 4–5-fold increase in neutrophils suggests that the neutrophil immune response is pathological in males compared to females, who demonstrated only slight alveolar edema on histological examination [11].

According to previous studies, lymphopenia is a characteristic laboratory sign of SARS-CoV-2 infection. The causes and consequences of lymphopenia in acute respiratory viral infections have not been thoroughly studied, and even less can be said about gender differences. However, women generally show higher cytotoxic T-cell activity along with upregulation of CD8+ genes, which is supposedly associated with the immunostimulatory effect of estrogens. One of the studies demonstrated that women had a stronger adaptive immune response compared to men: 7 and 14 days after the identification of the infection, women had significantly higher levels of B-cells. In general, decreased levels of CD4+ and CD8+ T-lymphocytes are associated with the severity of the disease and lead to elevated NLR, which is a sensitive biomarker of inflammation [20]. In our study, NLR among female survivors was lower compared to male survivors but did not differ between fatal groups.

It should be noted that the association of age, comorbidity, and elevated transaminases with mortality in patients with COVID-19 has been confirmed in many studies. In our study the predictive value of age in females was only confirmed in univariate analysis, but not in a multivariate one; in males, a significant relationship between age and the fatal outcome was preserved after correction with cofounders. In our study, in a multivariate model among comorbid conditions, the presence of CKD was associated with higher mortality rates in both men and women; for men MI and COPD also had a significant effect on mortality.

We were the first to demonstrate that NPR in women, NLR, and SII in men retain their association with mortality after adjustment for the percentage of lung tissue damage. This suggests that these indices may reflect specifically the lung damage that occurs in patients with COVID-19, not only the general worsening of their clinical condition due to any comorbidities.

The short follow-up period could be considered a limitation of our study, as it has been reported that patients who survive severe COVID-19 infection have an increased risk of 12-month mortality. Secondly, this was a retrospective study, however, it was the first study from Kazakhstan, so the results obtained confirm the relevance of other studies by authors from different countries. Further research is needed to better understand the factors that determine gender differences affecting the incidence and outcomes of COVID-19 infection.

Conclusion. Elevated NLR, NPR, and SII values are associated with the fatal outcome of COVID-19 and may be useful markers for predicting mortality, especially NPR in females and NLR in males. A better understanding of these factors will help implement a personalized approach to gender-dependent therapy.

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Correspondence to:
Mekhantseva Irina - Assistant of the Department of internal medicine, NJSC "Karaganda Medical University", the Republic of Kazakhstan, Karaganda.
Address: Kazakhstan, 100000, Karaganda, 40 Gogol Street.
E-mail: mehanceva@qmu.kz
Phone: +7 705 600 92 11