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SPHINGOSINE-1-PHOSPHATE AS A BIOMARKER AND PREDICTOR OF THE DEVELOPMENT OF SEVERE ACUTE RESPIRATORY SYNDROME IN PATIENTS WITH COVID-19 AND COMMUNITY-ACQUIRED PNEUMONIA

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Sphingosine has been shown to prevent and eliminate bacterial infections of the respiratory tract, but it is unknown whether sphingosine can be also employed to prevent viral infections. The involvement in lung injury and endothelial barrier function, sphingosine-1-phosphate could be a potential biomarker of community-acquired pneumonia and COVID-19. The purpose of the study was to determine the diagnostic and prognostic value of sphingosine-1-phosphate and to unravel the complex role of sphingosine-1-phosphate in the pathophysiological pathways of community-acquired pneumonia and COVID-19 in conditions of hyperglycemia. Survival analysis (the advent of severe acute respiratory syndrome within 30 days of hospitalization) was performed using the Kaplan–Meier method; univariate analys were undertaken using log rank test and Cox's regression model, respectively.

Sphingosine-1-phosphate levels were approximately 2–2.5 times lower in women and men with pneumonia associated with hyperglycemia, Type 2 Diabetes and COVID-19. Moreover, this decrease was greater in men than in women. Sphingosine-1-phosphate is a biomarker of development of severe acute respiratory syndrome within 30 days of hospitalization in patients with COVID-19, community-acquired pneumonia (with and without hyperglycemia and Type 2 Diabetes).

Key words: COVID-19, community-acquired pneumonia, sphingosine-1-phosphate

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СФІНГОЗИН-1-ФОСФАТ ЯК БІОМАРКЕР ТА ПРОГНОЗ РОЗВИТКУ ВАЖКОГО ГОСТРОГО РЕСПІРАТОРНОГО СИНДРОМУ У ХВОРИХ НА COVID-19 ТА НЕГОСПІТАЛЬНУ ПНЕВМОНІЮ

Показано, що сфінгозин запобігає та усуває бактеріальні інфекції дихальних шляхів, але невідомо, чи можна також використовувати сфінгозин для профілактики вірусних інфекцій. Сфінгозин-1-фосфат, беручи участь у пошкодженні легенів та ендотеліальному бар'єрному функціонуванні, може бути потенційним біомаркером негоспітальної пневмонія та COVID-19. Метою дослідження було визначити діагностичну та прогностичну цінність сфінгозин-1-фосфату та з'ясувати роль сфінгозин-1-фосфату в патофізіологічних шляхах негоспітальної пневмонії та COVID-19 в умовах гіперглікемії. Аналіз виживаності (поява тяжкого гострого респіраторного синдрому протягом 30 днів після госпіталізації) проводили за методом Каплана–Мейєра; однофакторний аналіз проводився з використанням логарифмічного рангового тесту та регресійної моделі Кокса відповідно. Рівні сфінгозин-1-фосфату були в 2–2,5 рази нижчими у жінок і чоловіків із пневмонією, пов'язаною з гіперглікемією, діабетом 2 типу та COVID-19. Більш того, це зниження було більшим у чоловіків, ніж у жінок. Сфінгозин-1-фосфат є біомаркером розвитку тяжкого гострого респіраторного синдрому протягом 30 днів після госпіталізації у пацієнтів із COVID-19, позалікарняною пневмонією (з гіперглікемією та без неї та ЦД2).

Ключові слова: COVID-19, негоспітальна пневмонія, сфінгозин-1-фосфат

The study is a fragment of the research projects "Clinical and pathogenetic features of the rehabilitation period of patients with mild community-acquired pneumonia in combination with type 2 diabetes", state registration No. 0118U006940 and "Development of new highly economical methods of biomarker diagnostics and prediction of the course and complications of COVID-19 and community-acquired pneumonia in military personnel and civilians", state registration number 0123U101246.

Lower respiratory tract infections are the most frequent infectious cause of death worldwide and impose a considerable burden on healthcare resources. Despite the advancement in treatment and diagnosis, the inpatient mortality rate of community-acquired pneumonia (CAP) is 5.7 % to 14.0 % [2, 7]. Early stratifying the severity of CAP is thus very important, especially in an acute emergency setting. Moreove, SARS-CoV-2 infection triggers distinct patterns of disease development characterized by significant alterations in host regulatory responses. Severe cases exhibit profound lung inflammation and systemic repercussions. Remarkably, critically ill patients display a "lipid storm", influencing the inflammatory process and tissue damage [14].

Sphingolipids (SLs) (sphingomyelin, glycolipids, gangliosides) are the second most abundant group of membrane lipids. Sphingomyelin and its metabolites (ceramide, sphingosine and sphingosine-1-

phosphate) modulate cellular processes such as differentiation, proliferation, growth, senescence and apoptosis [4, 14]. Sphingosine has been shown to prevent and eliminate bacterial infections of the respiratory tract, but it is unknown whether sphingosine can be also employed to prevent viral infections [6]. The sphingolipid rheostat plays an important role in regulating viral replication, the innate, adaptive, and hyperinflammatory immune response, and importantly, maintaining vascular endothelial integrity [12]. Hence, targeting sphingosine kinase (SphK), sphingosine-1-phosphate, and the S1P cognate receptors (high-affinity G-protein-coupled receptors) in the repertoire of therapies to control viral replication, hyperinflammation, and aid in the maintenance of vascular endothelial integrity is highly attractive [12].

Emerging evidence suggests that SLs play a crucial role in modulating SARS-CoV-2 infection. Furthermore, reduced levels of serum S1P were strongly associated with symptomatic COVID-19 compared to asymptomatic cases [15].

Additionally, sphingosine and sphingosine-1-phosphate have been suggested to prevent COVID-19 [8]. SARS–CoV-2 infects cells by the initial interaction of the surface unit S1 of the viral spike glycoprotein with its cellular receptor angiotensin-converting enzyme 2 (ACE2). The interaction of the two proteins allows viral entry and cellular infection [5]. Edwards M.J. et al. showed an antiviral function of endogenous sphingosine, which traps viruses in endosomes and thereby shuttles them to lysosomal degradation [3]. Because of the involvement in lung injury and endothelial barrier function, S1P could be a potential biomarker of community-acquired pneumonia and COVID-19.

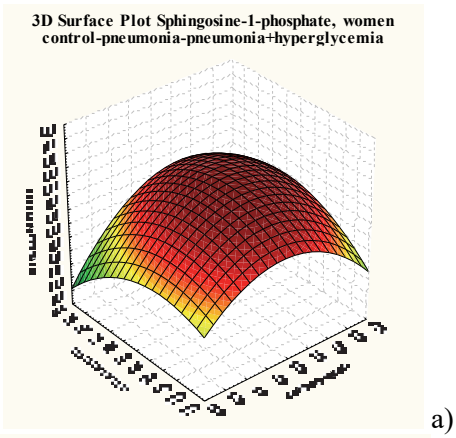
The purpose of the study was to determine the diagnostic and prognostic value of S1P and to unravel the complex role of S1P in the pathophysiological pathways of community-acquired pneumonia and COVID-19 in conditions of hyperglycemia.

Materials and methods. The studies were carried out on the basis of city and regional hospitals of the Luhansk region between 2020 to 2022. In accordance with the provisions of the Declaration of Helsinki by the World Medical Association of the last revision (1964-2013) and informed consent for the use of biological material was obtained in all patients prior to inclusion in the study. Research permission was obtained from the Bioethics Committee of the Lugansk State Medical University (Rubizhne, Ukraine, number 25/2015). The patients' epidemiological data, laboratory examination, complications, clinical outcomes, CT imaging data, and treatment plan were extracted from medical records. The date of onset of the disease was the date of the first symptom. All cases of SARS-CoV-2 infection confirmed by a positive result on real-time reverse transcriptase polymerase chain reaction tests of a nasal sample and/or diagnosed by a computed tomography chest scan were included and analyzed. The primary endpoint of this study was the advent of severe acute respiratory syndrome within 30 days of hospitalization.

To test our hypothesis, this case-control study consisted of 81 healthy donors (control group) (46 women and 35 men); 77 patients with a positive diagnosis of COVID-19 according to PCR analysis (44 women and 33 men); 60 patients with community-acquired pneumonia (CAP) (31 women and 30 men); 101 patients with CAP and hyperglicemia (CAP+HH) (44 women and 57 men); 70 patients with T2DM (37 women and 33 men); 42 patients with CAP in combination with T2DM (CAP+T2DM) (27 women and 15 men); 29 patients with a positive diagnosis of COVID-19 in combination with critical limb ischemia. The material for the study was the peripheral blood from the cubital vein of patients and healthy control. The levels of S1P were determined exactly as previously described [13]. Free sphingosine pool was quantified spectrophotometrically (SF-46) at λ= 415 nm according to the method of Lauter, Trams [13].

Data Processing. Statistical and graphical analyses were done using STATISTICA 7.0 (StatSoft Inc. USA, version 7.0) and and MedCalc Version 20.218 64 bit (MedCalc Software, Ostend, Belgium). Parametric data were summarized as mean (standard error) (Mean±SEM). Kolmogorov–Smirnov test was applied to examine the normality of data distribution. To examine group-wise differences, unpaired Student's t-test was used. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden index. Survival analysis (the advent of severe acute respiratory syndrome within 30 days of hospitalization) was performed using the Kaplan–Meier method; univariate analys were undertaken using log rank test and Cox's regression model, respectively. A p-value below 0.05 was considered statistically significant. The Cox proportional hazards regression model was used to assess the effect of serum Sphingosine-1-phosphate levels on clinical outcomes in survival analysis.

Results of the study and their discussion. Descriptive statistics and results of comparison of groups of patients according to the studied parameters included in the analysis of predictors of the advent of severe acute respiratory syndrome within 30 days of hospitalization are presented in Fig.1.



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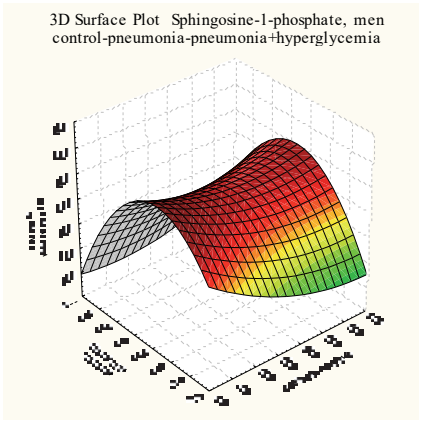

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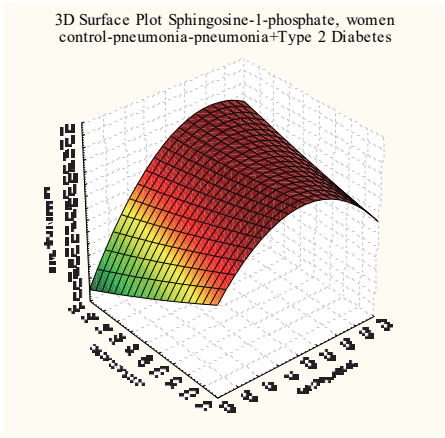

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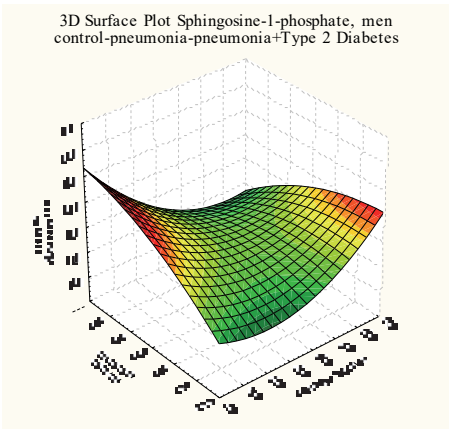

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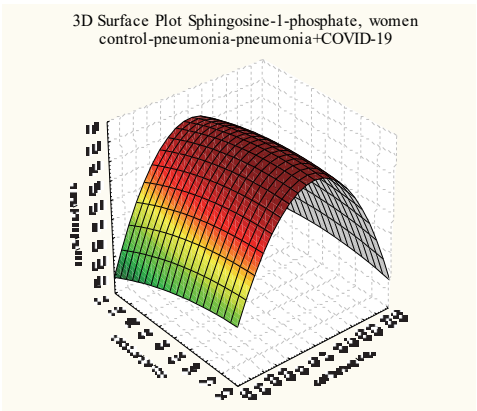

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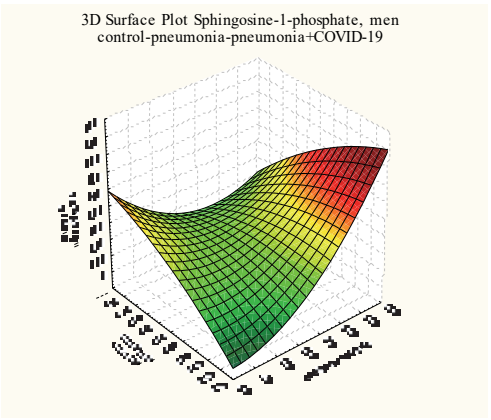

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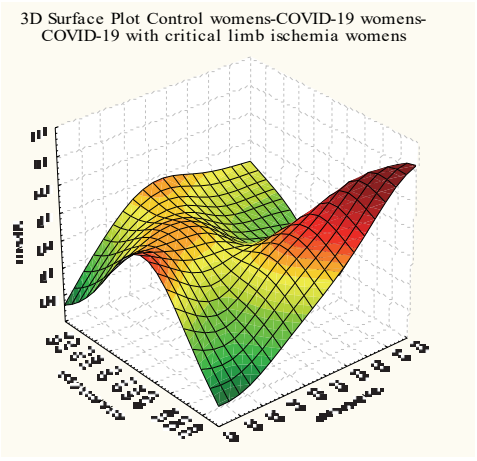

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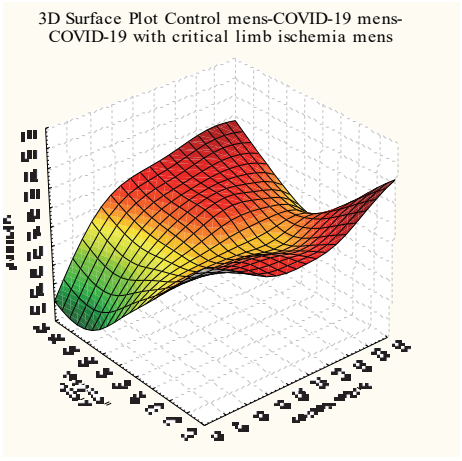

h)

Fig. 1. Sphingosine-1-phosphate concentration in patients with community-acquired pneumonia and COVID-19: a) women healthy-pneumonia-pneumonia+hyperglycemia; b) men healthy-pneumonia-pneumonia+hyperglycemia; c) women healthy-pneumonia-pneumonia+Type 2 Diabetes; d) men healthy-pneumonia-pneumonia+Type 2 Diabetes; e) women healthy-pneumonia-COVID-19; f) men healthy-pneumonia- COVID-19; g) women healthy-COVID-19-women- COVID-19 in combination with critical limb ischemia-women; h) men healthy-COVID-19-men-COVID-19 in combination with critical limb ischemia-men. Notes: SP1 data are means ± SEM for Gaussian variables. Intergroup by the Student's t-test; $p < 0.00001$.

Levels of S1P were higher (1.5 fold higher) in women healthy than in men healthy (558.07±5.27 nmol/l *vs* 519.9±6.42 nmol/l, p<0.000014).

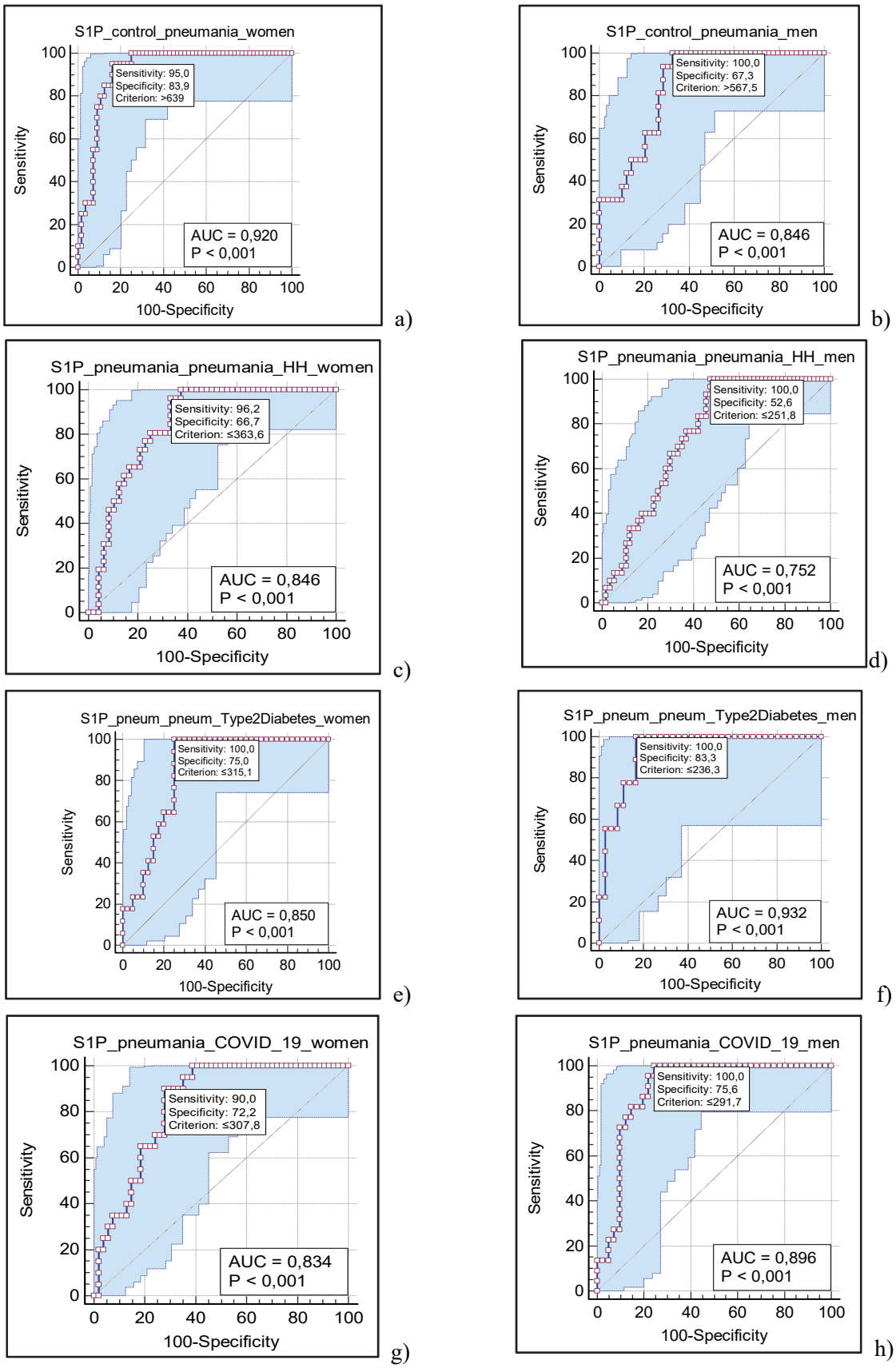

Fig. 2. ROC analysis: receiver operating characteristic (ROC) curves for Sphingosine-1-phosphate measured in a) women healthy-pneumonia; b) men healthy-pneumonia; c) women pneumonia-pneumonia+hyperglycemia; d) men pneumonia-pneumonia+hyperglycemia; e) women healthy-pneumonia-pneumonia+Type 2 Diabetes; f) men healthy-pneumonia-pneumonia+Type 2 Diabetes; g) women healthy-pneumonia-COVID-19; h) men healthy-pneumonia- COVID-19. Note: Here and in the following figures: p<0.001 – calculated by univariate logistic regression analysis.

Patients with community-acquired pneumonia had higher S1P values as compared to those in control objects (controls women: 558.07±5.27 nmol/l; patient with CAP women: 686.4±7.21 nmol/l; $p < 0.00001$; controls men: 519.9±6.42 nmol/l; patient with CAP men: 621.17±5.01 nmol/l; $p < 0.00001$).

In contrast, S1P levels were approximately 2–2.5 times lower in women with pneumonia associated with hyperglycemia and in men with pneumonia associated with hyperglycemia (patient with CAP women: 686.4±7.21 nmol/l; patient with CAP+hyperglycemia women: 300.09±6.08 nmol/l; $p < 0.00001$; patient with CAP men: 621.17±5.01 nmol/l; patient with CAP+hyperglycemia men: 200.61 ±3.42 nmol/l; $p < 0.00001$). The same decrease in the level of S1P was observed in patients with pneumonia against the background of Type 2 Diabetes compared to patients without diabetes. Moreover, this decrease was greater in men than in women: (patient with CAP women: 686.4±7.21 nmol/l; patient with CAP+Type 2 Diabetes women: 257.47±8.33 nmol/l; $p < 0.00001$; patient with CAP men: 621.17±5.01 nmol/l; patient with CAP+Type 2 Diabetes men: 175.24±7.22 nmol/l; $p < 0.00001$).

Differences were observed in S1P levels between COVID-19 and control groups and COVID-19 groups and patients with pneumonia (patient with CAP women: 686.4±7.21 nmol/l; patient with COVID-19 women: 286.62±5.94 nmol/l; $p < 0.00001$; patient with CAP men: 621.17±5.01 nmol/l; patient with COVID-19 men: 225.06±6.4 nmol/l; $p < 0.00001$).

The level of S1P in COVID-19 patients in combination with critical limb ischemia in women and men was lower than in the control groups, but higher than in COVID-19 patients (controls women: 558.07±5.27 nmol/l; patient with COVID-19 women: 286.62±5.94 nmol/l; $p < 0.00001$; COVID-19 in combination with critical limb ischemia-women: 464.6±10.08 nmol/l; controls men: 519.9±6.42 nmol/l; patient with COVID-19 men: 225.06±6.4 nmol/l; COVID-19 in combination with critical limb ischemia-women: 350.9±2.72 nmol/l; $p < 0.00001$).

Analysis of the ROC curve in patients with community-acquired pneumonia and COVID-19 is shown in Fig. 2.

Analysis of the ROC curve in patients with community-acquired pneumonia and COVID-19 showed S1P as a predictor of the development of severe acute respiratory syndrome within 30 days of hospitalization. The area under ROC curve of S1P was greatest in all groups patients with community-acquired pneumonia (women – 0.920, optimal cut-off values of S1P – 639.0 nmol/l ; men – 0.846, $p< 0.001$, optimal cut-off values of S1P – 567.5 nmol/l), community-acquired pneumonia with hyperglycemia (women – 0.846, optimal cut-off values of S1P – 363.6.0 nmol/l; men – 0.752, optimal cut-off values of S1P – 251.8 nmol/l, $p< 0.001$), community-acquired pneumonia with Type 2 Diabetes (women – 0.850, optimal cut-off values of S1P – 315.1 nmol/l; men – 0.932, optimal cut-off values of S1P – 236.3 nmol/l, $p< 0.001$), and patients with COVID-19 (women – 0.834, optimal cut-off values of S1P – 307.8 nmol/l; men – 0.896, optimal cut-off values of S1P – 291.7 nmol/l, $p< 0.001$), which reflects the high predictive effectiveness of this index for assessing the development of severe acute respiratory syndrome within 30 days of hospitalization.

Kaplan-Meier survival curves after classifying patients based on Youden cut-off values obtained using ROC curves showed significantly earlier development of severe acute respiratory syndrome within 30 days of hospitalization as a function of S1P levels: patients with community-acquired pneumonia (women: HR = 563.51; 95 % CI 157.9 to 2009.97, $p = 0.0001$; men: HR = 88.34; 95 % CI 23.95 to 325.86, $p < 0.0001$), patients with community-acquired pneumonia with hyperglycemia (women: HR = 6.97; 95 % CI 3.15 to 15.42, $p = 0.0001$; men: HR = 5.47; 95 % CI 2.55 to 11.71, $p < 0.0001$), patients with community-acquired pneumonia with Type 2 Diabetes (women: HR = 11.74; 95 % CI 4.31 to 31.96, $p = 0.0001$; men: HR = 32.96; 95 % CI 7.15 to 151.93, $p < 0.0001$), patients with COVID-19 (women: HR = 8.29; 95 % CI 3.29 to 20.87, $p = 0.0001$; men: HR = 13.4 ; 95 % CI 7.5.48 to 32.8, $p < 0.0001$).

Next, we performed a Cox proportional hazards regression analyses of predictors for assessing the development of severe acute respiratory syndrome within 30 days of hospitalization in all groups patients with community-acquired pneumonia and COVID-19 are presented in Table 1.

Harrell's C-index, also known as the concordance index, is a goodness of fit measure for models which produce risk scores. All parameters that were significant at a p value less than 0.10 could predict the development of severe acute respiratory syndrome within 30 days of hospitalization in patients with community-acquired pneumonia (women – C-index=0.888, men C-index=0.826), patients with community-acquired pneumonia with hyperglycemia (women – C-index=0.738, men C-index=0.701), patients with community-acquired pneumonia with Type 2 Diabetes (women – C-index=0.788, men C-index=0.835), patients with COVID-19 (women – C-index=0.746, men C-index=0.8) increases the risk of a poor prognosis of the development of severe acute respiratory syndrome.

Table 1

Unadjusted and adjusted hazard ratios (HR) for respective univariate Cox proportional hazard models for assessing the development of severe acute respiratory syndrome within 30 days of hospitalization

Factor	Univariable		
	HR (95 % CI)	Harrell's C-index	p-Value
women pneumonia	73.27 (15.9 –336.7)	0.888	p<0.0001
men pneumonia	21.43 (6.01 –76.4)	0.826	p<0.0001
women pneumonia with hyperglycemia	13.97 (3.3–59.29)	0.738	p<0.0003
men pneumonia with hyperglycemia	20.3 (2.76–149.3)	0.701	p<0.0031
women pneumonia with Type 2 Diabetes	26.35 (3.48–99.47)	0.788	p=0.0015
men pneumonia with Type 2 Diabetes	24.78 (3.08 –199.18)	0.835	p=0.0025
women with COVID-19	9.7 (2.83–33.24)	0.746	p<0.0003
men with COVID-19	35.5 (4.74–65.48)	0.8	p<0.0005

Note: Here and in the following figures: p<0.0001 – calculated by univariate logistic regression analysis.

As in our study, the prospective case-control study Hsu S-C., et al. [7] indicated that plasma S1P levels were significantly increased in patients with CAP, compared to those of the healthy controls. The level of circulating S1P at the time of Emergency department admittance was found to predict mortality, intensive care unit admission and the hospital stay longer than ten days in patients with pneumonia. Our study established a gender difference in S1P levels in both healthy donors and patients with CAP, with women being greater than men. Based on the level of circulating S1P using ROC-analysis and Kaplan-Meier survival curves, we were able to establish the possibility of predicting the development of severe respiratory syndrome.

Plasma concentrations of these sphingolipids can be altered upon metabolic disorders and could serve as predictive biomarkers of these diseases. Recent important advances suggest that circulating sphingolipids not only serve as biomarkers but could also serve as mediators in the dysregulation of glucose homeostasis. Circulating sphingolipids could be an important lipid pool in the context of monitoring the development of diabetes, as some of them have been described as biomarkers to identify individuals at risk of developing insulin resistance, Type 2 Diabetes [1].

As we were able to establish, more than 2/3 of patients with community-acquired pneumonia develop hyperglycemia, as do COVID-19 patients. The level of circulating S1P in patients with CAP against the background of hyperglycemia and Type 2 Diabetes was sharply reduced and was a predictor of severe respiratory syndrome.

Recent data indicates that serum level of sphingosine-1-phosphate is a prognostic factor for COVID-2 severity. Since patients with diabetes have been associated with a poor prognosis of COVID-19, and COVID-19 tends to worsen dysglycemia in these patients [10], we searched for one of the pathogenetic links in the interaction between diabetes and COVID-19.

The main findings of our study are that serum S1P levels are significantly lower in patients with COVID-19 than in patients with CAP and at the same level in patients with COVID-19 with hyperglycemia and diabetes mellitus.

As Marfia G. et al. [11] showed, the decrease in S1P was closely related to the number of red blood cells, the main source of S1P in plasma, as well as apolipoprotein M and albumin, the main carriers of S1P in the blood. Not least, S1P has been found to be an important predictor of intensive care unit admission and disease outcome. Similar to our study, circulating S1P was found to be a negative biomarker of severity/mortality (in our study – the development of severe acute respiratory syndrome.) in COVID-19 patients. Restoring abnormal S1P levels to normal levels could potentially be a therapeutic target in patients with COVID-19.[11]

We have been studying the role of S1P as a non-receptor modulator of apoptosis for more than 20 years. Including, our clinical studies have shown that dysregulation of apoptosis can contribute to the development and maintenance of community-acquired pneumonia and COVID-19 [9]. Our study is one of the first to analyze cfDNA level for prediction of COVID-19 and community-acquired pneumonia (with and without complications and comorbidity diseases). During the study, we established significantly high

levels of circulating cell-free cfDNA in men and women with COVID-19 – significantly higher than in all groups of patients with community-acquired pneumonia. The cfDNA profiles in patients with community-acquired pneumonia, were significantly lower than in patients with pneumonia with hyperglycemia (women and men) and pneumonia with T2DM (women and men). Our results show that cfDNA profiles have differential diagnostic significance in groups of patients with COVID-19 and community-acquired pneumonia [9].

Considering that sphingosine-1-phosphate promotes proliferation, cell survival and inhibits apoptosis, the data we obtained in this study on a sharp decrease in the level of S1P in patients with CAP (with and without hyperglycemia and T2DM) explains the high level of apoptosis in these same patients.

Thus, we have established that sphingosine-1-phosphate is not only a biomarker that can serve as a diagnostic and prognostic index, but also revealed the complex role of S1P in the pathophysiological pathways of COVID-19 associated with apoptosis.

Conclusions

1. S1P levels were 2–2.5 times lower in women and men with pneumonia associated with hyperglycemia, Type 2 Diabetes and COVID-19. Moreover, this decrease was greater in men than in women.
2. Sphingosine-1-phosphate is a biomarker of development of severe acute respiratory syndrome within 30 days of hospitalization in patients with COVID-19, community-acquired pneumonia (with and without hyperglycemia and T2DM).

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