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ALFA-1-ANTITRYPSIN PREDICTS SEVERE COVID-19, GASTRIC AND RENAL CANCER IN CONDITIONS OF HYPERGLYCEMIA

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Hyperglycemia with or without blood glucose in diabetes range is an emerging finding not uncommonly encountered in patients with COVID-19. This work is to investigate the association between serum alpha-1-antitrypsin, hyperglycemia, and clinical outcomes in COVID-19, and community-acquired pneumonia, gastric cancer and renal cell carcinoma. Alpha-1-antitrypsin levels in serum was determined by the immunoturbidimetric method. We have set the level of alpha-1-antitrypsin in patients with community-acquired pneumonia and COVID-19 with or without hyperglycemia. Levels of alpha-1-antitrypsin in COVID-19 patients with hyperglycemia who survived > those who did not survive. Concentration of alpha-1-antitrypsin levels in COVID-19 men-patients with hyperglycemia who survived was significantly higher than compared with COVID-19 women-patients with hyperglycemia who survived. The obtained data convincingly demonstrate the value of testing the level of alpha-1-antitrypsin in the blood as one of the important indicators of the effectiveness of cancer diagnosis and prognosis.

Key words: alpha-1-antitrypsin, COVID-19, community-acquired pneumonia, gastric cancer, renal cell carcinoma, hyperglycemia.

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АЛЬФА-1-АНТИТРИПСИН ПРОГНОЗУЄ ВАЖКИЙ ПЕРЕБІГ COVID-19, РАКУ ШЛУНКУ ТА НИРОК В УМОВАХ ГІПЕРГЛІКЕМІЇ

Гіперглікемія з діабетом в анамнезі та без нього є новою знахідкою, що нерідко зустрічається у пацієнтів із COVID-19. Ця робота спрямована на вивчення зв'язку між рівнем альфа-1-антитрипсином, гіперглікемією та клінічними наслідками COVID-19 та позалікарняної пневмонії, раку шлунку та нирково-клітинній карциномі. Рівні альфа-1-антитрипсину у сироватці крові визначали імунотурбідиметричним методом. Нами встановлено рівень альфа-1-антитрипсину у пацієнтів хворих на позалікарняну пневмонію та COVID-19 на тлі гіперглікемії або без неї. Рівні альфа-1-антитрипсину у пацієнтів хворих на COVID-19 на тлі гіперглікемії, які вижили більш тих, хто не вижив. Рівень альфа-1-антитрипсину у чоловіків-пацієнтів хворих на COVID-19 на тлі гіперглікемії, що вижили, була значно вищою, ніж у жінок-пацієнтів хворих на COVID-19 на тлі гіперглікемії, що вижили. Отримані дані переконливо демонструють значення тестування рівня альфа-1-антитрипсину в крові як одного з важливих показників ефективності діагностики та прогнозування онкологічних захворювань.

Ключові слова: альфа-1-антитрипсин, COVID-19, позалікарняна пневмонія, рак шлунку, нирково-клітинний рак, гіперглікемія.

The study is a fragment of the research projecst "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 "Biomarker diagnostics of oncourological diseases", state registration No. 0118U001025.

Hyperglycemia with or without blood glucose in diabetes range is an emerging finding not uncommonly encountered in patients with COVID-19. Increasingly, all evidence currently available hints that both new-onset hyperglycemia without diabetes and new-onset diabetes in COVID-19 is associated with a poorer outcome compared with normoglycemic individuals and people with pre-existing diabetes [6, 14]. Understanding COVID-19 pathophysiology is crucial for a better understanding of the disease and development of more effective treatments. Alpha-1-antitrypsin (α1-AT) is a constitutive tissue protector with antiviral and anti-inflammatory properties. α1-AT inhibits SARS-CoV-2 infection and two of the most important proteases in the pathophysiology of COVID-19: the transmembrane serine protease 2 (TMPRSS2) and the disintegrin and metalloproteinase 17 (ADAM17) [2].

Alpha 1-antitrypsin belongs to a family of serum proteinase inhibitors. Alpha 1-antitrypsin plays a critical role in modulating immunity, inflammation, apoptosis, and possibly cellular senescence programs. The absence of this multifunctional protein is associated with increased risks of lung, liver, and colorectal cancers, whereas the serum level of alpha 1-antitrypsin has been reported to increase in patients with breast and prostate cancers [7]. α1-AT treatment can prevent overt hyperglycemia, increase insulin secretion, and reduce cytokine-mediated apoptosis of pancreatic β-cells in diabetes [15].

Alpha-1 antitrypsin has established anti-inflammatory and immunomodulatory effects in chronic obstructive pulmonary disease but there is increasing evidence of its role in other inflammatory and

immune-mediated conditions, like diabetes mellitus (DM) [10]. There is an emerging role of α1-AT in the onset and pathogenesis of diabetes mellitus. The role that α1-AT plays in type 2 diabetes mellitus (T2DM) pathogenesis is less clear and further research is needed to elucidate this association and possible therapeutic interventions [10].

An association between acute-phase proteins (APPs) and cancer has long been established and there are numerous reports correlating altered levels and/or molecular forms of APPs with different types of cancers [4]. Many authors have shown a positive correlation between high levels of APPs, like alpha1-antitrypsin, and unfavorable clinical outcome in cancers [4, 5, 9]. Conversely, others proposed that high levels of APPs are probably just a part of nonspecific inflammatory response to cancer development. However, this might not be always true, because many cancerous cells produce or take up exogenous APPs. What is the biological significance of this and what benefit do cancer cells have from these proteins remains largely unknown. Recent data revealed that some APPs, including α1-AT, are able to enhance cancer cell resistance against anticancer drug-induced apoptosis and autophagy [4].

Our hypothesis is based on the possible role of alpha-1-antitrypsin as a biomarker of poor prognosis in COVID-19 and cancer (for example, gastric cancer (GC) and renal cell carcinoma (RCC)) in hyperglycemic conditions.

The purpose of the study was to investigate the association between serum alpha-1-antitrypsin, hyperglycemia, and clinical outcomes in COVID-19, and community-acquired pneumonia, gastric cancer and renal cell carcinoma.

Materials and methods. The studies were carried out on the basis of city and regional hospitals in Lysychansk, Severodonetsk, Rubizhne, Kreminna of the Luhansk region in 2015–2021. 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.

To test our hypothesis, we included in the study patients:

33 patients with a positive diagnosis of COVID-19 according to PCR analysis (17 women and 16 men); 26 patients with COVID-19+hyperglycemia (COVID-19+HH) (12 women and 14 men); 60 patients with community-acquired pneumonia (CAP) (30 women and 30 men); 101 patients with CAP and hyperglicemia (CAP+HH) (44 women and 57 men); 29 healthy donors (14 women and 15 men) (control group).

We also studied a cohort of 32 gastric cancer (of them 14 with T2DM) and 29 renal cell cancer (of them 12 with T2DM) patients who underwent gastrectomy with lymph node dissection. None of the patients received preoperative radiotherapy or chemotherapy. We assessed the following clinicopathologic factors according to the American Joint Committee on Cancer Staging Manual, 7th edition: site, gross type, tumour size, depth of invasion, histologic classification (i.e., intestinal or diffuse), and lymphovascular invasion. The average follow-up period was 60 months. Cases lost to follow-up or death from any other causes were defined as censored data for the analysis of survival rates.

The material for the study was the peripheral blood from the cubital vein of patients and healthy donors. 10 ml of blood was collected in vacuum tubes (BD Vacutainer, heparin-sodium). The blood tubes were inverted 5-6 times to mix the blood with the anticoagulant and placed on ice. Then the blood was centrifuged at 2000 g at 4°C for 15 minutes. on a refrigerated centrifuge K-24 (Germany). Serum was aliquoted and transferred to cryogenic tubes for storage at -40°C prior to the study. Before testing, all samples underwent one freeze-thaw cycle.

Alpha-1-antitrypsin levels in serum was determined by the immunoturbidimetric method using an automatic biochemical analyzer Mindray BS 120. Blood glucose was measured by the Rayto RT-1904C analyzer (Rayto Life and Analytical Sciences), using the glucose oxidase method (GLUCOSE PAP AD727GP).

Data Processing. Statistical and graphical analyses were done using STATISTICA 7.0 (StatSoft Inc. USA, version 7.0). Parametric data are presented as a mean±standart deviation (SD). Kolmogorov–Smirnov test was applied to examine the normality of data distribution. To examine group-wise differences, unpaired Student's t-test was used. Frequency calculations were performed using Fisher's exact test. A *p*-value below 0.05 was considered statistically significant. The Cox proportional hazards regression model was used to assess the effect of alpha-1-antitrypsin levels on clinical outcomes in survival analysis.

Results of the study and their discussion. During the study, we divided patients with community-acquired pneumonia and COVID-19 into two groups with hyperglycemia and normal blood glucose levels. We have set the level of alpha-1-antitrypsin in patients with community-acquired pneumonia and COVID-19 (Tables 1, 2).

Table 1

Level of alpha-1-antitrypsin in patients with community-acquired pneumonia

Groups	Valid N	Mean, g/l	Std. Dev.	p-value
healthy women	14	2.69	0.19	
healthy men	15	2.17	0.24	p=0.000001^{0}
pneumonia women	30	1.27	0.20	p=0.0000001*
pneumonia men	30	1.09	0.11	p=0.0000001$^{\#}$ p=0.000039^{0}
pneumonia+ hyperglycemia -women	44	1.42	0.30	p=0.0000001* p=0.019069**
pneumonia+ hyperglycemia men	57	1.85	0.38	p=0.003394$^{\#}$ p=0.0000001$^{\#\#}$ p = 0.0000001^{0}

Notes: Data are means ± SD for Gaussian variables. Intergroup by the T-test Students * – p – significant differences between control (healthy women) and test groups (women) ** – p – between pneumonia group (women) and test other groups (women) $^{\#}$ – p – between control (healthy men) and test groups (men) $^{\#\#}$ – p – between pneumonia group (men) and test other groups (men) ^{0} – p – between groups women and test groups men

Table 2

Level of alpha-1-antitrypsin in COVID-19 patients

Groups	Valid N	Mean, g/l	Std. Dev.	p-value
healthy women	14	2.69	0.19	
healthy men	15	2.17	0.24	p=0.000001^{0}
COVID-19 – women	17	1.35	0.14	p=0.0000001* p=0.187302**
COVID-19 + hyperglycemia- women – Total	12	1.82	0.44	p=0.000001* p=0.000002** p=0.000253$^{\&}$
COVID-19 + hyperglycemia- women-non-survivors	3	1.37	0.48	p=0.000001* p=0.499285** p=0.868965$^{\&}$ p=0.138709$^{\&\&}$
COVID-19 + hyperglycemia- women-survivors	9	1.97	0.32	p=0.000001* p=0.0000001** p=0.0000001$^{\&}$ p=0.396168$^{\&\&}$ p= 0.030558$^{\&\&\&}$
COVID-19-men	16	1.34	0.10	p=0.0000001$^{\#}$ p=0.0000001$^{\#\#}$ p=0.809541^{0}
COVID-19 + hyperglycemia-men-Total	14	2.01	0.66	p=0.389871$^{\#}$ p=0.0000001$^{\#\#}$ p=0.000410$^{@}$ p=0.413691^{0}
COVID-19 + hyperglycemia-men-non-survivors	5	1.20	0.10	p=0.0000001$^{\#}$ p=0.033050$^{\#\#}$ p=0.024504$^{@}$ p=0.016821$^{@@}$ p=0.469042^{0}
COVID-19 + hyperglycemia-men-survivors	9	2.45	0.28	p=0.015877$^{\#}$ p=0.0000001$^{\#\#}$ p=0.0000001$^{@}$ p=0.071441$^{@@}$ p=0.0000001$^{@@@}$ p=0.004039^{0}

Notes: Data are means ± SD for Gaussian variables. Intergroup by the T-test Students $^{\&}$ – p – significant differences between COVID–19– women and test groups of COVID-19- women $^{\&\&}$ – p – significant differences between COVID-19+hyperglycemia- women and test groups of COVID-19+hyperglycemia- women $^{\&\&\&}$ – p – significant differences between COVID-19+hyperglycemia- women-survivors and test groups of COVID-19+hyperglycemia- women-non-survivors $^{@}$ – p – significant differences between COVID–19-men and test groups of COVID-19-men $^{@@}$ – p – significant differences between COVID-19+hyperglycemia-men and test groups of COVID-19+hyperglycemia-men $^{@@@}$ – p – significant differences between COVID-19+hyperglycemia-men-survivors and test groups of COVID-19+hyperglycemia-men-non-survivors ^{0} – p – between groups women and test groups men

The pneumonia patients had a significantly lower mean alpha-1-antitrypsin concentration in their serum than did the reference subjects (women – 1.27±0.2 g/l; men – 1.09±0.11 g/l; p=0.0000001) and (women – 2.69±0.19 g/l; men – 2.17±0.24 g/l) respectively.

Patients with community-acquired pneumonia+hyperglycemia showed higher values of alpha-1-antitrypsin (women – 1.42±0.3 g/l, p=0.019069; men – 1.85±0.38 g/l; p=0.0000001) in comparison with pneumonia group (women – 1.27±0.2 g/l; men – 1.09±0.11 g/l). At the same time, the level of α1-AT in this group was higher in men than in women.

The serum alpha-1-antitrypsin level of patients with COVID-19 (women –1.35±0.14 g/l; men – 1.34±0.1 g/l) was significantly lower than healthy control group (women –2.69±0.19 g/l; men – 2.17±0.24 g/l; p=0,0000001).

We found 1,5-fold higher concentration of α1-AT levels in COVID-19 patients with hyperglycemia (women –1.82±0.44 g/l, p=0.000253; men – 2.01±0.46 g/l, p=0.000410) compared with COVID-19 patients without hyperglycemia (women –1.35±0.14 g/l; men – 1.34±0.1 g/l).

Further we studied the level of α1-AT in COVID-19 patients with hyperglycemia who survived and those who did not survive. In group patients COVID-19+hyperglycemia- women-survivors level of α1-AT were approximately 1,5-fold higher in COVID-19+hyperglycemia- women-non-survivors (1.97±0.32 g/l; and 1.37±0.48 g/l, respectively, p=0.030558). In group patients COVID-19+hyperglycemia-men-non-survivors level of α1-AT were 2-fold lower mean alpha-1-antitrypsin concentration in their serum than did the COVID-19+hyperglycemia-men-survivors (1.2±0.1 g/l; and 2.45±0.28 g/l, respectively, p=0.0000001). Wherein, concentration of α1-AT levels in COVID-19 men-patients with hyperglycemia who survived was significantly higher than (men – 2.45±0.28 g/l, p=0.004039) compared with COVID-19 women-patients with hyperglycemia who survived (women – 1.97±0.32 g/l).

Data obtained in this work demonstrated that α_1-AT blood levels were significantly higher in renal cell carcinoma with T2DM patients than in healthy donors and RCC patients without T2DM (fig.1).

Patients with RCC+T2DM (n=12) showed higher values of alpha-1-antitrypsin (5.02±0.6 g/l) in comparison with RCC without T2DM (n=17) group (3.66±0.92 g/l; p=0.0000001) and healthy donors (n=29) (2.42±0.34 g/l; p=0.0000001).

The level of alpha-1-antitrypsin in patients with gastric cancer without T2DM was opposite (fig.2).

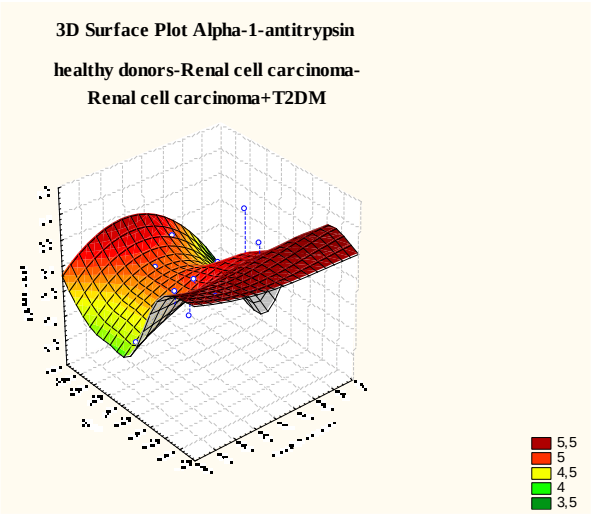

Fig.1. α_1-AT blood levels in healthy donors and RCC patients without and with T2DM. Note: Data are means ± SD for Gaussian variables Intergroup by the T-test Students. p<0.0000001 - were statistically significant.

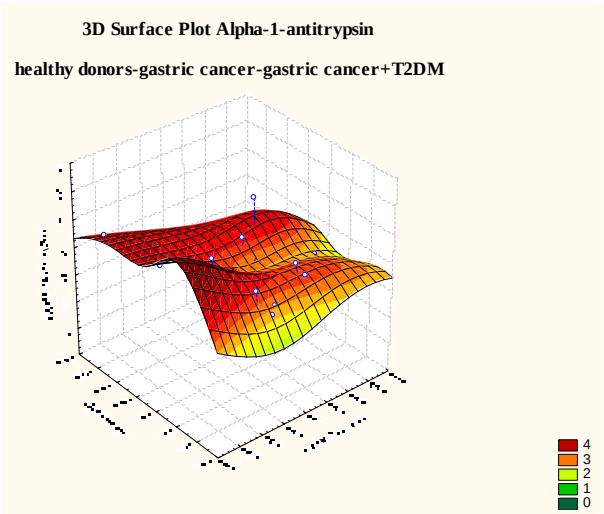

Fig.2. α_1-AT blood levels in healthy donors and gastric cancer patients. without and with T2DM. Note: Data are means ± SD for Gaussian variables Intergroup by the T-test Students. p<0.0000001 - were statistically significant.

The serum alpha-1-antitrypsin level of patients with gastric cancer (n=18) (1.76±0.35 g/l) was significantly lower than healthy control (n=29) group (2.42±0.34 g/l; p=0.0000001). At the same time, the level of α1-AT in gastric cancer with T2DM (n=18) group was higher (3.21±0.78 g/l) than in patients with gastric cancer without T2DM (n=18) (1.76±0.35 g/l; p=0.0000001) and healthy control (n=29) group (2.42±0.34 g/l; p=0.000033).

Multivariable logistic regression analysis was used to assess the risk factors for poor outcomes (death) in patients with RCC (Fig.3) and gastric cancer with T2DM (fig.4).

The analysis showed that the presence of a history of T2DM in patients with RCC α1-AT above 4,5 g/l at admission were independent predictors of 5-year survival. The probability of death among patients stratified by α1-AT tertiles at admission was higher in the highest tertile (≥5.6 g/l). A Cox proportional hazards analysis showed that compared with α1-AT < 4.69 g/l, α1-AT levels of 4.69 -5.6 g/l and ≥ 5.6 g/l were associated with an increased hazard ratio (α1-AT) of death.

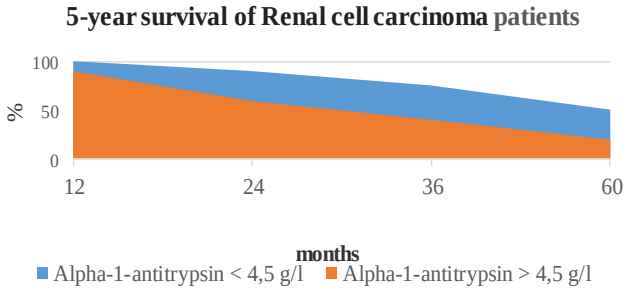

Fig.3.Overall and disease-free survival of RCC patients depending. on α_1-AT blood levels. Note: Here and in the following figures: p<0.0000001 - calculated by Multivariable l logistic regression analysis.

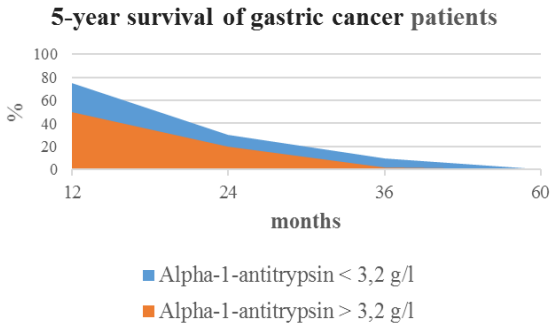

Fig.4. Overall and disease-free survival of gastric cancer patients depending on α_1-AT blood levels. Note: Here and in the following figures: p<0.0000001 - calculated by univariate logistic regression analysis.

In patients with gastric cancer the analysis showed that the presence of a history of T2DM α1-AT above 3,2 g/l at admission were independent predictors of 5-year survival. The probability of death among patients stratified by α1-AT tertiles at admission was higher in the highest tertile (≥3.7 g/l). A Cox proportional hazards analysis showed that compared with α1-AT < 2.69 g/l, α1-AT levels of 2.69 -3.7 g/l and ≥ 3.7 g/l were associated with an increased hazard ratio of death.

Data from different epidemiological data suggest that DM and chronic hyperglycemia may even increase the risk and mortality of community-acquired pneumonia, COVID-19 [8, 14], RCC [13] and GC patients [12]. Although there is compelling clinical data supporting this association, the molecular mechanisms underlying this association are not fully understood [1].

In this study alpha1-antitrypsin has been identified as a prognostic marker of poor prognosis in COVID-19 and cancer (for example, gastric and kidney cancer) in hyperglycemic conditions. Recent data of other authors also indicate that lower IL-6:α1-AT levels are related to worse prognosis in COVID-19 patients [2]. Patients admitted due to severe COVID-19 had lower α1-AT levels in comparison to patients admitted due to non-COVID pneumonia. This observation may suggest an association between mildly diminished α1-AT and higher risk of SARS-CoV-2 infection with severe COVID-19 disease [11]. Another study observed that middle-aged men showed a decrease in α1-AT levels, while women did not show any variation. Altogether, as in our study, women presented higher levels than men and no significant variation was observed in older groups [2].

α1-AT plasma level can increase 3- to 5-fold in states of systemic inflammation and / or infection, perhaps indicative of a homeostatic role of α1-AT but which may be deficient or overwhelmed in severe cases of COVID-19 [2].

Multivariate analysis for independent risk factors for mortality among COVID-19 patients showed that diabetes mellitus, older age, and high α1-AT levels were all associated with increased mortality. Patients admitted due to severe COVID-19 had lower α1-AT levels in comparison to patients admitted due to non-COVID pneumonia. This observation may suggest an association between mildly diminished α1-AT and higher risk of SARS-CoV-2 infection with severe COVID-19 disease [11].

Hyperglycaemia thus impaired serum α1-AT concentration in vivo. While the underlying mechanisms and clinical implications of these observations are unknown, the abnormally low α1-AT levels in diabetics may worsen the severity and contribute to the chronicity of their infections [8].

Alpha-1 antitrypsin, an endogenous acute phase protein being used for treatment of α1-AT deficiency, has multiple functions including anti-inflammatory, immunomodulatory, anti-apoptosis and cytoprotective effects [15]. Several reports have shown that high α1-AT blood levels in cancer cases are associated with cancer spreading and worse prognosis [3].

Conclusions

1. Our results obtained from COVID-19 and cancer patients with and without hyperglycemia revealed that lower serum levels of α1-AT are prognostic for the patient's worse outcome.

2. Levels of α1-AT in COVID-19 patients with hyperglycemia who survived > those who did not survive. Concentration of α1-AT levels in COVID-19 men-patients with hyperglycemia who survived was significantly higher than compared with COVID-19 women-patients with hyperglycemia who survived.

3. The obtained data convincingly demonstrate the value of testing the level of α1-AT in the blood as one of the important indicators of the effectiveness of cancer diagnosis and prognosis.

References

1. Berezniakov VI, Korzh AN, Pavlov SB, Yeroshenko GA, Shevchenko KV, Zvyagolska IM. General description of patients with community-acquired pneumonia Who passed an open comparative study. World of Medicine and Biology. 2022; 81(3): 017–021. 10.26724/2079-8334-2022-3-81-21-25

2. de Loyola MB, dos Reis TTA, de Oliveira GXLM, da Fonseca Palmeira J, Argañaraz GA, Argañaraz ER. Alpha-1-antitrypsin: A possible host protective factor against Covid-19. Rev Med Virol. 2021;31(2). doi:10.1002/rmv.2157

3. El-Akawi. Alpha-1 Antitrypsin Blood Levels as Indicator for the Efficacy of Cancer Treatment. World J Oncol. Published online 2013. doi:10.4021/wjon663e

4. Janciauskiene S, Wrenger S, Günzel S, Gründing AR, Golpon H, Welte T. Potential Roles of Acute Phase Proteins in Cancer: Why Do Cancer Cells Produce or Take Up Exogenous Acute Phase Protein Alpha1-Antitrypsin? Front Oncol. 2021;11. doi:10.3389/fonc.2021.622076

5. Jiang L, George Hu L. Serpin peptidase inhibitor clade A member 1-overexpression in gastric cancer promotes tumor progression in vitro and is associated with poor prognosis. Oncol Lett. 2020;20(6). doi:10.3892/OL.2020.12141

6. Komarevtseva I, Ihnatova A, Rudenko I, Balabanova K, Komarevtsev V. Liquid biopsy as a tool for predicts of severe COVID-19 and hospitalised community-acquired pneumonia. Pol. Merkur. Lek (Pol Med J), 2022; L (297); 155–159. http://pml.medpress.com.pl/ePUBLI/free/PML297-155.pdf.

7. Lin SY, Chang CH, Wu HC, et al. Proteome profiling of urinary exosomes identifies alpha 1-antitrypsin and H2B1K as diagnostic and prognostic biomarkers for urothelial carcinoma. Sci Rep. 2016;6. doi:10.1038/srep34446

8. Liu Sping, Zhang Q, Wang W, et al. Hyperglycemia is a strong predictor of poor prognosis in COVID-19. Diabetes Res Clin Pract. 2020;167. doi:10.1016/j.diabres.2020.108338

9/ Mandili G, Notarpietro A, Khadjavi A, et al. Beta-2-glycoprotein-1 and alpha-1-antitrypsin as urinary markers of renal cancer in von Hippel–Lindau patients. Biomarkers. 2018; 23(2): 123–130. doi:10.1080/1354750X.2016.1269132

10. Park SS, Ortega RR, Agudelo CW, et al. Therapeutic potential of alpha-1 antitrypsin in type 1 and type 2 diabetes mellitus. Med. 2021;57(4). doi:10.3390/medicina57040397

11. Pertzov B, Shapira G, Abushkara S, Cohen S, Turjeman A, et. al. Lower serum alpha 1 antitrypsin levels in patients with severe COVID-19 compared with patients hospitalized due to non-COVID-19 pneumonia. 2022 Dec;54(12):846–851. doi: 10.1080/23744235.2022.2111464.

12. Rojas A, Lindner C, Schneider I, et al. Diabetes mellitus contribution to the remodeling of the tumor microenvironment in gastric cancer. World J Gastrointest Oncol. 2021;13(12):1997–2012. doi:10.4251/wjgo.v13.i12.1997

13. Saddam H, Abdus S, Foysal A, et. al. System biology approaches identified novel biomarkers and their signaling pathways involved in renal cell carcinoma with different human diseases. Biosci. Rep. 2022 Nov 30; 42(11): BSR20221108. doi: 10.1042/BSR20221108

14. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020;167. doi:10.1016/j.diabres.2020.108382

15. Zhang X, Ostrov DA, Tian H. Alpha-1 antitrypsin: A novel biomarker and potential therapeutic approach for metabolic diseases. Clin Chim Acta. 2022;534:71–76. doi:10.1016/j.cca.2022.07.005

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