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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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No 4 (337) 2023

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IMPACT OF THE ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ON THE COURSE OF THE SEPTIC SHOCK DEVELOPED DURING COVID-19 AND OTHER SEVERE RESPIRATORY INFECTIONS IN PRESENCE OF HYPERFERRITINEMIA

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Abstract.

Introduction: SARS-CoV-2 can cause sepsis regardless of the presence of secondary bacterial or fungal infections. The virus itself likely causes sepsis through a variety of possible mechanisms, including immune dysregulation, with respiratory dysfunction, which as a result of circulatory dysfunction leads to hypoxemia and metabolic acidosis.

Methods and Objectives: We conducted cohort study, comparing outcomes of 212 critically ill patients with Septic shock (134 men (63.3%) and 78 women (36.7%), with a mean age between 40-70 years) were evaluated, who were treated in the intensive care unit of First University Clinic during 2020-2021 years. All four groups had documented Hyperferritinemia (HF). Patients were divided according to ferritin concentrations: moderate HF (ferritin <1500ng/ml) and severe HF (ferritin >1500ng/ml).

The study aimed to reveal the impact of the Angiotensin-Converting enzyme -2 (ACE2) inhibitors on the course of the Septic shock developed during COVID-19 and other severe respiratory infections in conditions of hyperferritinemia (HF).

Results: Study results show that severe HF in patients with Septic shock is associated with a high risk of mortality and can be considered an indicator of the severity of the disease. The consumption of ACE2 inhibitors plays an important role in the regulation of inflammatory processes in both COVID-19-infected and non-infected patients with Septic shock: ACE2 inhibitors reduce the levels of Ang II and C reactive protein (CRP) in the blood in both COVID-19-infected and non-infected patients with Septic shock in conditions of moderate and severe HF; regulate the activity of leukocytes and the blood pro-coagulation system in both COVID-19-infected and non-infected patients with Septic shock in conditions of moderate HF; reduce the expression of pro-inflammatory cytokines (IL-6), decrease the level of D dimer in COVID-infected patients in conditions of moderate HF; Procalcitonin levels do not differ between COVID-19 infected and non-infected patients with Septic shock.

Conclusion: Based on our study, we can assume that there is the important link between elevated Ang 2 and the quality of immunological disorders and inflammation. The consumption of ACE2 inhibitors plays an important role in the regulation of inflammatory processes in both COVID-19-infected and non-infected patients with Septic shock.

Key words. ACE 2 inhibitors, Septic shock, Ferritin.

Introduction.

COVID-19 is characterized by heterogeneous clinical manifestations, complex pathophysiology, and a wide spectrum of the clinical picture. COVID-19 is not only a localized "respiratory infection" but a "multisystem disease" caused by diffuse systemic processes involving complex interactions of immunological, inflammatory, and coagulation cascades. Genetic and acquired alterations in the patient's immune system further complicate his condition, which leads to wide heterogeneity in the clinical picture, course, and outcome of the disease. To properly, with the highest accuracy, assess the disease outcomes of COVID-19 it's especially important to effectively analyze the combination of the visual observations results, clinical trial outcomes, and disease-specific parameters [1-3].

SARS-COV-2 can cause sepsis regardless of the presence of secondary bacterial or fungal infections. The virus itself likely causes sepsis through a variety of possible mechanisms, including immune dysregulation, with respiratory dysfunction, which as a result of circulatory dysfunction leads to hypoxemia and metabolic acidosis. Thus, the multiorgan failure observed in COVID-19 can be explained by hypoxia and blood circulation disorders that develop as a result of microvascular dysfunction.

SARS-COV enters alveolar cells via a membrane-bound angiotensin-converting enzyme 2 (ACE2), which is the binding site for the coronavirus spike protein, promoting its adhesion to the cell surface, followed by internalization of the SARS-COV/ACE2 complex, endosome formation, release of viral RNA and its subsequent transcription and replication to spread the infection [1,3]. The ACE isoform, ACE2, unlike ACE, producing Ang II with potent vasopressor effects, enhancing sympathetic tone, and revealing pro-inflammatory and mitogenic properties over the endothelial and epithelial cells, produces a heptapeptide called Ang 1–7 characterized vasodilatory, anti-inflammatory activity [1,4]. ACE2 is expressed on the surfaces of alveolar epithelial cells and vascular endothelial cells and plays an important role in blood pressure (BP) regulation [5].

During SARS-COV infection, virus-bound ACE2 is internalized into the cytoplasm which reduces ACE2 expression on the membrane surface [6-8], and leads to the weakened ACE2-Ang (1–7)-MasR axis, mainly manifested by the increase of Ang II and decrease of vasodilator Ang (1–7) level [2], and can cause dysregulation of vascular tone, inflammation of the endothelium, thrombosis, initiating life-threatening respiratory distress, blood pressure dysregulation and development of thrombotic complications. The potential anti-inflammatory effects of Ang 2 have generated much interest from the point of view of revealing the relationship between Ang 2, organ failure, and mortality [9-11] inhibitors interrupt ACE which catalyzes cleavage of angiotensin I to angiotensin II. There have been several studies to evaluate whether ACE inhibitors can be beneficial in sepsis, but contradictory results have been reported [12,13]. Several studies have shown that sepsis is associated

with the downregulation of AT-1 receptors, which is driven by inflammatory cytokines, which in turn leads to a decrease in catecholamine release and aldosterone production from the adrenal medulla [14].

Hyperferritinemia is associated with a multitude of clinical conditions and with a worse prognosis in critically ill patients. Ferritin is known to be a pro-inflammatory mediator inducing the expression of pro-inflammatory molecules, yet it has opposing actions as a pro-inflammatory and as an immunosuppressant. We propose that the exceptionally high ferritin levels observed in these uncommon clinical conditions are not just the product of the inflammation but rather may contribute to the development of a cytokine storm. In addition, ferritin is also able to directly modulate the lymphocyte function and thus regulate the immune response. Ferritin represents a biomarker of disease progress and an independent predictor of various clinical outcomes in different patients [15].

The study aimed to reveal the impact of the AGE2 inhibitors on the course of the Septic shock developed during COVID-19 and other severe respiratory infections in conditions of hyperferritinemia.

Materials and methods.

We conducted cohort study, comparing outcomes of 212 critically ill patients with Septic shock (134 men (63.3%) and 78 women (36.7%), with a mean age between 40-70 years) were evaluated, who were treated in the intensive care unit of First University Clinic during 2020-2021 years.

Inclusion criteria for the study were: Age>40ys; COVID-19 and other respiratory diseases associated with Septic shock, with respiration dysfunctions in presence of hyperferritinemia (HF) (a) with prior exposure to ACE2 inhibitors or (b) no history of treatment with the ACE2 inhibitors.

Patients enrolled in the study were divided into 4 target groups: Group I comprised of individuals who were diagnosed with COVID – 19 infection and septic shock and were undergoing treatment with ACE2 inhibitors. Group 2 included patients with septic shock who were not infected with COVID -19 but were receiving ACE2 inhibitors. Group 3 patients were those with septic shock and COVID -19 infection who were not taking ACE 2 inhibitors; Group 4 comprised of patients diagnosed with septic shock who did not exhibit COVID -19 infection nor were administered ACE 2 inhibitors. In patients with septic shock who were not infected with COVID-19 (Groups 2, 4) the main Causative microorganisms were gram negative bacteria.

All four groups had established HF. Patients were divided according to ferritin concentrations: moderate HF (<1500ng/ml) and severe HF (>1500ng/ml).

Laboratory tests:

The routine laboratory tests including biochemistry, coagulation function, and blood cells (platelets, leucocytes) count were performed in each patient. We evaluated also changes in variables such as Angiotensin II (ANG II), Interleukin-6 (IL-6), C reactive protein (CRP), lactate and procalcitonin (PCT).

The level of Ang II in the blood was measured by the ELIZA method, on the Huma Reader HS device with reagent Human ANGII ELISA Kit; IL-6 concentration in the blood - by the electrochemiluminescence (ECL) method on the Cobas e 411 (Roche) device with Elecsys IL-6 reagent; CRP was determined by spectrophotocolorometric method, on biochemical analyzer Cobas C 111 (Roche) with Cobas 111 CRP reagent. Procalcitonin was measured by immunofluorescence method using a Fin care III Plus device. Lactate was measured by spectrophotocolorometric method, on biochemical analyzer Cobas C 111.

Statistical analysis:

Analysis of variance (ANOVA) was used for statistical analysis. We used the Software Program SPSS-12 for Windows to process the data and visualize the results. Statistically significant differences between parameters were assumed at $p < 0.05$.

Results.

Patients infected with COVID-19 with no prior ACE2 inhibitors history had the initial level of Ang II higher than non-infected individuals with moderate HF (ferritin <1500) ($F = 4.8$, $p = 0.045$); with extreme HF (ferritin >1500) this difference was diminished ($F = 0.6$, $p = 0.45$). The level of Ang II significantly decreased (to 0) in ACE2 inhibitor groups ($F = 488$, $p<0.001$; $F = 468$, $p<0.001$) (Figure 1).

Leukocytes count did not differ in COVID-19-infected and non-infected patients [ACE2 inhibitor (+) F= 1,89; p = 0,18; ACE2 inhibitor (-) F = 0,19; p = 0,66] when the ferritin concentration was <1500. In the setting of extreme HF (ferritin >1500) in patients who didn't use ACE2 inhibitors, leukocytes level was higher in COVID-19-infected patients [ACE2 inhibitor (-) F = 4,58; p = 0,05], however, in the patients' group, who used ACE2 inhibitors difference in leukocyte level was not detected [ACE2 inhibitor (+) F = 1,05; p = 0,31]. ACE2 inhibitors cause a reduction in inflammatory markers, leukocytes count, in COVID-19-infected [F = 4,25; p = 0,05] and uninfected patients [F=14,56; p = 0,001] with a ferritin concentration was <1500, and in COVID-19-infected patients with a ferritin concentration >1500 [F=10,33; p = 0,004] (Figure 2).

IL-6 level in COVID-19-infected patients was higher than in non-infected patients without prior use of ACE2 inhibitors [ACE2 inhibitor (-) F = 10,95; p=0,003] when the ferritin concentration was <1500. In the setting of extreme HF (ferritin >1500) IL-6 level was not statistically important different in COVID-19-infected and noninfected patients [ACE2 inhibitor (-) F=1,78; p = 0,21; ACE2 inhibitor (+) F = 0,006, p = 0,93]. ACE2 inhibitors decreased IL-6 levels in COVID-19-infected patients, when ferritin concentration was <1500 [F = 5,03; p = 0,03] and did not affect the level of IL-6 in all other patients' groups [ferritin >1500; COVID-19(+) F = 0,35; p = 0,55; COVID-19(-) F= 0,25; p = 0,62] (Figure 3).

In patients infected with COVID-19, without prior use of ACE2 inhibitors, platelets count was higher than in those without COVID-19 when the ferritin concentration was <1500 [F = 4,92; p = 0,037]; in the setting of extreme HF (ferritin >1500), without prior use of ACE2 inhibitors there was not detected a statistically important difference in platelets count in COVID-19-infected and noninfected patients [F = 0,18; p = 0,67]. Chronic use of ACE2 inhibitors suppressed the increase in

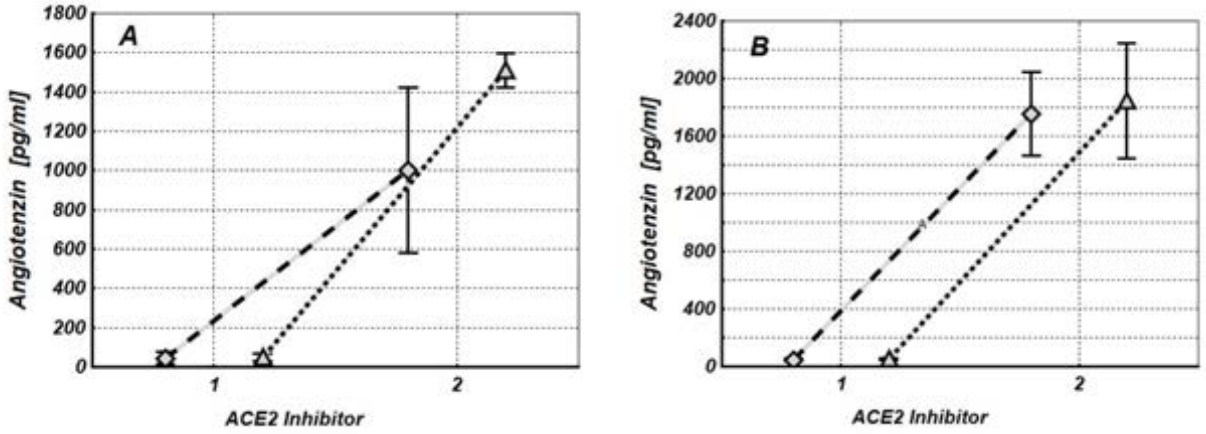

Figure 1. *Angiotensin II levels control level: (31.25-2000 g/ml) in COVID-19-infected and un-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500ng/ml; B - ferritin level >1500ng/ml) (- COVID-19-infected patients; - COVID-19-noninfected patients.*

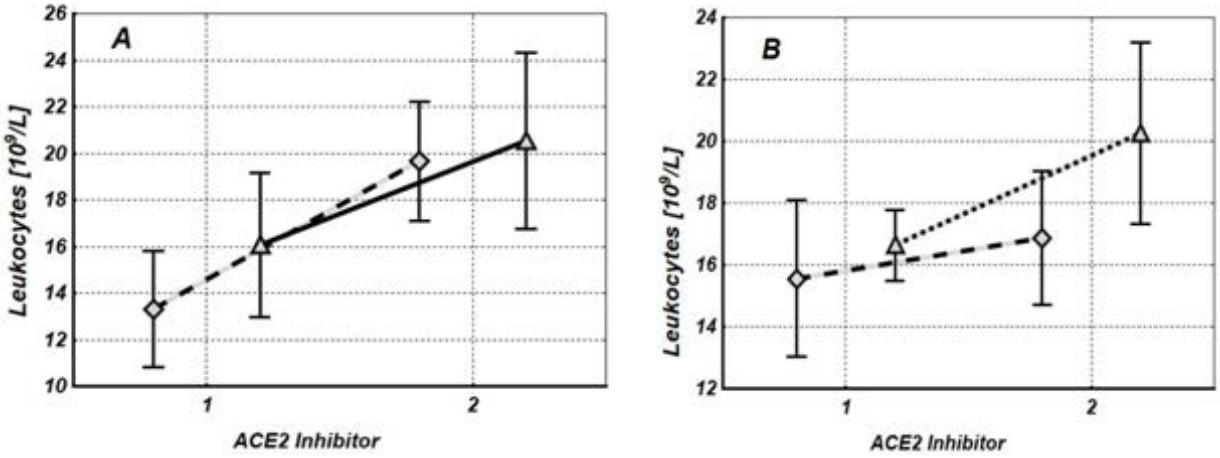

Figure 2*. Leukocyte levels in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (-COVID-19-infected patients; - Covid-19-noninfected patients).*

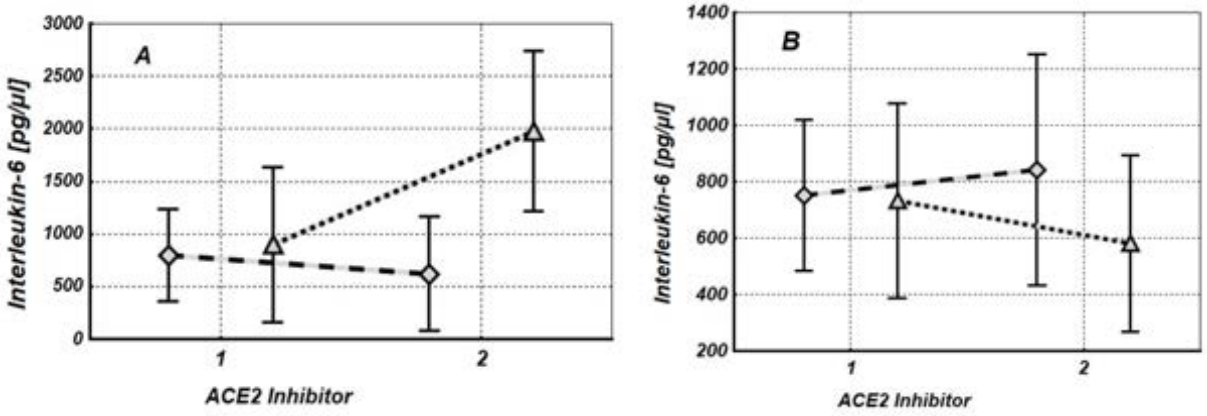

Figure 3. *Levels of interleukin-6 (control level :1-7pg/ml) in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (- COVID-19-infected patients; - COVID-19-noninfected patients).*

platelets count in COVID-19-infected and noninfected patients when the ferritin concentration was <1500 [COVID-19(+) F =15,72; p = 0,001; COVID-19(-) F = 4,7128; p = 0,031]. In patients with extreme HF (ferritin >1500) chronic use of ACE2 inhibitors suppressed the increase in platelets count in COVID-19-noninfected patients [F = 7,15; p = 0,02] but had no effect in COVID-19-infected patients HF (Figure 4).

In patients infected with COVID-19, D-dimer levels appear to be higher than in those without COVID-19 when the ferritin concentration was <1500 [F = 4,1142; p = 0,05]; while in the setting of extreme HF (ferritin >1500), D-dimer level was not statistically importantly different in COVID-19-infected and noninfected patients [F = 0,02; p = 0,88]. Chronic ACE2 inhibitors use was associated with a slight lowering of D-dimer levels in COVID-19-infected [F = 6,26; p = 0,02] and noninfected patients [F = 2,1; p = 0,07] when the ferritin concentration was <1500, but there was no notable difference in D-dimer levels between COVID-19-infected and non-infected patients with extreme HF was detected [COVID-19(-) F= 0,02; p = 0,88; COVID-19(+) F = 0,19; p = 0,75] (Figure 5).

CRP level did not differ between COVID-19-infected and non-infected patients when the ferritin concentration was <1500 [ACE2 inhibitor (+) F = 0,57; p = 0,45; ACE2 inhibitor (-) F = 0,14; p = 0,71]; CRP levels were significantly higher in COVID-19-non-infected patients compared to COVID-19-infected patients in the setting of extreme HF [ACE2 inhibitor(+) F = 4.19 p = 0,05 and ACE2 inhibitor(-) F = 11,85; p = 0,006]. ACE2 inhibitors cause the reduction in inflammatory markers - CRP in patients in all groups [COVID-19 (-) F = 3,8; p = 0,05 and COVID-19(+) F = 4,12; p = 0,045; ferritin< 1500]; and [COVID-19(-) F = 7,2711; p = 0,022; COVID-19(+) F= 3,77; p = 0,050; ferritin> 1500].

Lactate levels did not differ between COVID-19-infected and non-infected patients when the ferritin concentration was <1500 [ACE2 inhibitor (-) (F = 1.428; p = 0.246)]; ACE2 inhibitors didn't change lactate level in COVID-19-infected (F = 1,144; p = 0,291), while induced its increase significantly in COVID-19-noninfected patients F = 6,889; p = 0,012).

In the setting of extreme HF (ferritin >1500), a higher lactate level was observed in COVID-19-noninfected patients, although statistically insignificantly [ACE2 inhibitors (-) F = 0.385; p = 0.548; (ACE2 inhibitors (+) F = 2.491; p = 0.130]. ACE2 inhibitors practically do not change the lactate level either in COVID-19-infected (F=.092, p=.911) or in COVID-19-noninfected patients (F=.102, p=.791)).

In conditions when the ferritin level was <1500 procalcitonin

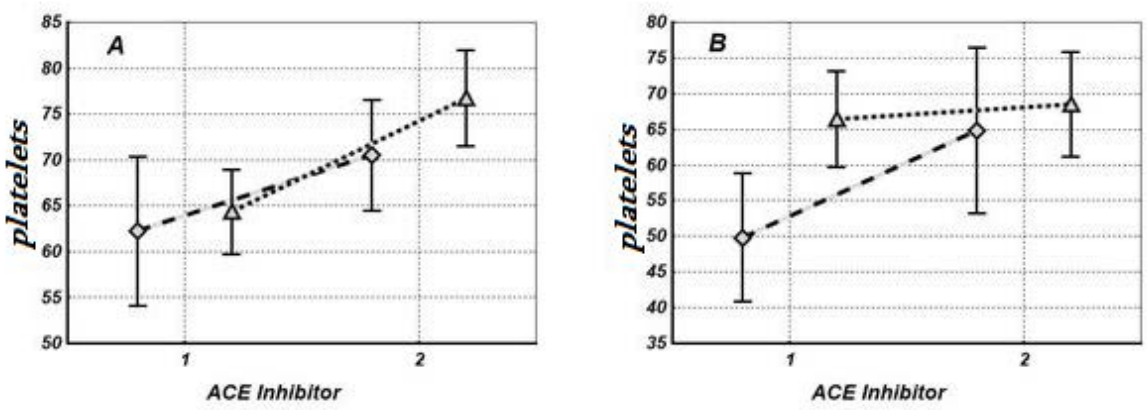

Figure 4. *Platelets count (Normal range 150-380 $10^3/\mu l$) in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (△ - COVID-19-infected patients; ◇ - COVID-19-noninfected patients).*

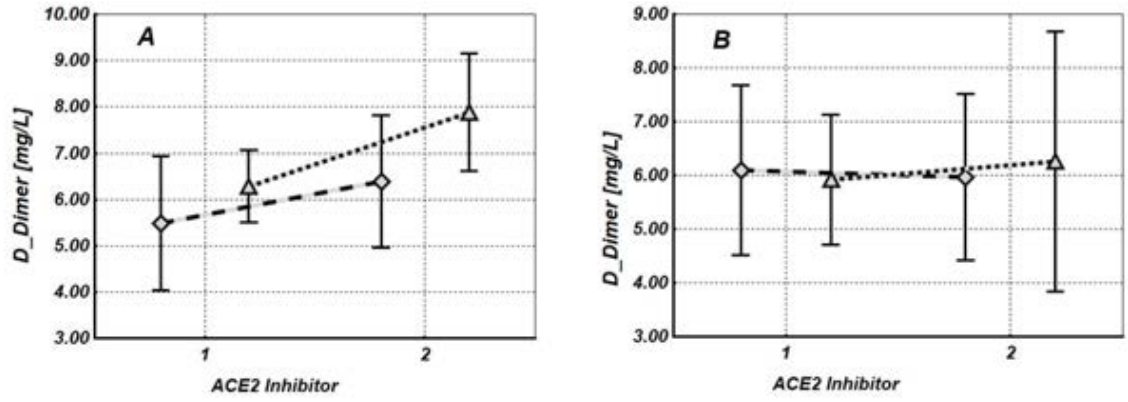

Figure 5. *D-dimer (control level: 0.10 -0.50 mg/l) in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (△ - COVID-19-infected patients; ◇ - COVID-19-noninfected patients).*

level was statistically significantly lower in COVID-19-infected patients (ACE2 inhibitors (-) F = 16.106; p < 0.001). ACE2 inhibitors induced statistically significant rice of procalcitonin level in COVID-19-infected patients [ACE2 inhibitors (+) F = 4.382; p = 0.041] but didn't affect procalcitonin level in COVID-19-uninfected patients ACE2 inhibitors (+) [ACE2 inhibitors (+) F = 1,28; p = 0,281).

In the setting of extreme HF (ferritin >1500), a higher lactate level was observed in COVID- 19-noninfected patients, although statistically insignificantly [ACE2 inhibitors (-) F = 0.385; p = 0.548; (ACE2 inhibitors (+) F = 2.491; p = 0.130]. ACE2 inhibitors practically do not change the lactate level either in COVID-19-infected (F=.092, p=.911) or in COVID-19-noninfected patients (F=.102, p=.791)).

In COVID-19-noninfected patients, the level of procalcitonin was higher, but statistically unreliable [ACE2 inhibitors (-) F = 0.688; p = 0.448; ACE2 inhibitors (+) F = 2.631; p = 0.081]. ACE2 inhibitors practically do not change the level of procalcitonin in either COVID-19-infected positive (ACE2 inhibitors (+) F=.097, p=.811) and COVID-19-uninfected patients (ACE2 inhibitors (+) F=.0652, P = o.958).

Discussion.

ACE2 was identified to be the cell receptor of SARS-CoV-2 [16], therefore, ACE2 distribution and expression in the human body may represent the possible routes of COVID-19 infection. High ACE2 expression was recognized in type II alveolar cells of the lungs, oral mucosa, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [17,18]. It was demonstrated that alveolar epithelial type II cells, being the main pathway for viral invasion, represent about 83% of ACE2-expressing cells [5].

After binding of SARS-CoV-2 to the ACE2 receptor, both SARS-CoV-2 -ACE2 complex is internalized in a cell by endocytosis, so that surface ACE2 receptors are downregulated, resulting in unopposed Ang II accumulation [19]. Acting via the type 1 Ang II receptor (AT1), Ang II induces the production of reactive oxygen species (ROS) by activation of NADP(H) oxidases [20,21], initiates an inflammatory cascade by reduced nicotinamide-adenine dinucleotide phosphate oxidase, and nuclear factor-κB, which mediates transcription and proinflammatory gene expression and increases ROS, adhesion molecules and chemokines levels, having a pro-inflammatory effect on leucocytes, endothelial, and vascular smooth muscle cells. An excess of ROS decreases nitric oxide (NO) bioavailability and causes vasoconstriction. Moreover, Ang II interrupts the anti-inflammatory effects of insulin. Together, these effects promote the formation of prothrombotic conditions, as well as plaques destabilization and rupture as well as plaques destabilization and rupture [22]. ACE2 down-regulation and elevation of Ang II level in severe COVID-19 patients can be crucial factors inducing excessive cytokine release and pro-thrombotic activation [23].

According to our study results, in patients infected with COVID-19 who did not receive ACE2 inhibitors, the initial level of Ang II was higher than in non-infected patients (Figure 1); accordingly, the content of leukocytes and IL-6 was higher in COVID-19-infected patients compared to their levels in COVID-19- non-infected critical patients (Figure 2, 3), the levels of platelets, and D-dimer in the blood of COVID-19-infected patients also increased (Figure 4, 5). Recent studies suggest that Ang II promotes thrombosis through increased platelet activation induced by T cell-dependent IL-6 signalling [24]. A high level of IL-6 contributes to hypercoagulation (by enhancing platelet production and activation), promoting an imbalance between plasma levels of coagulative and anti-coagulative factors, and the development of endothelial dysfunction. Hence, the elevated serum levels of pro-inflammatory cytokines in severe COVID-19 participate in Ang II-mediated thrombosis and vascular injury.

ACE2 inhibitors play an important role in the regulation functioning of the immune system by modifying T-cell populations and regulating cytokines and chemokines production, which is probably related to the inhibition of Ang II formation [25,23]. According to the results of our studies, ACE2 inhibitors by controlling systemic inflammation reduced inflammatory markers, leukocyte and IL-6, levels (Figure 2,3), CRP content (Figure 6), in COVID-19-infected and non-infected patients with septic shock, regulated the functioning of the blood coagulation system that revealed in the decrease of the platelets and D-dimer levels in the blood of COVID-19-infected patients with septic shock. As a result, the risk of vascular thrombosis in patients with septic shock was reduced. It is well known that the level of RAS expression sharply elevates in sepsis, which induces oxidative stress, vascular permeability, excess production of pro-inflammatory cytokines, and pro-coagulant effects [26].

Ferritin, known as a molecule storing iron ions, is a dynamic "buffer" of iron, in maintaining the steady-state availability of iron. Cellular ferritin values are regulated at the translational level by the iron regulatory proteins/iron-responsive elements (IRP/IRE) system, which is dependent on the amount of iron in the body [27]. In cells, it can be localized in the cytoplasm, nucleus, and mitochondria. The existence of ferritin in erythrocytes has also been proven, and it is also found in blood serum [28-30].

In response to the inflammatory state, cells produce large amounts of ferritin. Still is not clear whether ferritin is only a sign of disease progression or has a modulating role in the pathogenesis of the disease. Over the last few years, accumulated data implicates a role for ferritin as a signaling molecule and direct mediator of the immune system. Ferritin by the activation of NF-κB promotes the further release of pro-inflammatory mediators, and also directly modulates the lymphocyte function. Thus, acting as a modulator of the innate immune response, ferritin increases the inflammatory response, resulting in a vicious cycle [31,32]. HF during a multitude of clinical conditions, including COVID-19, is associated with worse prognosis in critically ill patients. It is believed, that in response to the virus-induced injury, cytokines (IL-1β, IL-6, and IFN-γ) stimulate the production of defense proteins in the liver, including ferritin and CRP [33]. As the concentrations of

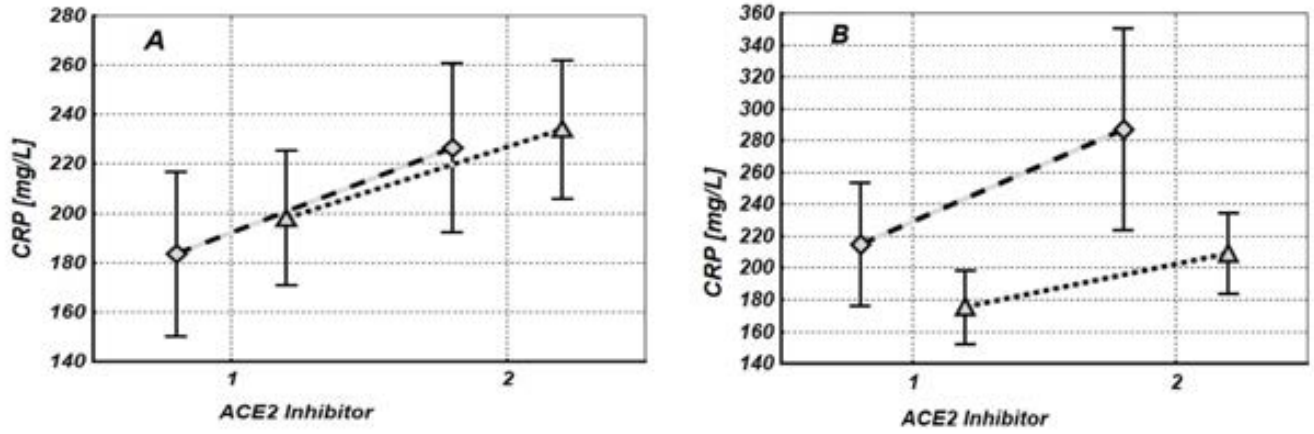

Figure 6. *CRP levels in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (△ - CoVID-19-infected patients; ◇ - COVID-19-noninfected patients).*

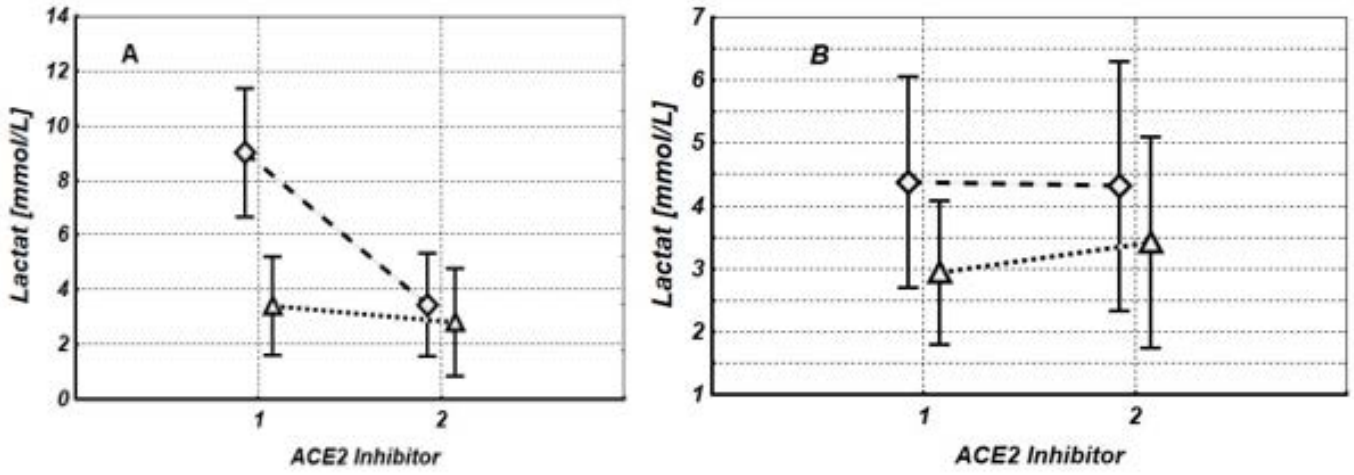

Figure 7. *Lactate level in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500 (△ - CoVID-19-infected patients; ◇ - COVID-19-noninfected patients).*

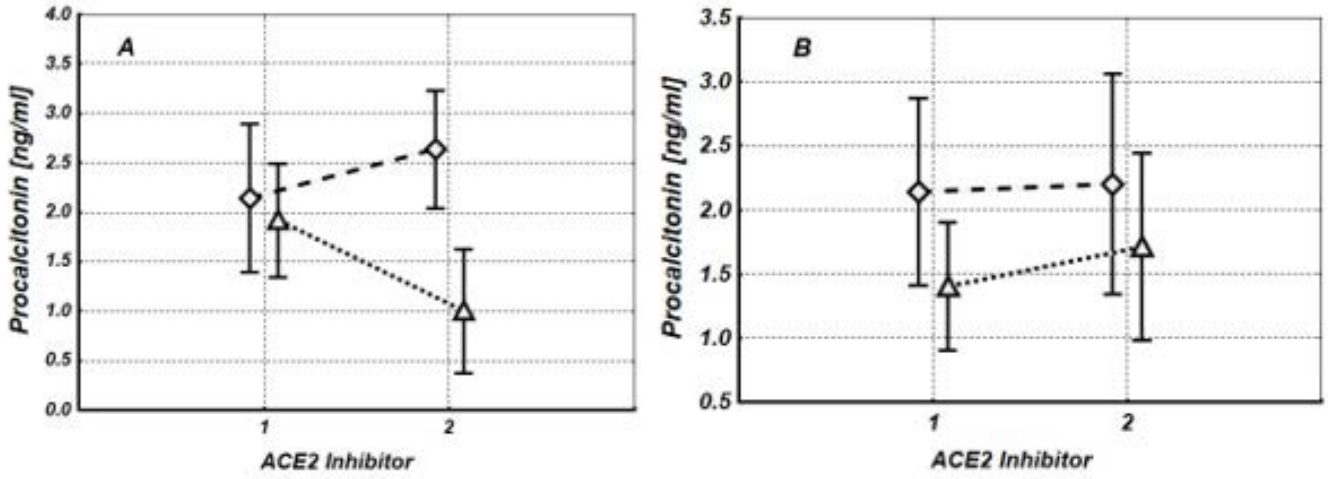

Figure 8. *Procalcitonin levels in COVID-19-infected and non-infected patients with (1) or without (2) prior ACE2 inhibitors use (A - ferritin level <1500; B - ferritin level >1500). (△ - CoVID-19-infected patients; ◇ - COVID-19-noninfected patients).*

ferritin in the cells are about 1000 times higher than those in the serum, the increase of serum ferritin can be the result of cellular stress and cell lysis [34-36]. HF promotes the production of ROS and lipoperoxidation, which leads to extensive cell and tissue damage resulting in cellular apoptosis, and cascade-amplified inflammatory events. In addition to damaged cells, macrophages are also an additional source of increased ferritin levels [37,38]. Possibly, during COVID-19-induced hyperinflammatory state high blood ferritin, as a prooxidative agent and immune response modulator, initiates a cycle of destructive events, which can cause additional lesions in tissues. Therefore, the level of iron metabolism plays a key role in the COVID-19 outcome [39,40]. It was proposed that the exceptionally high ferritin levels observed in clinical conditions are not just the product of the inflammation but rather may contribute to the development of a cytokine storm [15]. The role of ferritin in the pathophysiology of COVID-19 is not fully understood. The alterations of ferritin levels in patients with severe COVID-19 and the subsequent high mortality rates in patients with high ferritin levels need further investigation [33].

Our study results show that in COVID-19-infected patients with Septic shock at hyperferritinemia conditions the levels of Ang II, were especially high, at the same time. This data indicates the link between elevated Ang II and ferritin levels and inflammation, and lung alveoli dysfunction in COVID-19-infected critically ill patients. It was reported that Ang II participates in the induction of iron metabolism-related gene expression, including hepcidin [41], which is a key regulator controlling the delivery of iron to blood plasma from intestinal cells absorbing iron, erythrocyte-recycling macrophages, and iron-storing hepatocytes. Secretion of hepcidin can be increased during inflammatory states [42], including COVID-19, and IL-6 is the necessary and sufficient cytokine for the induction of hepcidin during inflammation [43]. During viral infections, the immune system supports increased serum ferritin levels in the cells, limiting the availability of iron to pathogens (necessary for their proliferation) [44,45]. As the result, the concentration of iron in the systemic circulation decreased, and serum ferritin increased, which was recorded in COVID-19. Additionally, based on the similarity of the hepcidin and part of the spike glycoprotein structure of the SARS-CoV-2 virus, it is hypothesized that this protein could have a hepcidin-like effect [37] and therefore, also may increase cellular and serum concentrations of ferritin regardless of the inflammatory effect.

Conclusion.

Based on our study, we can assume that severe HF (ferritin >1500 ng/ml) in patients with septic shock is associated with a high risk of mortality and can be considered an indicator of the severity of the disease.

ACE2 inhibitors reduce the levels of ANG II and markers of inflammation, CRP, in the blood in both COVID-19-infected and non-infected patients with septic shock in conditions of moderate (<1500) and severe (>1500) HF, regulate the activity of leukocytes and the blood pro-coagulation system in both COVID-19-infected and non-infected patients with septic shock in conditions of moderate HF (<1500).

In conditions of moderate HF (<1500), ACE2 inhibitors reduce the expression of pro-inflammatory cytokines (IL-6) in COVID-19-infected patients. Procalcitonin levels did not differ between COVID-19-infected and non-infected critically ill patients in case of severe HF.

This data indicates the important link between elevated Ag 2 and the quality of immunological disorders and inflammation. The consumption of ACE2 inhibitors plays an important role in the regulation of inflammatory processes in both COVID-19-infected and non-infected patients with Septic shock.

Limitation.

It should be noted that the studied cohort was quite limited (212 patients), and therefore, given the importance of comorbidities in the development of complications of COVID-19, it is unlikely to be representative of the general population. In this regard, it is considered less appropriate the generalization of the final conclusions according to the examined cohort, due to its probable low representativeness, however, considered less appropriate the generalization of the final conclusions according to the examined cohort, due to its probable low representativeness, however, the clinical value of the findings is obvious in the present article.

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