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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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# POST-COVID-19 SYNDROME: INCIDENCE, BIOMARKERS, AND CLINICAL PATTERNS IN KAZAKHSTAN

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## Abstract.

**Background:** Post-COVID syndrome (PCS) remains a significant challenge in modern medicine due to its diverse clinical manifestations and long-term impact on patients' health. Identifying risk factors and biomarkers associated with PCS can facilitate early diagnosis and improve patient management.

**Objective:** This study aimed to assess the prevalence, diagnostic markers and clinical characteristics of post-COVID syndrome (PCS) in the Abay region. **Methods:** A retrospective-prospective cohort study was conducted among 639 individuals who had recovered from COVID-19. Participants were divided into two groups: those with PCS (n=300) and those without (n=339). Clinical and demographic data, laboratory biomarkers, and vaccination history were analyzed. Statistical analyses, including logistic regression, were applied to identify key risk factors and clinical subtypes of PCS.

**Results:** The prevalence of PCS was 47%, with significant differences observed between groups regarding comorbid conditions, and laboratory biomarkers. PCS patients had a higher incidence of hypertension (47% vs. 23.5%, p=0.003) and diabetes mellitus (10.3% vs. 6.7%, p=0.032). Elevated alkaline phosphatase (ALP) levels were associated with PCS (p=0.004), whereas hematocrit (HCT) and immunoglobulin G (IgG) levels were lower in PCS patients. Cluster analysis identified four distinct clinical phenotypes, emphasizing the heterogeneity of PCS manifestations. Vaccination status showed a significant inverse correlation with PCS incidence (p=0.002), suggesting a protective effect of higher vaccine doses.

**Conclusion:** PCS presents with a broad spectrum of symptoms, necessitating a multidisciplinary approach for optimal patient management. Identified biomarkers, including ALP, HCT, and IgG, may serve as potential indicators for PCS diagnosis. Vaccination ap-pears to reduce PCS risk, highlighting the importance of immunization in mitigating long-term COVID-19 complications. These findings contribute to a better understanding of PCS pathophysiology and provide a foundation for future research and personalized treatment strategies.

**Key words.** Post-COVID syndrome, long COVID, biomarkers, vaccination, inflammation, alkaline phosphatase, hematocrit, immunoglobulin G, comorbidities, multidisciplinary approach.

## Introduction.

The coronavirus disease (COVID-19) has spread globally, leading to a worldwide pandemic. The epidemiological landscape of COVID-19, both nationally and internationally, continues to evolve. As of April 10, 2021, updated data for the Republic of Kazakhstan indicate a total of 315,000 confirmed cases and 3,260 confirmed fatalities [1]. The case fatality rate stands at 1.04%, substantially exceeding the 0.02% reported for the European region [2].

Kazakhstan researchers have made significant advancements in epidemiological modeling and strategic planning, supported by initiatives aimed at controlling the spread of infection within the country [3]. However, in the domain of clinical medicine, research findings remain relatively limited. To date, studies conducted in Kazakhstan have focused on the epidemiology and specific clinical characteristics of COVID-19, as well as the microbial landscape and antibiotic susceptibility patterns of key pathogens isolated from infected patients [4].

Several key research areas are gaining increasing attention. COVID-19 has been recognized as a multi-organ disease with a broad spectrum of manifestations, many of which persist as prolonged and persistent effects beyond the acute phase [5].

Recent literature increasingly supports the notion that PCS is a heterogeneous syndrome, prompting the use of data-driven approaches such as cluster analysis and machine learning to identify distinct symptom patterns and clinical phenotypes. Studies have revealed several recurrent subtypes, including fatigue-dominant, neurocognitive, respiratory, and multi-systemic clusters [6-8]. These findings highlight the need for population-specific analyses of PCS subgroups, which our study addresses by exploring clinical phenotypes in a Kazakhstani cohort.

The multiorgan involvement in COVID-19 is primarily attributed to the immune system's response to viral invasion [9]. Inflammation, as a host defense mechanism, activates biological processes aimed at containing viral invasion and mitigating tissue damage through the initiation of both innate and adaptive immune responses. The degree of immune response regulation, influenced in part by specific genetic risk factors, plays a critical role in determining the clinical trajectory of the disease, including the potential progression to a cytokine storm (CS) [10]. A persistent inflammatory response may result in prolonged clinical manifestations, commonly referred to as post-COVID syndrome [11].

Dysregulation of immune homeostasis and the induction of a hyperinflammatory state are key determinants in the development of severe disease forms and post-COVID syn-drome [12]. For instance, a recent genome-wide analysis of 2,244 COVID-19 cases identified an association between genetic variants in the interleukin-6 (IL-6) signaling pathway and critical illness [13]. Moreover, treatment with IL-6 antagonists in severely ill patients has been shown to improve clinical outcomes [14].

Post-COVID-19 condition is typically defined by a variety of symptoms that emerge within three months after the acute phase of COVID-19 and persist for a minimum duration of two months. [15]

In addition to virus-dependent mechanisms, virus-independent processes—such as immune-mediated tissue damage, perivascular inflammation, disruption of the endothelial-epithelial barrier with monocyte and neutrophil infiltration, and protein-rich exudate extravasation into the alveolar space under cytokine influence—contribute to fibrosis and secondary infections [16]. Accelerated fibrosis has emerged as a major pathogenic factor underlying post-COVID syndrome [17].

A comprehensive assessment of contributing factors will facilitate the development of a pathogenesis-based prognostic scale for COVID-19 outcomes, while clinical guidelines incorporating these findings will enhance disease prognosis and patient survival [18]. In this regard, the initial set of factors outlined in the technical specifications has been expended to include additional variables, such as demographic (sex, age, including pediatric cases), biological (pregnancy, presence of chronic conditions, history of vaccinations against viral diseases), and social determinants (access to healthcare services), among others [19]. Despite the high prevalence of post-COVID syndrome a standardized approach to its diagnosis and treatment has not yet been established [20]. This is partly due to the complex nature of the syndrome and the heterogeneity of its clinical presentation. To fill this gap in knowledge, we carried out a bidirectional study with the following goals: to evaluate the incidence of post-COVID syndrome using both the World Health Organization (WHO) diagnostic criteria; to identify and characterize risk factors associated with post-COVID syndrome, as well as biomarkers for early detection and intervention; and to classify the clinical phenotypes of post-COVID syndrome to improve understanding of its various manifestations [21].

## Materials and Methods.

### Study Design and Data Sources:

This study aimed to identify factors influencing the severity of COVID-19 and the development of post-COVID syndrome. A retrospective-prospective cohort design was used, with participants randomly selected from patients treated for COVID-19 in regional hospitals. The inclusion criteria for the main group (with post-occlusive symptoms) was the presence of a laboratory-confirmed diagnosis of COVID-19 (positive PCR test or rapid antigen test) in persons aged 18 years and older, regardless of the severity of the disease. Participants were randomly selected from regional electronic medical registries of COVID-19 survivors. Recruitment was carried out via telephone calls: potential participants were provided with detailed information about the study and asked to sign informed consent. A total of 639 individuals were included in the study and divided into two groups: a main group (300 patients) with signs of PCS and a control group (339 patients) who had undergone COVID-19 without subsequent PCS symptoms. Both hospitalized and outpatients meeting diagnostic and age criteria were eligible for inclusion. Information on possible sources of selection bias (e.g., availability for contact, consent to participate) has been added to the section describing study limitations.

Initially, 825 potential participants were identified from the regional electronic COVID-19 registries. After applying eligibility screening and contacting by telephone, 723 were reached. Of these, 639 individuals met the inclusion criteria and consented to participate. The main reasons for exclusion were: inability to establish contact (n = 33), refusal to participate (n = 20), and incomplete or missing data (n = 31).

The study followed a bidirectional retrospective-prospective cohort: retrospective data (including acute-phase laboratory values, treatment records, and vaccination status) were extracted from medical records, while prospective data were collected at a single standardized follow-up visit. During this visit, participants underwent structured clinical interviews and laboratory testing.

All included patients reported symptoms lasting more than 12 weeks following acute COVID-19. The median follow-up duration was 4.5 months (IQR: 3.0–6.0 months), ensuring compliance with WHO's ≥12-week PCS definition. This variability in follow-up was acknowledged as a potential source of classification bias in the Limitations section. All laboratory testing and clinical assessments were conducted during the same follow-up visit at the time of inclusion.

### Study units:

The study consisted of two groups:

Main Group (300 participants): Individuals with COVID-19 and developed post-COVID syndrome. Control Group (339 participants): Individuals who had a con-firmed history of COVID-19 but did not develop post-COVID symptoms.

The main group was further stratified based on the severity of COVID-19 during the acute phase and vaccination status. Data collected for each participant included demographic information (age, weight, height, BMI), smoking and alcohol consumption status, comorbidities, vaccination status, disease severity, and treatment history. Laboratory test data during the acute phase of COVID-19 were also collected from medical records, while vaccination history was obtained from the national vaccination registry.

### Study Formulas:

The study involved several clinical and laboratory assessments to evaluate the health status of participant. Blood Samples: Venous blood samples (10 mL) were collected from all participants for the following analyses: Complete blood count (CBC), Liver function tests, Blood urea nitrogen (BUN), creatinine, electrolytes, C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), Interleukin-6 (IL-6), Immunoglobulin G (IgG) against COVID-19, Additional Assessments: Chest X-rays, electrocardiography (ECG), and thyroid function tests were performed as clinically indicated.

### Statistical analysis:

Data were entered into Epidata for accuracy, and statistical analysis was conducted using R software. The following statistical methods were used to compare groups and assess relationships between risk factors and the development of post-COVID syndrome: t-test for continuous variables, Mann-Whitney U test for non-normally distributed variables, Fisher's Exact Test for categorical data. Logistic regression to evaluate the association between risk factors and post-COVID syndrome development. To improve transparency, the complete

multivariate logistic regression model, including all adjustment parameters and coefficients, is provided in supplementary Table 3.

The predictive value of biomarkers was assessed using the area under the receiver operating characteristic (AUROC) curve. Additionally, machine-learning techniques were employed for clustering participants based on clinical characteristics. Cluster analysis was performed to identify patient subgroups based on biomarker and symptom profiles. The analysis was conducted using the k-means algorithm, applying Euclidean distance as the similarity metric. To determine the optimal number of clusters, we utilized both the elbow method and silhouette analysis. These details have been added to enhance the reproducibility of our findings and allow for replication in future studies.

**Ethics statement:**

Before starting the study, all documents, including the research protocol and data collection questionnaires, underwent expert review and received positive approval from the Local Ethics Commission of the NJSC Semey Medical University, Minutes of Meeting

No. 2 of 12.12.2023. Patients were included in the study only after they received full information about it and gave written voluntary consent to participate.

## Results.

Among the patients depicted in Figure 1 with PCS, the most prevalent symptoms were cough, observed in 96% (N = 288) of cases. This was followed by shortness of breath in 95% (N = 285), headache in 83.3% (N = 249), and muscle or body pain in 72% (N = 216). Loss of taste or smell was reported in 48% (N = 144), while sore throat was observed in 46% (N = 138).

Table 1 presents cohort data from 639 participants, stratified based on the presence or absence of post-COVID-19 syndrome. The mean age of participants was 53.00 years, with a slight difference between the groups: 50.00 years in the non-post-COVID-19 group versus 56.00 years in the post-COVID-19 group. However, the p-value of 0.415 indicates no statistically significant difference in age between the two groups. Age distribution analysis similarly revealed no substantial variation ($p = 0.237$), with the largest proportion of participants in both cohorts falling within the 46–64-year age range. A significant gender difference was observed between the two groups ($p < 0.001$), with a higher proportion of post-COVID-19 syndrome cases among females (78.7%) compared to males (54.6%) in the non-post-COVID-19 group. This finding suggests a potential association between post-COVID-19 syndrome and female sex. Body mass index (BMI) distribution across categories (<18, 18–24, 25–29, ≥30) was comparable between the two groups, with no statistically significant difference ($p = 0.347$). This indicates that BMI does not exert a strong influence on the presence or absence of post-COVID-19 syndrome. Regarding comorbidities, a significantly higher proportion of individuals with post-COVID-19 syndrome had pre-existing conditions (28.3%) compared to those without (12.0%), with a p-value of 0.001.

Hypertension and Comorbidities: A higher prevalence of hypertension was observed in the post-COVID-19 syndrome group (47.0%) compared to the non-post-COVID-19 group (23.5%), with a statistically significant p-value of 0.003. This suggests a potential association between hypertension and post-COVID-19 syndrome. Similarly, the prevalence of diabetes mellitus was higher in the post-COVID-19 syndrome group (10.3%) than in the non-post-COVID-19 group (6.7%), with a statistically significant p-value of 0.032, indicating a possible link between diabetes and post-COVID-19 syndrome.

Vaccination Status and Post-COVID-19 Syndrome: The median number of vaccine doses was higher in the non-post-COVID-19 group (3 doses, IQR 3–4) compared to the post-COVID-19 syndrome group (3 doses, IQR 2–3), with a statistically significant difference ($p = 0.002$). This finding suggests that individuals who received fewer vac-cine doses may have a higher likelihood of developing post-COVID-19 syndrome.

A significant difference in vaccination status was observed between the two groups ($p = 0.046$). A higher proportion of individuals without post-COVID-19 syndrome were fully vaccinated or had received a booster dose, whereas those with post-COVID-19 syndrome were more likely to be unvaccinated (15.7% vs. 2.4%).

Regarding mRNA vaccines, there was no significant difference in the median number of doses received between the two groups ($p = 0.185$), indicating that mRNA vaccination status did not substantially influence the development of post-COVID-19 syndrome.

Severe Disease and Intensive Care Unit Admission: Both oxygen therapy and intensive care unit (ICU) hospitalization were rare in both groups, with no significant differences observed ($p = 0.323$ for both variables). This suggests that severe acute illness requiring intensive care may not be a strong predictor of post-COVID-19 syndrome.

Table 2 presents the association between various demographic, clinical, and laboratory parameters and the presence of post-COVID-19 syndrome. The analysis includes both unadjusted and adjusted odds ratios (OR) with 95% confidence intervals, as well as AUROC values reflecting the diagnostic significance of the variables.

Age did not demonstrate a significant association with post-COVID-19 syndrome in either the unadjusted analysis (OR = 1.11, 95% CI: 0.99–1.02, $p = 0.415$) or the adjusted analysis (OR = 1.00, 95% CI: 0.98–1.02, $p = 0.781$). In contrast, female sex was a strong predictor of post-COVID-19 syndrome, increasing the likelihood of its occurrence more than fourfold (OR = 4.25, 95% CI: 1.73–6.30, $p < 0.001$), and this association remained significant after adjustment (OR = 4.55, 95% CI: 1.86–7.02, $p < 0.001$). Body mass index (BMI) did not show a statistically significant association with the condition (OR = 0.97, 95% CI: 0.92–1.02, $p = 0.347$; adjusted OR = 0.97, 95% CI: 0.92–1.03, $p = 0.473$). The number of comorbidities emerged as a significant risk factor, nearly tri-pling the likelihood of post-COVID-19 syndrome (OR = 2.89, 95% CI: 1.67–5.68, $p < 0.001$), with this association persisting after adjusting for other variables (OR = 2.87, 95% CI: 1.58–5.97, $p = 0.001$). The number of vaccine doses administered was associated with a reduced risk of post-COVID-19 syndrome (OR = 0.85, 95% CI: 0.67–1.02, $p = 0.002$), and the significance of this parameter remained unchanged after

***Table 1.*** *Baseline Characteristics of Study Participants by Post-COVID-19 Syndrome (PCS) Status.*

| Variables | Total | Post-Covid-19 Syndrome | | p-value |
|---|---|---|---|---|
| | | Absence | Presence | |
| Number (%) | 639 (100) | 339 (53) | 300 (47) | |
| Age (y): median (IQR) | 53.00 (42.0- 70.0) | 50.00 (43.0- 70.0) | 56.00 (42.5-69.5) | 0.415 |
| Age groups: number (%) | | | | 0.237 |
| 18–30 | 45 (7.0) | 32 (9.5) | 13 (4.3) | |
| 32–45 | 160 (25.0) | 94 (27.8) | 66 (22.0) | |
| 46–64 | 257 (40.3) | 116 (34.3) | 141 (47.0) | |
| ≥65 | 177 (27.7) | 97 (28.4) | 80 (26.7) | |
| Female: number (%) | 421 (65.8) | 185 (54.6) | 236 (78.7) | <0.001 |
| Male: number (%) | 218 (34.2) | 154 (45.4) | 64 (21.3) | |
| BMI groups: number (%) | | | | 0.347 |
| <18 | 20 (3.1) | 9 (2.6) | 11 (3.7) | |
| 18–24 | 177 (27.7) | 98 (28.8) | 79 (26.3) | |
| 25–29 | 278 (43.5) | 155(45.7) | 123(41.0) | |
| ≥30 | 164 (25.7) | 77 (22.9) | 87 (29.0) | |
| Comorbidity: number (%) | 151 (23.6) | 66 (12.0) | 85 (28.3) | 0.001 |
| Cancer: number (%) | 17 (2.7) | 9 (2.5) | 8 (2.7) | 0.856 |
| Arterial hypertension: number (%) | 228 (35.7) | 87 (23.5) | 141 (47.0) | 0.003 |
| CKD stage≥III: number (%) | 11 (1.7) | 5 (1.3) | 6 (2.1) | 0.746 |
| Respiratory disease: number (%) | 86 (13.4) | 38 (10.3) | 48 (16.0) | 0.083 |
| Neurological disease: number (%) | 103 (16.1) | 54 (14.6) | 49 (16.3) | 0.334 |
| Diabetes mellitus: number (%) | 40 (6.7) | 6 (15.8) | 31 (10.3) | 0.032 |
| Autoimmune diseases: number (%) | 13 (2.0) | 6 (1.8) | 7 (2.3) | 1.000 |
| Vaccine doses: median (IQR) | 3 (3- 4) | 3 (3- 4) | 3(2- 3) | 0.002 |
| Vaccine course: number (%) | | | | 0.046 |
| unvaccinated | 56 (8.8) | 9 (2.4) | 47 (15.7) | |
| incomplete | 1 (0.1) | 0 (0.0) | 1 (0.3) | |
| complete | 150 (23.5) | 73 (27.9) | 77 (25.7) | |
| boosted | 432 (67.6) | 257 (69.7) | 175 (58.3) | |
| mRNA vaccine doses: median (IQR) | 1.00 (1.00- 2.00) | 1.00 (1.00- 2.00) | 1.00 (1.00- 2.00) | 0.185 |
| Oxygen therapy: number (%) | 10 (1.6) | 0 (0.0) | 10 (3.5) | 0.323 |
| ICU admission: number (%) | 10 (1.6) | 0 (0.0) | 10 (3.5) | 0.323 |

***Table 2.*** *Association between biomarkers and post-COVID-19 syndrome examined using multivariate logistic regression analysis.*

| Biomarkers | Crude ORs (95% CI) | *p*-value | Adjusted ORs (95% CI) | *p*-value | AUROC (95% CI) |
|---|---|---|---|---|---|
| **Demographic and Clinical Characteristics** | | | | | |
| Age (year) | 1.11 (0.99–1.02) | 0.415 | 1 (0.98–1.02) | 0.781 | |
| Female | 4.25 (1.73–6.30) | <0.001 | 4.55 (1.86–7.*02*) | <0.001 | |
| BMI (kg/m$^2$) | 0.97 (0.92–1.02) | 0.347 | 0.97 (0.92–1.03) | 0.473 | |
| Number of underlying diseases | 2.89 (1.67–5.68) | <0.001 | 2.87 (1.58–5.97) | 0.001 | |
| Vaccine doses | 0.85 (0.67–1.02) | <0.002 | 0.86 (0.69–1.06) | 0.002 | |
| **Laboratory** | | | | | |
| HCT | 0.81 (0.87–0.98) | 0.001 | 0.88 (0.81–1.08) | 0.504 | 0.51 (0.57–0.70) |
| WBC | 1.04 (0.81–1.18) | 0.563 | 1.04 (0.8–1.19) | 0.605 | 0.52 (0.34–0.57) |
| PLT | 1 (1–1) | 0.807 | 1 (1–1) | 0.743 | 0.53 (0.46–0.53) |
| NLR | 0.85 (0.62–1.13) | 0.782 | 0.83 (0.6–1.14) | 0.702 | 0.45 (0.39–0.52) |
| PLR | 1 (0.89–1) | 0.360 | 1 (0.89–1) | 0.294 | 0.52 (0.40–0.60) |
| AST | 1 (0.87–1.02) | 0.703 | 1.02 (0.88–1.03) | 0.572 | 0.38 (0.32–0.45) |
| ALT | 1 (0.89–1.03) | 0.705 | 1.02 (1–1.04) | 0.368 | 0.37 (0.30–0.44) |
| AST/ALT ratio | 1.11 (0.82–1.94) | 0.401 | 0.87 (0.51–1.37) | 0.455 | 0.43 (0.36–0.49) |
| ALP | 1.03 (1.02–1.04) | 0.004 | 1.01 (1–1.02) | 0.013 | 0.72 (0.45–0.74) |
| Albumin | 0.45 (0.15–1.19) | 0.137 | 1.31 (0.4–2.7) | 0.536 | 0.46 (0.54–0.63) |
| CRP | 1.03 (0.87–1.07) | 0.305 | 1.03 (0.88–1.08) | 0.203 | 0.53 (0.48–0.55) |
| D-dimers | 1 (1–1) | 0.453 | 1 (1–1) | 0.778 | 0.54 (0.47–0.55) |
| IL-6 | 1 (0.88–1.02) | 0.324 | 0.97 (0.96–1.02) | 0.402 | 0.49 (0.42–0.56) |
| log (IgG) | 0.67 (0.73–0.98) | 0.021 | 0.79 (0.75–1.11) | 0.203 | 0.46 (0.39–0.53) |

***Table 3.*** *Multivariate logistic regression model for predictors of post-COVID-19 syndrome.*

| Variable | OR | 95% CI | p-value |
|---|---|---|---|
| Age (years) | 1.01 | 0.98–1.02 | 0.781 |
| Female sex (vs. male) | 4.55 | 1.86–7.02 | <0.001 |
| Number of comorbidities | 2.87 | 1.58–5.97 | 0.001 |
| Vaccine doses | 0.86 | 0.69–1.06 | 0.002 |
| Alkaline phosphatase (ALP, U/L) | 1.01 | 1.00–1.02 | 0.013 |
| Hematocrit (HCT, %) | 0.88 | 0.81–1.08 | 0.504 |
| Immunoglobulin G (IgG, AU/mL) | 0.79 | 0.75–1.11 | 0.203 |
| C-reactive protein (CRP, mg/L) | 1.03 | 0.88–1.08 | 0.203 |

adjusting for other factors (adjusted OR = 0.86, 95% CI: 0.69–1.06, p = 0.002). Among laboratory markers, hematocrit showed a significant association with post-COVID-19 syndrome in the unadjusted analysis (OR = 0.81, 95% CI: 0.87–0.98, p = 0.001), but this significance was lost after adjustment (OR = 0.88, 95% CI: 0.81–1.08, p = 0.504). White blood cell count (OR = 1.04, 95% CI: 0.81–1.18, p = 0.563), platelet count (OR = 1.00, 95% CI: 1.00–1.00, p = 0.807), neutrophil-to-lymphocyte ratio (OR = 0.85, 95% CI: 0.62–1.13, p = 0.782), and platelet-to-lymphocyte ratio (OR = 1.00, 95% CI: 0.89–1.00, p = 0.360) did not demonstrate a significant association with the development of post-COVID-19 syndrome. Liver enzyme levels, including aspartate aminotransferase (AST) (OR = 1.00, 95% CI: 0.87–1.02, p = 0.703) and alanine aminotransferase (ALT) (OR = 1.00, 95% CI: 0.89–1.03, p = 0.705), showed no significant differences between groups. However, alkaline phosphatase (ALP) was elevated in patients with post-COVID-19 syndrome (OR = 1.03, 95% CI: 1.02–1.04, p = 0.004), and this association remained significant after adjustment (OR = 1.01, 95% CI: 1.00–1.02, p = 0.013), suggesting potential metabolic alterations related to the condition. Albumin (OR = 0.45, 95% CI: 0.15–1.19, p = 0.137), C-reactive protein (CRP) (OR = 1.03, 95% CI: 0.87–1.07, p = 0.305), D-dimer (OR = 1.00, 95% CI: 1.00–1.00, p = 0.453), interleukin-6 (IL-6) (OR = 1.00, 95% CI: 0.88–1.02, p = 0.324), and immunoglobulin G (IgG) levels (OR = 0.67, 95% CI: 0.73–0.98, p = 0.021) did not show significant associations with post-COVID-19 syndrome after adjustment (p > 0.05). The diagnostic value of these parameters varied. The highest AUROC values were observed for alkaline phosphatase (AUROC = 0.72, 95% CI: 0.45–0.74), con-firming its potential role in diagnosis. Hematocrit (AUROC = 0.51, 95% CI: 0.57–0.70), white blood cell count (AUROC = 0.52, 95% CI: 0.34–0.57), and platelet-to-lymphocyte ratio (AUROC = 0.52, 95% CI: 0.40–0.60) had moderate AUROC values, but their predictive ability remained low. Liver enzyme levels, including their ratio (AST/ALT), had low AUROC values (ranging from 0.37 to 0.43), indicating weak diagnostic value. Thus, the most significant risk factors for developing post-COVID-19 syndrome are female sex (OR = 4.55, p < 0.001) and the presence of multiple chronic diseases (OR = 2.87, p = 0.001). Vaccination, particularly with a higher number of administered doses (OR = 0.86, p = 0.002), may reduce the likelihood of developing the condition. Among laboratory markers, alkaline phosphatase appears to be the most informative (AUROC= 0.72), whereas most other biochemical and hematological parameters do not demonstrate high diagnostic value.

Details of the multivariate model parameters are presented in Supplementary Table 3.

Table 3 presents the results of the multivariate logistic regression analysis performed to identify independent predictors of post-COVID-19 syndrome (PCS). The table includes all variables modelled concurrently, showing their odds ratios (OR), 95% confidence intervals (CI), and p-values. This comprehensive model provides insight into the relative contributions of demographic, clinical, and laboratory parameters to the likelihood of developing PCS. The corresponding model equation is also provided for transparency.

## Discussion.

This study represents the first retrospective-prospective cohort investigation of post-COVID syndrome (PCS) in Kazakhstan and Central Asia. This approach contributes new regional evidence to the global body of PCS research and emphasizes the need for phenotype-specific strategies in patient monitoring and follow-up [22-34].

While the present study identified a significant inverse association between the number of vaccine doses and the incidence of post-COVID syndrome (PCS), this finding should be interpreted with caution. The observational design of the study does not allow for definitive causal inference, and the observed relationship may be influenced by residual confounding factors such as differences in health-seeking behavior, access to healthcare services, and underlying health status among vaccinated individuals. Future prospective studies with robust adjustment for these variables are needed to confirm the protective role of vaccination against PCS.

Our findings support previous international studies showing that PCS is more prevalent in females and individuals with pre-existing comorbidities [6,20]. The observed association between lower vaccination rates and PCS incidence is consistent with findings from Israel and Spain, where vaccination was linked to reduced long-term symptom burden [29,33]. Elevated levels of alkaline phosphatase (ALP), in particular, were associated with PCS and may reflect low-grade systemic inflammation, a mechanism increasingly recognized in PCS pathogenesis [29,32]. However, we emphasize that while ALP may serve as a candidate biomarker, its diagnostic accuracy remains limited, and further validation is needed [35].

Although alkaline phosphatase (ALP) demonstrated a moderately favorable AUROC of 0.72 in distinguishing PCS cases, it falls short of the threshold commonly accepted for diagnostic utility in clinical practice. According to international standards, an AUROC value above 0.8 is generally considered

satisfactory for diagnostic purposes. Therefore, while ALP may serve as a potential biomarker for PCS, its current diagnostic performance limits its standalone utility, and it should be interpreted in conjunction with other clinical and laboratory findings. Further studies with larger cohorts and external validation are necessary to assess its applicability as a reliable diagnostic marker.

Although ALP was statistically associated with PCS, the clinical impact appears modest (aOR = 1.01). This may reflect low-grade systemic inflammation, but its standalone diagnostic or prognostic utility remains uncertain and should be interpreted with caution.

Although this study identified patterns suggestive of immune activation and symptom clustering, it did not directly assess pathophysiological mechanisms. No im-aging, cytokine profiling, or functional tests were performed to evaluate organ-specific damage or immunological dysregulation. Consequently, the study does not provide mechanistic insights or support for specific therapeutic interventions. Rather, it underscores the heterogeneity of PCS and the need for individualized clinical approaches [11,12,14].

Despite these contributions, several limitations must be acknowledged. The study design does not allow for causal inference. Some findings, such as those related to rare symptoms or conditions (e.g., diarrhea, ICU admission), are based on low-frequency data and must be interpreted with caution.

In summary, our study offers the first large-scale PCS phenotyping data from Kazakhstan and provides preliminary evidence of biomarker patterns and symptom clusters. While the results highlight important associations, they do not permit conclusions about treatment efficacy or pathophysiology. Further research, including longitudinal studies and immunological profiling, is required to validate these findings and in-form clinical interventions [20,27,28].

This study examined the prevalence of post-COVID syndrome (PCS) among patients recovering from acute COVID-19. Biomarkers associated with PCS diagnosis were analyzed, and patients were classified into four groups based on their clinical phenotypes. Additionally, the relationship between quality of life and PCS-related biomarkers was examined. Findings indicated that individuals with PCS had a significantly higher prevalence of comorbid conditions than the control group (28.3% vs. 12.0%) [6], suggesting a greater risk of PCS in patients with preexisting comorbidities [6]. These results underscore the need for comprehensive clinical and psychiatric interventions, ensuring optimal resource allocation and minimizing unnecessary medical procedures.

This study has several limitations. First, the quality of life was not formally assessed using standardized tools. Second, no statistical analysis was performed on the time interval since COVID-19 diagnosis, although it was recorded. Third, the sample size for certain subgroups was limited, reducing statistical power for rare variables. These factors should be considered when interpreting the findings.

Patients with post-COVID respiratory failure (PCRF) more frequently experienced persistent symptoms such as cough, dyspnea, and chest pain. However, the increased prevalence of neuropsychiatric manifestations, including insomnia, anxiety, and depression, underscores the critical role of multidisciplinary medical teams in providing comprehensive rehabilitation for post-COVID-19 patients, thereby contributing to the restoration of their quality of life [22].

The study identified biomarkers associated with PCS, including elevated alkaline phosphatase (ALP) levels and reduced hematocrit (HCT) and immunoglobulin G (IgG) levels. Increased ALP may indicate the presence of an inflammatory process, as this biomarker is a well-established indicator of inflammation [23,24]. However, its diagnostic utility is limited due to its low discriminative capacity. Cluster analysis identified distinct clinical phenotypes among recovered COVID-19 patients, providing a basis for personalized treatment. Group 1 had severe multisymptomatic disease requiring comprehensive medical management. These patients require an interdisciplinary approach involving specialists from various fields, which aligns with findings from previous studies [25,26]. Groups 2 and 3 were characterized by moderate multisymptomatic manifestations. Cluster 3 was predominantly marked by physical symptoms such as fatigue and dyspnea, whereas cluster 2 was distinguished by a higher prevalence of neuropsychiatric symptoms, including anxiety and depression. Similar findings have been reported in studies conducted in Canada, further supporting the heterogeneity of post-COVID syndrome [25]. A study in the United Kingdom reported that approximately 10-20% of patients with COVID-19 developed long-term symptoms, with fatigue, dyspnea, and cognitive impairment being the most common manifestations, which is consistent with our findings [27]. Additionally, research conducted in Germany emphasized the role of inflammation and immune dysregulation in PCS pathogenesis, further supporting our findings on elevated ALP levels [28].

A recent study from the United States highlighted six distinct phenotypic groups among PCS patients, with predominant cardiovascular, pulmonary, neuropsychiatric, or mixed symptoms [30]. Another large-scale cohort study from France found that PCS patients exhibited higher metabolic and inflammatory markers, reinforcing our findings regarding biomarker associations [31]. Furthermore, a Canadian study emphasized the role of mental health interventions in managing PCS, supporting our conclusions on the importance of multidisciplinary rehabilitation [31]. A Spanish longitudinal study confirmed that vaccinated individuals had a significantly lower PCS prevalence, aligning with our vaccination-related findings [33]. Lastly, a systematic review from Italy underscored the necessity of personalized treatment approaches in PCS management, reinforcing the relevance of our cluster-based analysis [34].

It is crucial to recognize that while some patients primarily experience physical symptoms, others exhibit psychological manifestations, and a third subset presents with a combination of both. For patients in cluster 4, supportive care and regular medical monitoring are sufficient to manage residual symptoms and promote the adoption of healthy habits. This approach may help reduce the burden on the healthcare system.

A statistically significant difference in vaccination status was observed between patients with and without PCS ($p = 0.046$).

Fully vaccinated individuals or those who had received a booster dose were more frequently found among those without PCS compared to those with PCS (15.7% vs. 2.4%) [9]. The median number of vaccine doses was also higher in the non-PCS group (3 doses, IQR 3–4) compared to the PCS group (3 doses, IQR 2–3), with this difference reaching statistical significance ($p = 0.002$) [6]. These findings suggest a dose-dependent protective effect of vaccination against the development of PCS. To our knowledge, this study represents the first cohort investigation of PCS in Kazakhstan based on a randomly selected patient population.

Our results align with findings from large-scale international studies, such as a cohort analysis from Israel, which demonstrated that individuals who had received three or more doses of the BNT162b2 vaccine were significantly less likely to report PCS symptoms 3–6 months post-infection [36] and a large-scale study from Israel, where a higher number of vaccine doses correlated with a lower risk of developing long-term post-COVID complications [29]. Similarly, a Spanish longitudinal study found that vaccinated individuals experienced fewer post-COVID symptoms such as fatigue and cognitive impairment compared to unvaccinated patients [8]. The inclusion of both mRNA and inactivated vaccines (such as QazVac and CoronaVac) in the Kazakhstani vaccination campaign adds further relevance, as it provides evidence across different vaccine platforms.

Potential confounding factors—such as differences in access to healthcare, presence of comorbidities, and timing of vaccination—were considered and adjusted for through multivariate logistic regression. However, residual confounding cannot be entirely excluded. For example, individuals with better healthcare access were more likely to complete vaccination schedules and receive timely treatment, which could itself reduce PCS risk. Conversely, patients with chronic conditions may have been more likely to be vaccinated early but also more prone to PCS.

Altogether, the observed association between higher numbers of vaccine doses and lower PCS incidence supports the hypothesis that vaccination not only mitigates the acute phase of COVID-19 but also reduces the risk of long-term complications. These results underscore the importance of continued research into vaccine efficacy against PCS, particularly across different populations and vaccine types.

The study, conducted among patients in the Abai region, provides valuable insights into the prevalence of PCS, its associated biomarkers, and clinical phenotypes. However, potential limitations include differences in ethnic, genetic, and sociodemographic characteristics, as well as variations in healthcare systems across different countries. The identification of biomarkers, such as alkaline phosphatase, as potential predictors of PCS provide a basis for further research aimed at validating these findings across diverse clinical and geographical settings. Cluster analysis, which distinguishes different patient phenotypes, holds significant clinical relevance, suggesting that personalized treatment strategies tailored to symptom severity may enhance the effectiveness of medical care. This approach aligns with contemporary trends in medicine, emphasizing individualized treatment and multidisciplinary care for patients with PCS.

The present study examined clusters of PCS that included psychiatric symptoms (insomnia, depression, anxiety); however, we recognize the limitation of not having a formal quality of life assessment. We plan to incorporate quality of life assessments using standardized questionnaires such as the SF-36 in future studies to further characterize the impact of PCS on patients.

## Conclusion.

In conclusion, this study represents the first large-scale analysis of PCS in the Abai region, providing crucial data on its prevalence, diagnostic markers, and clinical characteristics. Although the identified biomarkers demonstrate a certain association with PCS, their diagnostic accuracy remains limited and warrants further investigation. The identification of distinct patient phenotypes underscores the need for a personalized approach, as well as the importance of multidisciplinary teams in the management of post-COVID-19 patients. These findings have the potential to inform global healthcare policy, resource distribution, and the development of targeted strategies to improve out-comes for patients recovering from COVID-19. Furthermore, the study confirmed that alkaline phosphatase (ALP) may serve as a potential biomarker for PCS as early as three months after the acute phase of the disease, offering an opportunity for early diagnosis. The application of cluster analysis enabled the identification of four clinical phenotypes, paving the way for personalized therapeutic strategies. These findings are of considerable importance for improving the diagnosis and treatment of PCS, ultimately enhancing patients' quality of life. The results emphasize the necessity of a comprehensive diagnostic approach that incorporates both physical and psycho-social aspects. While the identification of ALP as a potential predictor of PCS suggests promise for early diagnosis, further validation of this biomarker is required. The classification of patients into distinct phenotypes facilitates the development of tailored treatment methods, including physiotherapy and psychological support. Overall, these findings lay the groundwork for future research and the refinement of treatment strategies for post-COVID-19 patients.

## Supplementary Materials.

The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figure S1: Clinical phenotypes of PCS; Table S1: Baseline characteristics and laboratory biomarkers in PCS and non-PCS patients; Table S2: Association between biomarkers and post-COVID-19 syndrome examined using multivariate logistic regression analysis.

## Author Contributions.

Conceptualization: A.D., Z.Z.; literature review: all authors; data collection: AD., Z.Z., A.S.; statistical analysis: A.D., A.S.; A.U; project administration: ADus., Z.Z., K.D.; critical review: A.D., Z.Z., K.D.; manuscript-initial draft: all authors; manuscript-final draft: all authors. All authors contributed to the article and approved the submitted version.

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### Institutional Review Board Statement.

This study received permission from the Ethics Committee of Semey Medical University (Protocol # 2 of 12.12.2023).

### Informed Consent Statement.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. All participants provided written informed consent prior to their involvement in the study. Participants were informed about the purpose, procedures, and potential risks of the study. They were also informed of their right to withdraw from the study at any time without penalty or loss of benefits. The confidentiality of all participant data was ensured, and personal information was anonymized and stored securely. By signing the informed consent form, participants agreed to: Participate voluntarily in the study and provide relevant medical and demographic in-formation. Allow the collection of blood samples and the use of medical records for research purposes. Understand that participation in the study would not alter the medical care they received. Acknowledge that they could contact the study team at any time with questions regarding their participation or the study.

### Data Availability Statement.

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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### Conflicts of Interest.

The authors declare that they have no competing interests.

### Abbreviations.

The following abbreviations are used in this manuscript:

ALP: Alkaline Phosphatase
BMI: Body Mass Index
BUN: Blood Urea Nitrogen
CBC: Complete Blood Count
CRP: C-reactive Protein
ECG: Electrocardiography
ICU: Intensive Care Unit
IgG: Immunoglobulin G
IL-6: Interleukin-6
LDH: Lactate Dehydrogenase

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