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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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Содержание:

P.V. Fedorych, T.V. Kuts, S.B. Koval.
DETERMINATION OF THE SENSITIVITY OF GARDNERELLA VAGINALIS TO FENTICONAZOLE….....6-10

Giuseppe Taccardo, Andrea Perna, Alessandro Domenico Santagada, Marco Passiatore, Calogero Velluto, et al.
DOES AN EARLY POST-OPERATIVE PAIN RELIEVE INFLUENCE THE FUNCTIONAL OUTCOME OF PATIENTS WITH COLLES FRACTURES TREATED WITH EG-BLOCK SYSTEM?.....11-16

Oksana Knyzhenko, Svitlana Knyzhenko, Krainyk Hryhorii, Kseniia Kotlubaieva.
IMPROPER PERFORMANCE OF PROFESSIONAL DUTIES BY A MEDICAL PROFESSIONAL: CURRENT ISSUES OF RESPONSE AND INVESTIGATION UNDER CRIMINAL LAW…….....17-22

Fana Lichoska-Josifovikj, Kalina Grivceva-Stardelova, Beti Todorovska, Vladimir Andreevski, Filip Nikolov, Dzem Adem.
THE VALUE OF SERUM-ASCITES ALBUMIN GRADIENT AS A PREDICTOR OF SPONTANEOUS BACTERIAL PERITONITIS IN PATIENTS WITH LIVER CIRRHOSIS AND ASCITES…….....23-25

Mher S. Bisharyan, Ara B. Dallakyan.
ASSESSMENT OF THE SOCIAL AND MEDICAL ASPECTS OF SUICIDE IN THE REPUBLIC OF ARMENIA….....26-31

Nadiya Ye. Barabash, Tetiana M. Tykhonova, Diana M. Dorosh, Larysa O. Martymianova.
HETEROGENEITY OF CLINICAL MANIFESTATIONS OF HYPERPROLACTINEMIA (REVIEW AND OWN OBSERVATIONS) 32-36

Alexander Schuh, Philipp Koehl, Stefan Sesselmann, Tarun Goyal, Achim Benditz.
INCIDENTAL INTRAOSSEOUS CALCANEAL LIPOMA IN A PATIENT SUFFERING FROM PLANTARFASZIITIS 37-39

Alexander Schuh, Philipp Koehl, Stefan Sesselmann, Tarun Goyal, Achim Benditz.
INTRAMUSCULAR MYXOMA OF THE BUTTOCK- A CASE REPORT …….....40-42

Tsvetkova M. A., Kovalenko A. YU.
ALGORITHM OF ORTHODONTIC TREATMENT PATIENTS WITH A BURDENED DRUG ANAMNESIS. DRUGS THAT CAN INHIBIT TOOTH MOVEMENT…….....43-48

Mazin M. Hammady, Shaymaa J. Mohammed.
IMPLEMENTING NEW TECHNIQUE TO EVALUATE COGNITIVE FUNCTION IN PATIENTS WITH MIGRAINE DURING THE ATTACK…….....49-53

Nataliia O. Shevchenko, Liliya S. Babinets, Iryna M. Halabitska.
AGE–DEPENDENT IMMUNE STATUS CHANGES IN CHRONIC PANCREATITIS PATIENTS…….....54-58

Salah Kadhim Muslim.
A SINGLE SURGEON'S EXPERIENCE IN DEFINING THE LEARNING CURVE FOR TRANSORAL ENDOSCOPIC THYROIDECTOMY –VESTIBULAR APPROACH (TOETVA)…….....59-64

Muradyan A.E.
CORRELATION AND INFRASTRUCTURE OF SOME PHYSICAL HEALTH INDICATORS BEFORE AND DURING COVID-19 PANDEMIC…….....65-69

Brych V.V., Vasylynets M.M., Shmanko O.P., Bilak-Lukyanchuk V.Y
PARTICIPATION OF TRAUMATOLOGISTS IN PROVIDING MEDICAL REHABILITATION OF PATIENTS WITH INJURIES AT THE REGIONALLEVEL…….....70-73

Soldatiuk V.M., Rozhko M.M., Pantus A.V
CLINICAL-MORPHOLOGICAL SUBSTANTIATION OF THE FIBROUS MATRIX WITH BIOGEL CENO BONETM APPLICATION FOR PRESERVATION OF THE ALVEOLAR PROCESS OF THE JAWS AFTER THE TEETH REMOVAL…….....74-80

O. Rotar, I. Khomiak, R. Sydorchuk, S. Boiko, I. Bilyk, O. Hrama, Y. Migaichuk.
EFFICACY OF THE ALGORITHMIC STEP-UP APPROACH OF INTERVENTIONAL TREATMENT OF PATIENTS WITH ACUTE NECROTIZINGPANCREATITIS…….....81-85

V.V. Ohorenko, A.V. Shornikov, A.G. Kyrychenko, Y.N. Zavalko, V.N. Khomyakov, N.V. Tomakh.
IMPROVEMENT OF QUALITY OF LIFE FOR PATIENTS WITH ASEPTIC NECROSIS OF THE FEMORAL HEAD AND NON-PSYCHOTIC MENTAL DISORDERS…….....86-89

Nigar Karimova Ildirim.
CYP2B6 SINGLE NUCLEOTIDE POLYMORPHISMS IN AN AZERBAIJANI POPULATION…….....90-93

Olha Filyk, Yaroslav Pidhirnyi.
RESPIRATORY MUSCLES FUNCTION IN CHILDREN 6-18 YEARS OLD WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE: THE PROSPECTIVE OBSERVATIONAL COHORT STUDY…….....94-98

Héctor M. Ramos-Zaldívar, Karla G. Reyes-Perdomo, Nelson A. Espinoza-Moreno, Ernesto Tomás Dox-Cruza, Thania Camila Aguirre Urbinaa, et al.
SAFETY AND EFFICACY OF THYMIC PEPTIDES IN THE TREATMENT OF HOSPITALIZED COVID-19 PATIENTS IN HONDURAS…….....……99-105

Melnychenko MH, Kvashnina AA, Sytnikova VA.
PROGNOSTIC MODEL OF POSTOPERATIVE ADHESIVE INTESTINAL OBSRUCTION RISK IN CHILDREN…….....……..106-109

Musayev SA.
EVALUATION OF THE QUALITY OF LIFE AFTER REVASCULARIZATION AND RECONSTRUCTIVE OPERATIONS ON MITRAL VALVE IN PATIENTS WITH CORONARY HEART DISEASE….....……..110-114

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No 9 (330) 2022

SAFETY AND EFFICACY OF THYMIC PEPTIDES IN THE TREATMENT OF HOSPITALIZED COVID-19 PATIENTS IN HONDURAS

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Introduction.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (Covid-19) global pandemic, continues to spread rapidly with increasing daily hospitalizations and deaths worldwide [1]. Even though vaccine platforms are expected to significantly reduce the burden of disease [2], the amount of active Covid-19 cases continue to demand the development of effective treatments. Emerging viral variants [3,4] and vaccination hesitancy [5,6] may extend or aggravate this problem, particularly in developing countries where access to vaccines is already limited [7].

The pathogenesis of Covid-19 is thought to be driven by SARS-COV-2 replication in the early stages of the disease, while a dysregulated immune/inflammatory response appears to promote tissue damage in later phases [8]. Therefore, the use of thymic peptides might improve immunomodulation and clinical outcomes in the complex management of COVID-19 in moderate-to-severe cases. We report a nonrandomized phase 2 clinical trial with historical controls, using propensity score matching (PSM) from the registry data of the Hospital Santa Bárbara Integrado, to evaluate the safety and efficacy of oral thymic peptides in the treatment of hospitalized Covid-19 patients in Honduras. The trial protocol was approved by the Catholic University of Honduras IRB in Tegucigalpa and registered by the General Directorate for Regulatory Framework Surveillance of the Ministry of Health of Honduras. Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent. ClinicalTrials.gov ID: NCT04771013.

Materials and methods.

Hospitalized patients aged ≥ 21 years with confirmed Covid-19 by detection of viral nucleic acid (RNA) using reverse transcription polymerase chain reaction (RT-PCR), viral antigen, or IgM antibodies to the virus were eligible for enrollment. Unfortunately, there were no laboratories in Honduras that performed analyses for specific viral variants. Patients were required to present with at least one of the following: oxygen saturation level below 94%; complete blood count showing lymphopenia, neutrophilia, or both; positive C-reactive protein; and chest radiography or computed tomography scan with ground-glass opacities. All patients were hospitalized with oxygen by mask or nasal prongs, which corresponds to a score of 5 according to the World Health Organization (WHO) clinical progression scale [9]. Pregnant and breastfeeding women, as well as organ transplant recipients, were not eligible.

Thymic peptides were isolated from 25 thymus glands of 6- to 10-month-old calves bred in an organic production system through acid lysis. The entire cervical and thoracic thymus gland portions were used to obtain 100 g of the lyophilized product. Thymic peptides were administered orally once a day by trained physicians either one hour before or two hours after a meal, in a 250-mg dose, dissolved in 50 mL of water, until hospital discharge or death within a 20-day period. The dose used was in accordance with previous clinical safety reports and trials that have used oral thymic peptides in respiratory infections, the elderly, and other conditions [10,11], and the availability of calves in our production system to cover a maximum of 20 days of treatment for each patient.

Outcomes.

Patients were evaluated daily during hospitalization from days 1 through 20. The primary outcome measures included the time to recovery and number of participants with treatment-related adverse events and side effects. The first primary endpoint of this study was measured in days to clinical recovery, defined as the first day, during the 20 days after enrollment, on which a patient met the criteria for categories 1, 2, or 3 on an eight-category ordinal scale (as described by Beigel et al.) [12]. The categories were as follows: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or other medical conditions); 5, hospitalized, requiring supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, death. Adverse events ≥ Grade 3 were registered using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) and side effects were evaluated as defined by the Generic Assessment of Side Effects in Clinical Trials (GASE).

The secondary outcome measure was overall survival, defined as the time from the start of treatment until death for any reason in the 20-day period. The average length of hospital stay was analyzed as a complementary analysis using the Kaplan-Meier method.

Statistical analysis.

For the comparison group, propensity score matching using IBM SPSS ver.25 (IBM Co., Armonk, NY, USA) was performed based on registry data. Heatmap and dimensional reduction techniques using principal component analysis were applied to determine the global comparison between the two groups.

Analyses of time to recovery, mortality, length of hospital stay, and time to supplemental oxygen withdrawal were estimated using the Kaplan–Meier method. Cumulative incidence curves were compared between the two groups using the log-rank test. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). For time to recovery, data for patients who died or did not recover were censored on day 20. For mortality, patients who did not die were censored on day 20. For length of stay, patients who were not discharged on day 20 and those who died were censored on day 20. For supplemental oxygen withdrawal, patients who still required oxygen therapy after day 20 and those who died were censored at day 20.

Differences in base drug treatments among groups were analyzed using the chi-square test or Fisher's exact test, when appropriate. Safety analysis findings are descriptive in nature and not based on formal statistical hypothesis testing. The number of patients who presented with adverse events in the prospectively treated group, which was ≥ Grade 3 according to CTCAE v5.0, and the number that manifested side effects according to GASE, were considered. All P-values were two-sided, and all analyses were performed according to the intention-to-treat principle.

Results.

A total of 44 patients were analyzed in this study: 22 in the thymic peptide group and 22 in the standard care group (Figure 1). Between February 10, 2021, and April 12, 2021, patients were prospectively assessed for eligibility for the intervention group. For the comparison group, registry data from June 2020 to February 2021 were considered, as the standardization of the therapeutic management of the Honduran national guideline for the entire study period occurred in May 2020 [13]. Within the thymic peptide group, acute infection for COVID-19 was confirmed by antigen detection in 86.4% (19/22), RT-PCR in 4.5% (1/22), and IgM in 9.1% (2/22) of participants. Within the standard care group, acute infection for COVID-19 was confirmed by RT-PCR in 63.6% (14/22), antigen detection in 31.8% (7/22), and IgM in 4.5% (1/22) of patients. Dimensionality reduction by principal component analysis demonstrated the overlapping of both groups, and heatmap analysis showed homogeneous baseline characteristics (Figure 2). Together, these results indicate that the groups were globally similar in their severity indices after matching.

Demographic and clinical characteristics of the patients at baseline are shown in Table 1. The median number of days between symptom onset and hospitalization/enrollment was 11.5 (interquartile range: 9–13) in the intervention group and 10 (interquartile range: 9–14) in the standard care group. In the thymic peptide and standard care groups, 15 (68.2%) and 13 (59.1%) were men, and the mean (±SD) age was 52±16 years and 57±17 years, respectively. All patients were mestizo. Most patients had one or more comorbidities (75%), mainly hypertension (36.4%) and diabetes (31.8%). Notably, 61.4% of patients in both groups had elevated liver enzyme or creatinine levels at admission. All patients were WHO clinical progression score 5 at hospitalization/enrollment, and most (86.4%) had an oxygen saturation of ≤91%.

The median time to recovery in the thymic peptide group was 6 days, compared with 12 days of standard care. Kaplan-Meier analysis revealed a significantly shorter time to recovery in the intervention group (log-rank test, P=0.002) (Figure 3). The hazard ratio for recovery was 2.75, with a 95% confidence interval of 1.34 to 5.62. No side effects or adverse events related to thymic peptides were reported during the 20-day follow-up hospitalization period. This is in accordance with previous literature of thymic peptide safety and toxicity studies [11,14,15].

No deaths occurred in the thymic peptide group by day 20. In contrast, the Kaplan-Meier estimate of mortality for the standard care group by day 20 was 24% (Figure 4). This difference was statistically significant (log-rank, test P=0.02). Kaplan-Meier analysis showed a median time to oxygen therapy withdrawal of 4 days in the thymic peptide group, as compared with 10 days in the standard care group (hazard ratio, 2.3; 95% CI, 1.13 to 4.67; log-rank P=0.01). Patients in the intervention group had a shorter length of in-hospital stay (median, 6 days, compared with 12 days; hazard ratio for discharge, 2.34; 95% CI, 1.16-4.75; log-rank P=0.01), which may have influenced the lack of side effects and adverse events reported in the intervention group.

Table 1. *Demographic and clinical characteristics of the patients at baseline. **

Characteristic	**Thymic peptides (N=22)**	**Standard care (N=22)**	**Total (N=44)**
Age			
Mean -yr	52±16	57±17	54±16
Distribution - no. (%)			
≤60 years	15 (68.2)	12 (54.5)	27 (61.4)
61-64 years	2 (9.1)	3 (13.6)	5 (11.4)
≥ 65 years	5 (22.7)	7 (31.8)	12 (27.3)
Sex – no. (%)			
Female	7 (31.8)	9 (40.9)	16 (36.4)
Male	15 (68.2)	13 (59.1)	28 (63.6)
Race - no. (%) †			
Mestizo	22 (100)	22 (100)	44 (100)
Median no. of days since symptom onset (IQR)	11.5 (9-13)	10.0 (9-14)	10.5(9-13)
No. of comorbidities	2±1	2±2	2±1
Coexisting conditions - no. (%)			
Diabetes ‡	11 (50)	3 (13.6)	14 (31.8)
Hypertension	7 (31.8)	9 (40.9)	16 (36.4)
Obesity	2 (9.1)	4 (18.2)	6 (13.6)
COPD	1 (4.5)	1 (4.5)	2 (4.5)
Heart Failure	0 (0)	1 (4.5)	1 (2.3)
Organ damage (other than lung) §	12 (54.5)	15 (68.2)	27 (61.4)
WHO clinical progression score 5 - no. (%)	22 (100)	22 (100)	44 (100)
Heart rate distribution- no. (%)			
51-90 beats/min	14 (63.6)	10 (45.5)	24 (54.5)
91-110 beats/min	6 (27.3)	10 (45.5)	16 (36.4)
111-130 beats/min	2 (9.1)	2 (9.1)	4 (9.1)
Systolic blood pressure distribution- no. (%)			
90-219 mmHg	22 (100)	22 (100)	44 (100)
Respiratory rate distribution- no. (%)			
21-24 breaths/min	2 (9.1)	3 (13.6)	5 (11.4)
≥ 25 breaths/min	20 (90.9)	19 (86.4)	39 (88.6)
Oxygen saturation distribution- no. (%)			
92-93%	3 (13.6)	3 (13.6)	6 (13.6)
≤91%	19 (86.4)	19 (86.4)	38 (86.4)
Temperature distribution- no. (%)			
35.6-37.9 °C	19 (86.4)	19 (86.4)	38 (86.4)
38-39 °C	3 (13.6)	2 (9.1)	5 (11.4)
≥39.1 °C	0 (0)	1 (4.5)	1 (2.3)
SARS-CoV-2 positive test result- no. (%)	22 (100)	22 (100)	44 (100)

** Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, COPD Chronic obstructive pulmonary disease, WHO World Health Organization, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.*
† Race was recorded in the patient's electronic health record.
‡ There was a significant (P=0.01) difference in the percentage of diabetic patients between the thymic peptide group and the standard care group, but there were no significant differences between the groups in any other baseline characteristic.
§ Liver damage was defined as elevated liver enzymes, and kidney damage as elevated creatinine level.

Figure 1. Enrollment and Propensity Score Matching.

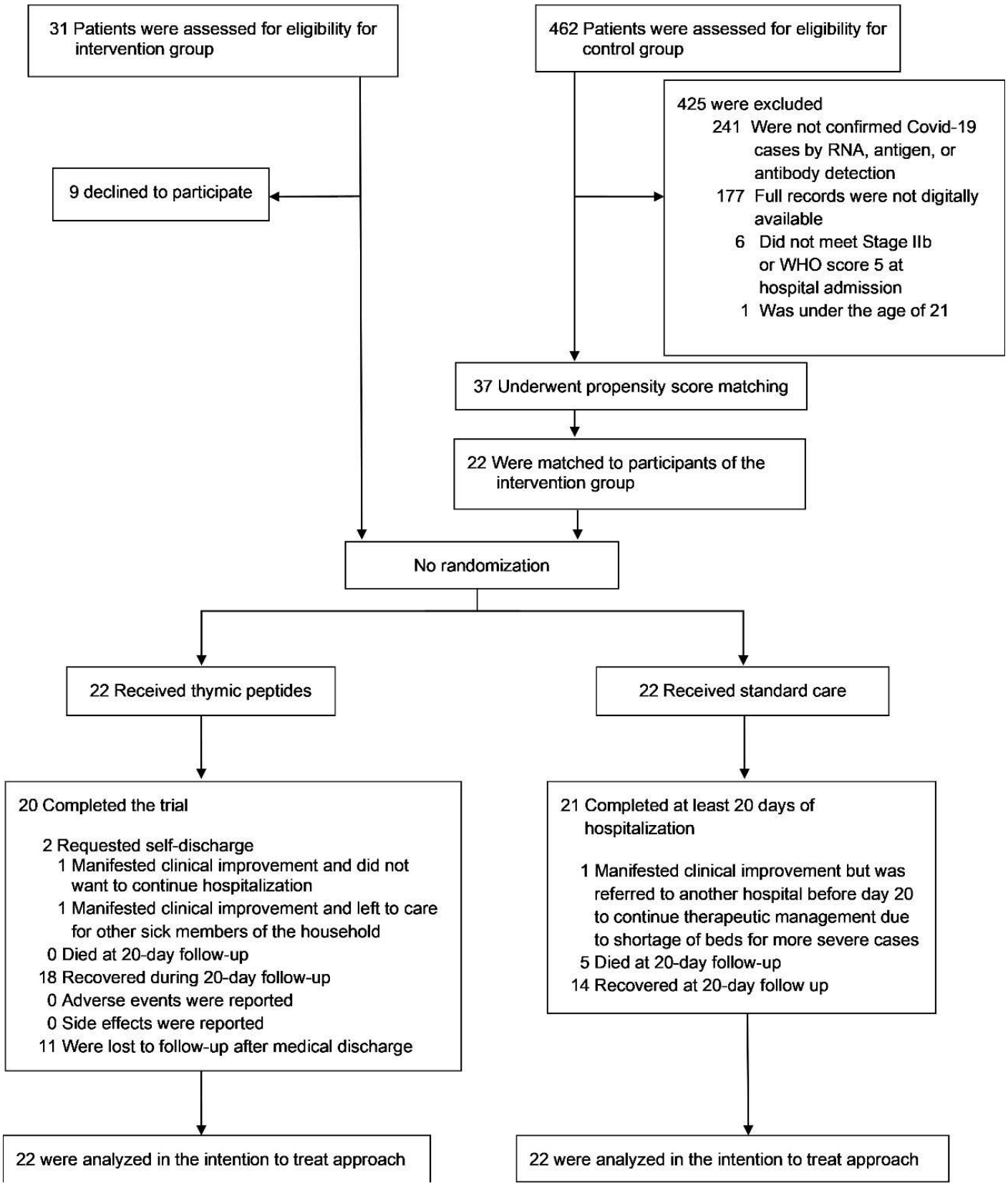

Figure.1. *Enrollment and propensity score matching.*

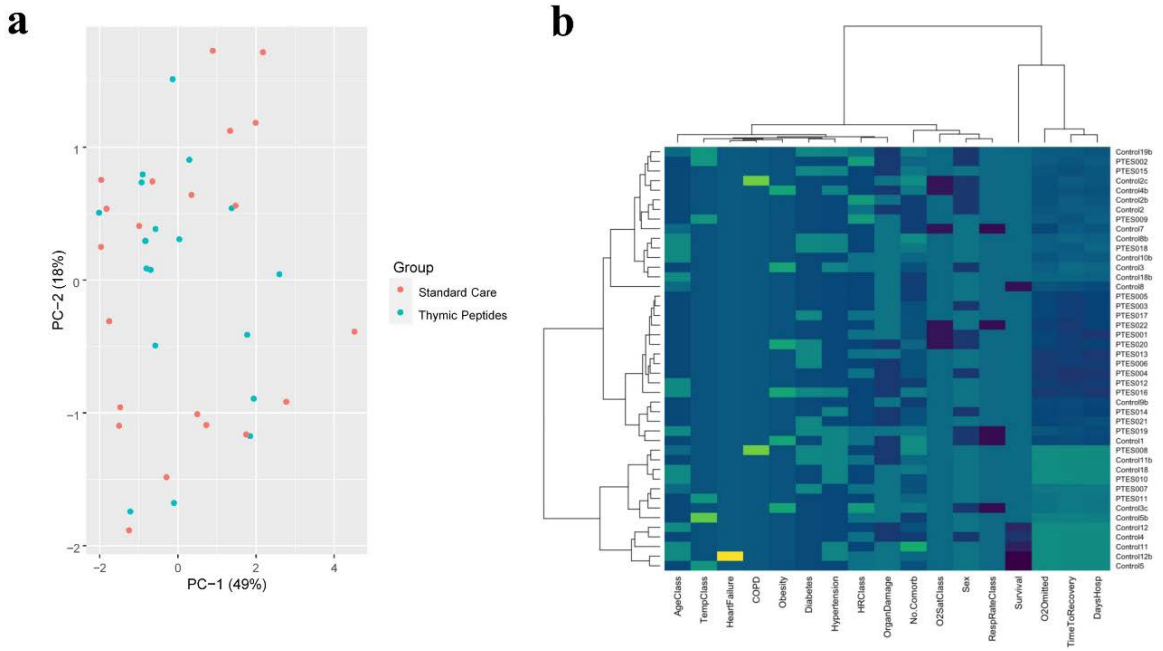

Figure. 2. Principal component analysis (PCA) and hierarchical heat map cluster of group characteristics. *The percentage of variation explained by each component is indicated in parenthesis in panel A. PCA considered the following variables: confirmatory covid test, number of comorbidities, sex, WHO clinical progression score, need for oxygen therapy, age distribution, heart rate distribution, systolic blood pressure distribution, respiratory rate distribution, oxygen saturation distribution, temperature distribution, and presence of diabetes, hypertension, obesity, overweight, chronic obstructive pulmonary disease, heart failure, organ damage, and dyspnea. Hierarchical heat map cluster of baseline patient characteristics and outcomes is shown in panel B. AgeClass indicates age distribution, TempClass temperature distribution, COPD Chronic obstructive pulmonary disease, HRClass heart rate distribution, No. Comorb number of comorbidities, O2SatClass oxygen saturation distribution, RespRateClass respiratory rate distribution, O2Omitted time to oxygen withdrawal by day 20, Days Hosp time to discharge by day 20.*

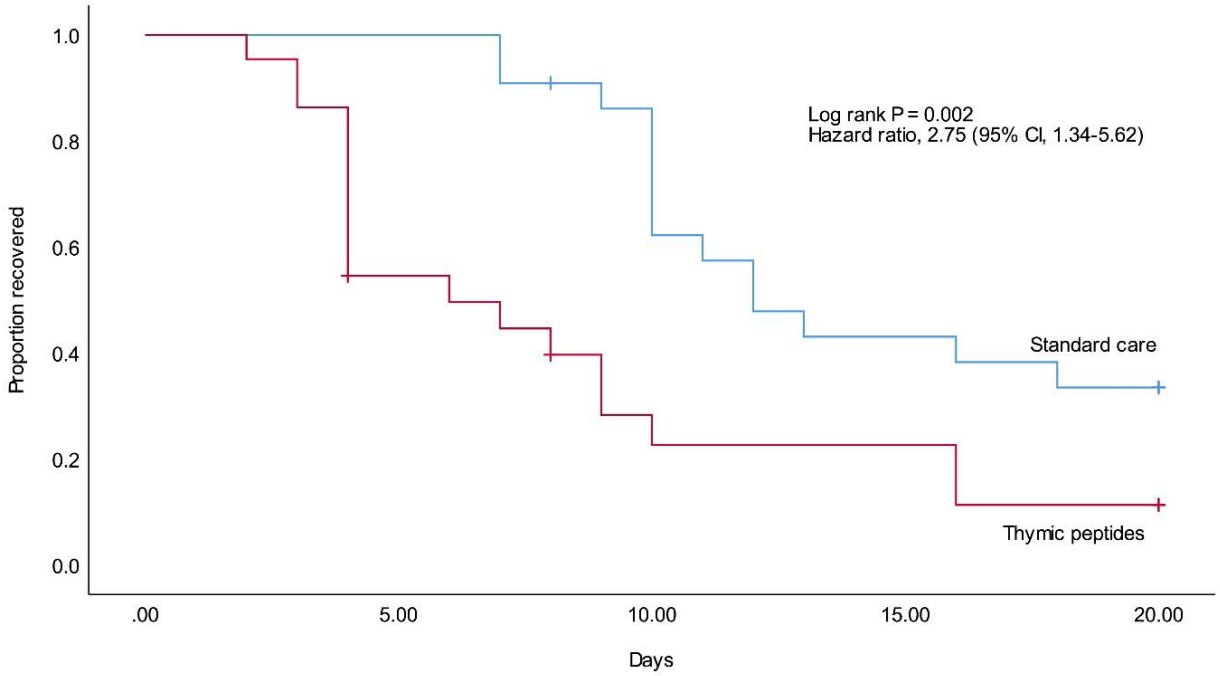

Figure. 3. Kaplan-Meier estimates of time to recovery by day 20. *The Kaplan-Meier method was used to estimate the cumulative proportion of patients and the log-rank test was used to compare the two groups. The Cox proportional-hazard model was used to estimate the hazard ratio and 95% confidence interval. Vertical dashes indicate censored data.*

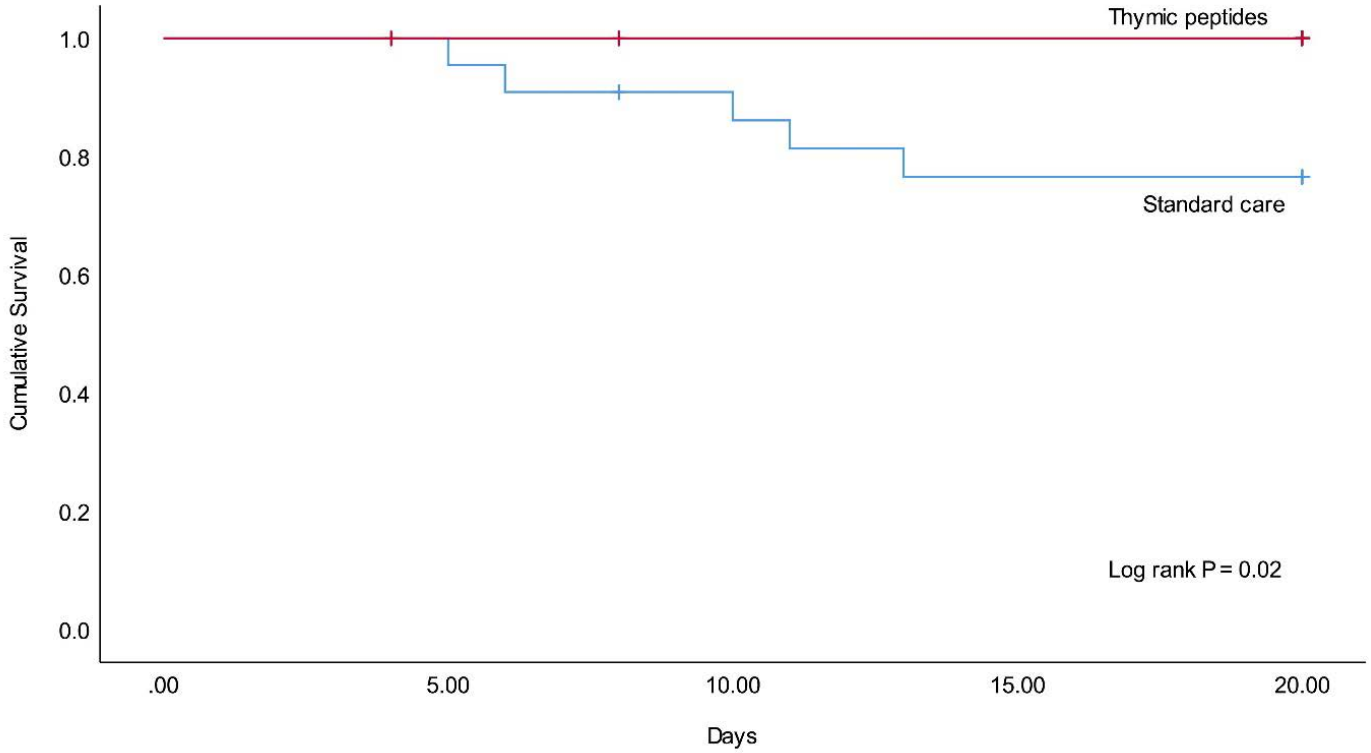

Figure. 4. Kaplan-Meier estimates of mortality by day 20. *The Kaplan-Meier method was used to estimate the cumulative proportion of patients and the log-rank test was used to compare the two groups. Vertical dashes indicate censored data.*

Conclusion.

In conclusion, given that a dysregulated immune/inflammatory response promotes tissue damage in the later phases of COVID-19, the use of thymic peptides should be further examined and considered to improve immunomodulation and clinical outcomes in the complex management of the disease. A daily oral dose of 250 mg of thymic peptides proved to be safe in a hospitalized Covid-19 group of patients in Honduras, reporting no deaths by day 20. When compared with registry data after PSM, shorter times to oxygen therapy withdrawal, recovery, and length of stay as well as a reduction in mortality were identified. This study's results suggest that administration of thymic peptides should be considered at hospitalization of patients with a WHO clinical progression score of 5, although benefits since symptom onset should be evaluated in future research. Trials with larger populations are required to confirm our findings and further describe efficacy with other oral thymic peptide doses. Our group is preparing a more extensive double-blind randomized controlled trial of oral thymic peptides in Covid-19 patients.

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Disclosure of interest.

HMRZ, KGRP, and HAAA designed the modified protocol for isolation of thymic peptides, which is patent pending. HMRZ receives a grant for education from the Universidad Católica de Honduras not related to this study. The rest of the authors declare no competing interests.

REFERENCES

1. COVID-19 Map - Johns Hopkins Coronavirus Resource Center, (n.d.). https://coronavirus.jhu.edu/map.html.
2. Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years - United States, January-March 2021, MMWR. Morb Mortal Wkly Rep.

2021;70:674-679.
3. Hacisuleyman E, Hale C, Saito Y, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. N Engl J Med. 2021;384:2212-2218.
4. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592:616-622.
5. Biswas N, Mustapha T, Khubchandani J. The Nature and Extent of COVID-19 Vaccination Hesitancy in Healthcare Workers. J Community Health. 2021;46:1244-1251.
6. Daly M, Robinson E. Willingness to Vaccinate Against COVID-19 in the U.S.: Representative Longitudinal Evidence from April to October 2020. Am J Prev Med. 2021;60:766-773.
7. Choi EM. COVID-19 vaccines for low- and middle-income countries. Trans R Soc Trop Med Hyg. 2021;115:447-456.
8. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health., (n.d.). https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/
9. WHO. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192-e197.
10. Calsini P, Mocchegiani E, Fabris N. The pharmacodynamics of thymomodulin in elderly humans. Drugs Exp Clin Res. 1985;11:671-674.
11. Kouttab NM, Prada M, Cazzola P. Thymomodulin: biological properties and clinical applications. Med Oncol Tumor Pharmacother. 1989;6:5-9.
12. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383:1813-1826.
13. Protocolo de Manejo Clínico del Paciente Adulto con COVID-19 según las etapas de la enfermedad en las redes de servicio de Salud - Secretaria de Salud Honduras. http://www.salud.gob.hn/site/index.php/component/edocman/protocolo-de-manejo-clinico-del-paciente-adulto-con-covid-19-segun-las-etapas-de-la-enfermedad-en-las-redes-de-servicio-de-salud
14. Maiorano V, Chianese R, Fumarulo R, et al. Thymomodulin increases the depressed production of superoxide anion by alveolar macrophages in patients with chronic bronchitis. Int J Tissue React. 1989;11:21-25.
15. Cazzola P, Mazzanti P, Kouttab NM. Update and future perspectives of a thymic biological response modifier (Thymomodulin). Immunopharmacol. Immunotoxicol. 1987;9:195-216.