

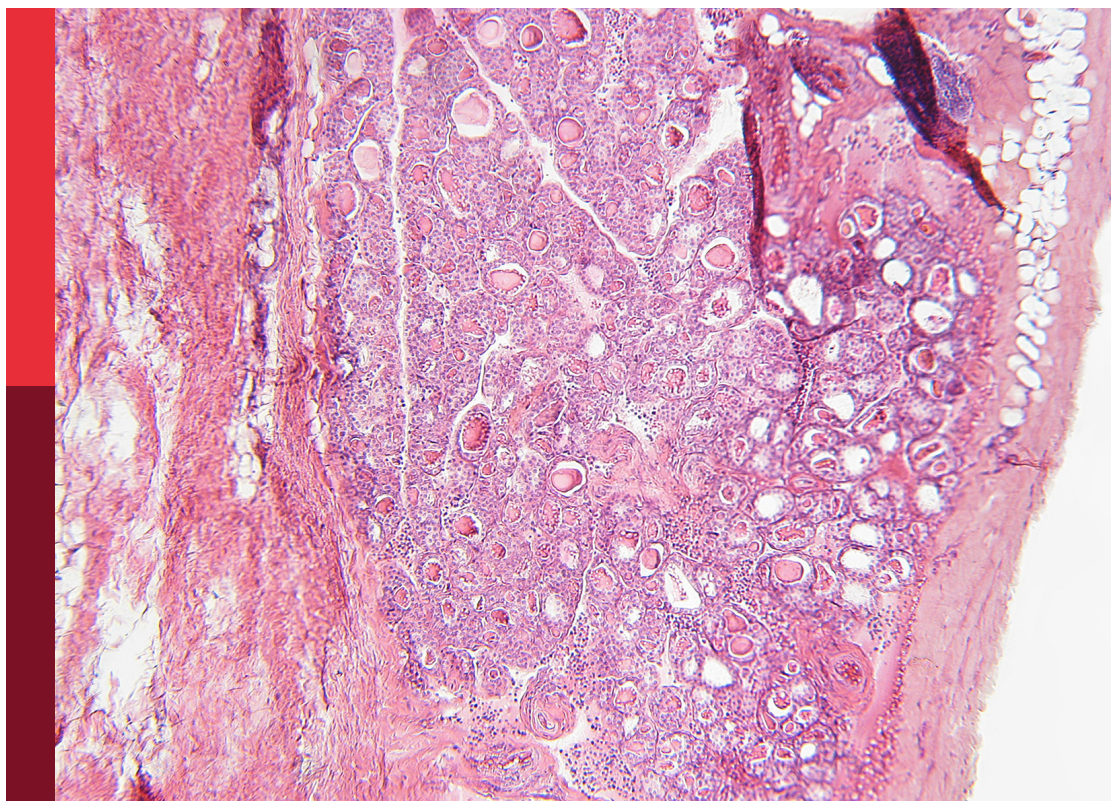
Endocrine complications of COVID-19: short and long

Edited by

Kamyar Asadipooya and Jeff M. P. Holly

Published in

Frontiers in Endocrinology



FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-6600-8
DOI 10.3389/978-2-8325-6600-8

Generative AI statement

Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Endocrine complications of COVID-19: short and long

Topic editors

Kamyar Asadipooya — University of Kentucky, United States

Jeff M. P. Holly — University of Bristol, United Kingdom

Citation

Asadipooya, K., Holly, J. M. P., eds. (2025). *Endocrine complications of COVID-19: short and long*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6600-8

Table of contents

- 05 **Editorial: Endocrine complications of COVID-19: short and long**
Kamyar Asadipooya
- 07 **The Thr92Ala polymorphism in the type 2 deiodinase gene is linked to depression in patients with COVID-19 after hospital discharge**
Daniele Carvalhal de Almeida Beltrão, Fabyan Esberard de Lima Beltrão, Giulia Carvalhal, Fabyanna Lethicia de Lima Beltrão, Amanda da Silva Brito, Hatilla dos Santos Silva, Helena Mariana Pitangueira Teixeira, Juliana Lopes Rodrigues, Camila Alexandrina Viana de Figueiredo, Ryan dos Santos Costa, Liana Clebia De Moraes Pordeus, Giciane Carvalho Vieira and Helton Estrela Ramos
- 17 **CT semi-quantitative score used as risk factor for hyponatremia in patients with COVID-19: a cross-sectional study**
Baofeng Wu, Ru Li, Jinxuan Hao, Yijie Qi, Botao Liu, Hongxia Wei, Zhe Li, Yi Zhang and Yunfeng Liu
- 27 **Thyroid dysfunction in the wake of Omicron: understanding its role in COVID-19 severity and mortality**
Qingfeng Zhang, Zongyue Zhang, Xu Liu, Yixuan Wang, Hao Chen, Yueying Hao, Shiqian Zha, Jingyi Zhang, Yang He, Beini Zhou and Ke Hu
- 38 **The relation between FT₃ and long-term fatigue in patients with COVID-19**
Shuo Dong, FanRui Ding, Yuan Wang, Shuo Liu, Ran Bai, YuanYuan Liu, Yin Zhao, YueRan Zhu, MengXue Liu, Yuenan Liu and Qian Xing
- 45 **Association of COVID-19 infection and the risk of new incident diabetes: a systematic review and meta-analysis**
Jingye Zhou, Yuzhu Wang and Ruolan Xu
- 56 **Mendelian randomization provides causal association between COVID-19 and thyroid cancer: insights from a multi-cancer analysis**
Shuhong Li, Zedong Du, Hui Ma, Liang Cai, Xiao Liu and Jie He
- 64 **Association between thyroid function and prognosis of severe COVID-19 among patients with SARS-CoV-2 infection: a retrospective cohort study in China**
Yaling Yang, Lifang Qian, Chenwei Wu, Xinyue Xu, Duoduo Qu, Lihua Zhou, Jia Liu, Qin Zhu, Chunhong Wang and Xiaolong Zhao
- 74 **COVID-19 and persistent symptoms: implications for polycystic ovary syndrome and its management**
Shanshan Zhang, Yanqun Wu, Richard Mprah and Mingming Wang

- 91 **Endocrine dysregulation in COVID-19: molecular mechanisms and insights**
Cristiana Iosef, Andrei M. Matusa, Victor K. M. Han and Douglas D. Fraser
- 102 **Unveiling risk factors for post-COVID-19 syndrome development in people with type 2 diabetes**
Anton Matviichuk, Viktoriia Yerokhovych, Sergii Zemskov, Yeva Ilkiv, Vitalii Gurianov, Zlatoslava Shaienko, Tetyana Falalyeyeva, Oksana Sulaieva and Nazarii Kobylak
- 115 **Thyroid function during COVID-19 and post-COVID complications in adults: a systematic review**
Anisha Panesar, Palma Gharanei, Natasha Khovanova, Lawrence Young and Dimitris Grammatopoulos
- 132 **Effect of COVID-19 inactivated vaccine on anti-Müllerian hormone in Chinese women: a retrospective cohort study**
Mingjie Bao, Leizhen Xia, Yan Ling, Quan Wen, Xin Shen, Ting Wang, Si Qian, Liqun Wang, Changhua Wang, Shiwei Peng, Yongping Zhang, Shaoping Zhong, Hongying Xu and Yuan Zhu



OPEN ACCESS

EDITED AND REVIEWED BY
Åke Sjöholm,
Gävle Hospital, Sweden

*CORRESPONDENCE
Kamyar Asadipooya
✉ kas224@uky.edu

RECEIVED 17 July 2025
ACCEPTED 21 July 2025
PUBLISHED 04 August 2025

CITATION
Asadipooya K (2025) Editorial: Endocrine
complications of COVID-19: short and long.
Front. Endocrinol. 16:1668201.
doi: 10.3389/fendo.2025.1668201

COPYRIGHT
© 2025 Asadipooya This is an open-access
article distributed under the terms of the
[Creative Commons Attribution License \(CC BY\)](#).
The use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Editorial: Endocrine complications of COVID-19: short and long

Kamyar Asadipooya *

Division of Endocrinology, Diabetes, and Metabolism, Barnstable Brown Diabetes and Obesity Center, University of Kentucky, Lexington, KY, United States

KEYWORDS

ACE2, complication, COVID-19, endocrine, management

Editorial on the Research Topic

Endocrine complications of COVID-19: short and long

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mainly affects the respiratory system by attaching to its primary receptor ACE2 (angiotensin-converting enzyme 2), and using co-factors TMPRSS2 (the host proteases transmembrane protease, serine 2) and ADAM17 (A Disintegrin and Metalloproteinase 17) to gain cell entry. It can likewise invade other organs that carry ACE2 and these co-factors. Therefore, direct invasion is a recognized mechanism by which SARS-CoV-2 damages human tissues, including the endocrine structures. Furthermore, heightened inflammatory responses and cytokine production following acute SARS-CoV-2 infection could be responsible for multiple organ injuries and potential endocrine system dysfunction (1). However, the immune response following exposure to SARS-CoV-2 antigens are not always associated with endocrine organ dysfunction. For instance, immune response following vaccination was not significantly associated with endocrine system damage, including human reproductive system (Bao et al.). Moreover, post-COVID-19 syndrome (long COVID) is a debilitating problem after recovery from COVID-19, which can cause additional organ impairments and encompass adverse outcomes including disruption of endocrine-organ function (Zhang et al.). Consequently, it is necessary to recognize the risk factors, improve diagnostic tools and identifying more effective medications to prevent the short- and long-term complications of acute SARS-CoV-2 infection.

Increasing awareness among healthcare providers with regards to endocrine complications of acute SARS-CoV-2 infection is important. This can be achieved through reviewing current scientific literature and providing more evidence about diagnosis and treatment of COVID-19. The Research Topic “Endocrine Complications of COVID-19: Short and Long” contains four review and eight original research articles that discuss the important aspects related to endocrine organs and acute SARS-CoV-2 infection. The review articles summarize the connection between acute SARS-CoV-2 infection and thyroid dysfunction (Panesar et al.), diabetes development (Zhou et al.), adrenal damage and pituitary disruption (Iosef et al.) and long COVID in polycystic ovary syndrome (PCOS) patients (Zhang et al.). The research articles discuss the risk of hyponatremia based on CT findings in COVID patients (Wu et al.), and risk factors for long COVID in patients with type 2 diabetes (Matviichuk et al.). The connection between

thyroid dysfunction and severe COVID-19 prognosis (Yang et al.), COVID severity (Zhang et al.), and long COVID (Dong et al.) are discussed separately.

Generally, management of acute SARS-CoV-2 infection is not limited to controlling viral replication and inflammation. We must consider the possible complications during acute infection or after recovery. The current therapeutic recommendation is mainly antivirals. However, this approach is probably facing a barrier, which is caused by the mutated forms of SARS-CoV-2. These mutations ultimately increase the transmission rate, escape the immune response following vaccination and endorse resistance to antiviral medications. Targeting ACE2 or other SARS-CoV-2 receptors may be a helpful strategy in reducing virus entry into host cells and mitigating severity of illness. Blocking virus interaction with its receptors or tackling receptors will bypass this defense mechanisms of SARS-CoV-2 mutated forms. This could be achieved by (1) reducing the interaction between ACE2 on cell membrane and SARS-CoV-2 spike protein (2), reducing the amount of soluble ACE2 or dipeptidyl peptidase 4 (DPP-4), which leads to less viral engulfment (3), capturing SARS-CoV-2 with a decoy receptor before entering into the cells, and (4) manipulating the expression or function of ACE2 genetically or with medications. However, ACE2 on cell membrane has protective roles and the fourth approach could be potentially harmful (2, 3).

In summary, providing more evidence about the complications and treatments of COVID-19 is necessary. Based on the possible complications, including long COVID, endocrine disruption etc., managing COVID-19 is not restricted to the treatment of acute SARS-CoV-2 infection and healthcare providers need to investigate the complications appropriately.

References

1. Anbardar N, Dixon SL, Munugoti S, Gaddam M, Kashfi K, Kasulis L, et al. Thyroid disorders and COVID-19: a comprehensive review of literature. *Front Endocrinol (Lausanne)*. (2025) 16:1535169. doi: 10.3389/fendo.2025.1535169
2. Asadipooya K, Asadipooya A, Adatorwovor R. Combination of spironolactone and DPP-4 inhibitors for treatment of SARS-CoV-2 infection: a literature review. *Arch Virol*. (2024) 169:122. doi: 10.1007/s00705-024-06043-1
3. Liu X. ACE2, a therapeutic target of COVID-19, needs to be treated with caution. *Arch Virol*. (2025) 170:143. doi: 10.1007/s00705-025-06327-0

Author contributions

KA: Writing – original draft, Writing – review & editing.

Conflict of interest

The author declares that the manuscript is written in the absence of any commercial or financial relationships that could be considered as potential conflicts of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Miriam Oliveira Ribeiro,
Mackenzie Presbyterian University, Brazil
Adriano Martimbianco De Assis,
Catholic University of Pelotas, Brazil

*CORRESPONDENCE

Helton Estrela Ramos
✉ ramoshelton@gmail.com

[†]These authors have contributed
equally to this work and share
first authorship

[†]These authors have contributed
equally to this work and share
last authorship

RECEIVED 06 January 2024

ACCEPTED 20 February 2024

PUBLISHED 07 June 2024

CITATION

Beltrão DCdA, Beltrão FE dL, Carvalho G,
Beltrão FLdL, Brito AdS, Silva HdS,
Teixeira HMP, Rodrigues JL,
de Figueiredo CAV, Costa RdS,
Pordeus LCDM, Vieira GC and Ramos HE
(2024) The Thr92Ala polymorphism in the
type 2 deiodinase gene is linked to
depression in patients with COVID-19
after hospital discharge.
Front. Endocrinol. 15:1366500.
doi: 10.3389/fendo.2024.1366500

COPYRIGHT

© 2024 Beltrão, Beltrão, Carvalho, Beltrão,
Brito, Silva, Teixeira, Rodrigues, de Figueiredo,
Costa, Pordeus, Vieira and Ramos. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

The Thr92Ala polymorphism in the type 2 deiodinase gene is linked to depression in patients with COVID-19 after hospital discharge

Daniele Carvalhal de Almeida Beltrão^{1,2†},
Fabyan Esberard de Lima Beltrão^{2,3†}, Giulia Carvalhal⁴,
Fabyanna Lethicia de Lima Beltrão⁵, Amanda da Silva Brito⁶,
Hatilla dos Santos Silva⁷, Helena Mariana Pitangueira Teixeira⁷,
Juliana Lopes Rodrigues⁸,
Camila Alexandrina Viana de Figueiredo⁸,
Ryan dos Santos Costa⁸, Liana Clebia De Moraes Pordeus¹,
Giciane Carvalho Vieira^{1†} and Helton Estrela Ramos^{5,8,9*}

¹Postgraduate Program in Cognitive Neuroscience and Behavior, Center for Health Sciences, Federal University of Paraíba, João Pessoa, Paraíba, Brazil, ²Department of Internal Medicine, University Centre of João Pessoa (UNIPÊ), João Pessoa, Paraíba, Brazil, ³Department of Internal Medicine, Lauro Wanderley University Hospital, Federal University of Paraíba, João Pessoa, Paraíba, Brazil, ⁴Center for Biological and Health Sciences, Federal University of Campina Grande, Campina Grande, Paraíba, Brazil, ⁵Post-Graduate Program in Medicine and Health, Medical School of Medicine, Federal University of Bahia, Salvador, Brazil, ⁶Department of Internal Medicine, Royal Portuguese Hospital of Beneficence, Recife, Pernambuco, Brazil, ⁷Bioregulation Department, Health and Science Institute, Federal University of Bahia, Salvador, Bahia, Brazil, ⁸Laboratory of Immunopharmacology and Molecular Biology, Health Sciences Institute, Federal University of Bahia, Salvador, Bahia, Brazil, ⁹Postgraduate Program in Interactive Processes of Organs and Systems, Health and Science Institute, Federal University of Bahia, Salvador, Bahia, Brazil

Background: The Thr92Ala-DIO2 polymorphism has been associated with clinical outcomes in hospitalized patients with COVID-19 and neuropsychiatric diseases. This study examines the impact of the Thr92Ala-DIO2 polymorphism on neuropsychological symptoms, particularly depressive symptoms, in patients who have had moderate to severe SARS-CoV-2 infection and were later discharged.

Methods: Our prospective cohort study, conducted from June to August 2020, collected data from 273 patients hospitalized with COVID-19. This included thyroid function tests, inflammatory markers, hematologic indices, and genotyping of the Thr92Ala-DIO2 polymorphism. Post-discharge, we followed up with 68 patients over 30 to 45 days, dividing them into depressive (29 patients) and non-depressive (39 patients) groups based on their Beck Depression Inventory scores.

Results: We categorized 68 patients into three groups based on their genotypes: Thr/Thr (22 patients), Thr/Ala (41 patients), and Ala/Ala (5 patients). Depressive symptoms were less frequent in the Thr/Ala group (29.3%) compared to the Thr/Thr (59.1%) and Ala/Ala (60%) groups ($p = 0.048$). The Thr/Ala heterozygous genotype correlated with a lower risk of post-COVID-19 depression, as shown by univariate and multivariate logistic regression analyses. These analyses, adjusted for various factors, indicated a 70% to 81% reduction in risk.

Conclusion: Our findings appear to be the first to show that heterozygosity for Thr92Ala-DIO2 in patients with COVID-19 may protect against post-COVID-19 depression symptoms up to 2 months after the illness.

KEYWORDS

post-COVID-19, Thr92Ala-DIO2 polymorphism, thyroid function, biomarkers, depression

1 Introduction

Since the onset of the COVID-19 pandemic on 11 March 2020, concerns about the increased risk of neuropsychiatric disorders among survivors have risen. Long-term COVID, involving post-acute sequelae after SARS-CoV-2 infection, can lead to various dysfunctions of extrapulmonary organs, including neuroinflammation, which may contribute to the development of depression (1, 2).

The peripheral cytokines may potentially affect brain function through direct action or via afferent pathways. Individuals with autoimmune diseases and severe infections are more likely to experience depression, and therapeutic cytokines can trigger depressive symptoms. The cytokines under extensive study include interleukin (IL) (IL-1 β , IL-5, IL-6, IL-12, and IL-17), tumor necrosis factor (TNF), and interferons (IFNs), representing the inflammatory aspect, and IL-10, associated with resolution (3).

Depression is a complex polygenic disorder influenced by environment. Depending on various studies, its heritability ranges from 30% to 50%, with stress and imbalances in the HPA axis being notable contributing factors. Genetic studies often neglect stress effects, contributing to inconsistent results (4, 5).

There is a statistically significant association between thyroid dysfunction and the development of mental distress, mood disorders, and depression (5, 6). A comprehensive meta-analysis of 12,315 individuals indicated that patients with subclinical hypothyroidism have a higher risk of depression compared to euthyroid controls (relative risk of 2.35, 95% CI: 1.84 to 3.02, $p < 0.001$) (7). Depression-related thyroid hormone (TH) level changes include increased reversed triiodothyronine (rT3) (8, 9) and decreased circulating T3 and TSH levels (10, 11).

The DIO2 gene encodes type 2 deiodinase (D2), a crucial enzyme in converting the pro-hormone T4 into its active form, T3. The Thr92Ala-DIO2 polymorphism is found in approximately half of the global population and has been linked to chronic diseases such as type 2 diabetes mellitus (12, 13), obesity (14), arterial hypertension (15), osteoporosis (16), mental distress (17, 18), and depression (19, 20).

Lately, we investigated 220 consecutive patients with moderate to severe COVID-19 that showed a protective role of the heterozygous state of the polymorphic variant DIO2 (Thr92Ala) in mortality and severity from COVID-19. The heterozygous genotype (Thr/Ala) was associated with a 47%–62% reduced in-hospital risk. The protective role of Thr92Ala's heterozygous advantage was supported in a meta-

analysis of 21 studies in more than 20,000 patients with diseases such as diabetes, obesity, ischemic stroke, myocardial infarction, and left ventricular hypertrophy (21).

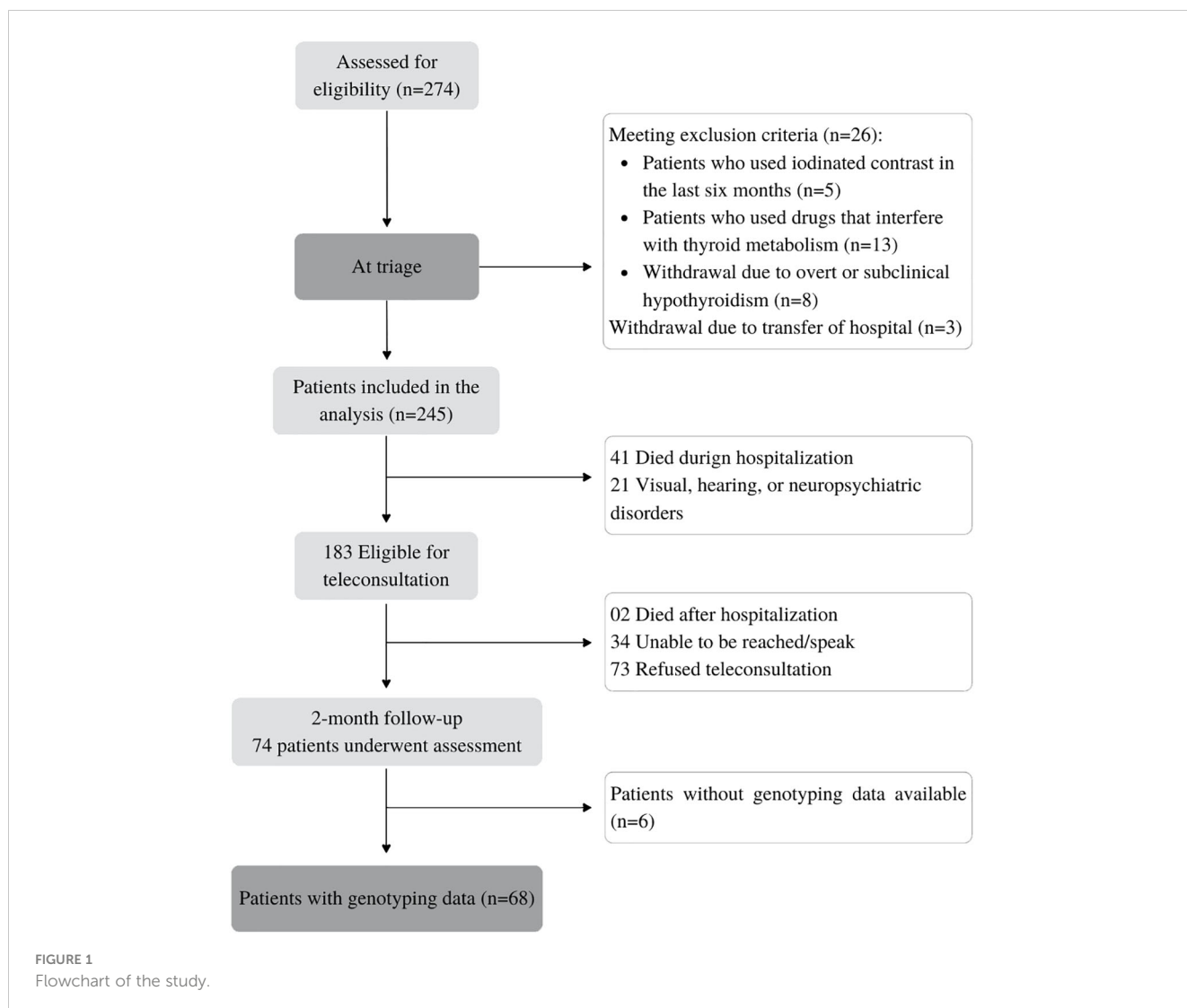
This study aims to investigate the potential correlation between the Thr92Ala-DIO2 polymorphism and depressive symptoms 2 months after COVID-19 hospital discharge. Additionally, it aims to explore various metabolic and hormonal biomarkers alongside tomographic measurements evaluated upon hospital admission. The results of this study could help stratify patients and enable early identification of neuropsychiatric disorders in COVID-19 survivors, facilitating future interventions.

2 Materials and methods

This research was a branch of a broader prospective, longitudinal cohort study, designed to assess thyroid dysfunction in patients with moderate to severe COVID-19 requiring intensive or semi-intensive care. We evaluated 273 consecutive patients hospitalized with COVID-19 between June and August 2020 at the Hospital Metropolitano Dom José Maria Pires (a tertiary referral hospital for COVID-19) in João Pessoa, Paraíba, Brazil. Following discharge, 78 patients were assessed as outpatients for neuropsychiatric issues (Figure 1). Ethical approval was granted by the Hospital Universitário Lauro Wanderley's Ethics Committee for Human Research (CAAE:31562720.9.0000.5183).

Inclusion criteria involved patients who tested positive for SARS-CoV-2 through quantitative real-time reverse transcription polymerase chain reaction (rRT-qPCR—Biomol OneStep/COVID-19, IBMP, Paraná, Brazil) with respiratory tract samples. In cases of negative rRT-qPCR, eligibility was determined based on clinical, radiological, and serological parameters (positive IgG for SARS-CoV-2). Exclusion criteria comprised patients with a history of thyroid disease or the use of drugs affecting thyroid metabolism, pregnancy, personal neuropsychiatric disorders, and the use of neuropsychiatric medications.

The primary outcomes were long-term depression symptomatology in previously hospitalized COVID-19 survivors according to the Thr92Ala-DIO2 polymorphism. Secondary outcomes were blood biochemistry, thyroid function tests, length of stay, comorbidities, complications, and severity scores according to Thr92Ala-DIO2 polymorphism and depressive symptomatology.



The research physicians gathered detailed clinical information on each patient within 48 h of admission using a standard questionnaire and severity scales (qSOFA and NEWS2). After discharge, patients were contacted and invited (30–45 days after discharge) by telephone for a medical consultation at the HULW, to evaluate post-COVID-19 symptoms and signs, including depression symptoms through Beck Depression Inventory (BDI). The BDI is a self-assessment instrument composed of 21 items with scores ranging from 0 to 63. The cutoff scores for the BDI were ≤ 9 (without depression) and > 10 (with depression) (22).

Blood samples (50 mL) were collected within the first 48 h of hospital admission (before any interventions or therapy, including steroids and heparin). Laboratory tests performed included interleukin 6, D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, high-sensitivity C-reactive protein (hs-PCR), and lactate dehydrogenase (LDH). The method used in all examinations was automated chemiluminescence (MAGLUMI-2000-PLUS; Shenzhen New Industries Biomedical Engineering Co., Shenzhen, China). The complete blood cell count with differential was performed on a MEK-7300 hematological analyzer (Nihon Kohden®, Tokyo, Japan).

Patients underwent chest CT to diagnose suspected SARS-CoV-2 pneumonia (ground-glass opacity, mosaic attenuation, and consolidation). A semiquantitative CT severity score proposed by Pan et al. was used in all cases (23).

Genomic DNA was extracted from peripheral blood leukocytes using standard techniques. In this study the polymorphism was determined by the TaqMan® SNP Genotyping method (7500 Real-Time PCR Systems, Applied Biosystems, Foster City, CA, USA), using the assay for genotyping with TaqMan® probes and primers, in a combination of hybridization and DNA polymerase activity, associated with fluorescence detection (24). We used the software Sequence Detection, version 1.3 (Applied Biosystems, CA) to analyze the data.

Statistical analysis: To determine the requisite sample size, we employed GPower 3.1.9.7 software, setting the significance level of $\alpha = 0.05$, the desired statistical power of 0.95, and the effect size (F2) of 0.10. The outcome indicated a minimum sample size of 158 patients from the initial 273. Using the Cochran formula with finite population correction (population size $n = 273$) and aiming for a 95% confidence level and a margin of error within $\pm 10\%$ for prevalence estimation, the analysis required a minimum of 53 patients. Thus, our study group of 68 patients was sufficiently large for a comprehensive analysis.

The data were represented as the median $\pm$ interquartile range (IQR). Non-parametric tests were used for quantitative analysis, including the Mann–Whitney test for two-variable comparisons, and the Kruskal–Wallis test with Dunn’s *post hoc* test for multiple comparisons. Chi-square or Fisher’s exact test was used for qualitative analyses. Spearman’s rank correlation coefficient assessed the linear association between variables. Univariate and multivariate logistic regression analyses evaluated the risk of post-hospital discharge depressive symptoms among patients.

3 Results

Of the 274 adult patients admitted with COVID-19 to a referral hospital, 183 were initially selected for post-discharge assessment. Eligibility assessment led to the exclusion of 109 individuals: 2 due to post-hospitalization death, 34 were unreachable, and 73 declined

participation. Furthermore, six patients were excluded due to incomplete genotype data, resulting in a final cohort of 68 patients (Figure 1).

The group of 68 patients was stratified into three subgroups based on genotype: Thr/Thr ($n = 22$), Thr/Ala ($n = 41$), and Ala/Ala ($n = 5$) (Figure 1). The Thr allele frequency was 0.62 and the Ala allele frequency was 0.37, with a distribution that was in Hardy–Weinberg equilibrium ($p = 0.07$; chi-square test). Baseline sociodemographic and clinical characteristics are summarized in Table 1. During follow-up, the median age of patients was 54.5 (45–67) years, 27 patients were over 60 years old (39.7%), and 48 patients (70.6%) were men. The median length of stay of patients in the hospital was 6 days (4.2–8), and seven patients (10.3%) were admitted to the ICU (Table 1).

Risk factors for post-discharge depressive symptoms were analyzed using Mann–Whitney and Fisher’s tests. There was no significant difference between the risk factors (hypertension,

TABLE 1 Demographic and clinical characteristics of the patient cohort and their association with Thr92Ala-DIO2 polymorphism and depressive symptomatology ($n = 68$).

Variables	Total ($n = 68$)	Thr/Ala ($n = 41$)	Thr/Thr + Ala/Ala ($n = 27$)	p -value	Non-depression ($n = 40$)	Depression ($n = 28$)	p -value
Age (years), median (IQR)	54.5 (45–67)	53 (42–65)	59 (50–68)	0.192	52 (42–59)	65.5 (53–72)	0.004
Age > 60 years, n (%)	27 (39.7)	15 (36.6)	12 (44.4)	0.516	10 (25)	17 (60.7)	0.0052
BMI (kg/m ²)	32 (27–36)	29.8 (26–35)	32.8 (30–38)	0.068	30.7 (28–35)	32.7 (26–38)	0.455
Gender male, n (%)	48 (70.6)	31 (75.6)	32.8 (30–38)	0.262	34 (85)	14 (50)	0.0028
Day to symptom (days)	9 (7–11)	10 (7–11)	9 (7–10)	0.295	9 (7–10.7)	10 (6.2–11)	0.805
Associated morbidities							
Hypertension, n (%)	43 (63.2)	25 (61)	18 (66.7)	0.633	22 (55)	21 (75)	0.126
Diabetes, n (%)	29 (42.6)	16 (39)	13 (48.1)	0.456	15 (37.5)	14 (50)	0.330
Obesity, n (%)	40 (58.8)	19 (46.3)	21 (77.8)	0.01	22 (55)	18 (64.3)	0.466
Cardiopathy, n (%)	7 (10.3)	3 (7.3)	4 (14.8)	0.319	2 (5)	5 (17.9)	0.115
Chronic pneumopathy (%)	3 (4.4)	1 (2.4)	2 (7.4)	0.329	0 (0)	3 (10.7)	0.065
Complications							
Use of vasoactive drugs, n (%)	2 (2.9)	1 (2.4)	1 (3.7)	0.762	0 (0)	2 (7.1)	0.165
Length of hospital stay (days), (IQR)	6 (4.2–8)	6 (4.5–8)	5 (4–10)	0.636	6 (4.2–8)	6 (4.2–9.5)	0.839
ICU admission, n (%)	7 (10.3)	4 (9.7)	3 (11.1)	0.857	2 (5)	5 (17.9)	0.115
Scores systems							
BDI score, median (IQR)	8 (3.2–14)	7 (3–10)	10 (5–22)	0.032	4.5 (2.2–7)	16 (11.2–26)	<0.0001
NEWS2 score, median (IQR)	5.5 (5–7)	6 (5–7.5)	5 (5–6)	0.544	6 (5–7)	5 (5–7)	0.478
q-SOFA score, median (IQR)	1 (0–1)	1 (0–1)	1 (1–1)	0.672	1 (0.25–1)	1 (0–1)	0.423
CT COVID score, median (IQR)	20 (15–20)	20 (15–20)	20 (15–20)	0.958	20 (15–20)	20 (15–20)	0.323

Mann–Whitney test was performed for continuous variables (age, NEWS2, qSOFA, and TC COVID Score) while Fisher’s exact test was performed for all other variables.

BDI, Beck’s Depression Inventory; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; NEWS2, National Early Warning Score 2; NTIS, Non-thyroidal Illness Syndrome; q-SOFA, quick sepsis related organ failure; CT COVID, Chest computed tomography score in COVID-19 patients.

The bold values correspond to the results assessed with significant p -values ($P < 0.01$).

diabetes mellitus, obesity, and heart disease), complications (use of vasoactive drugs, admission to the ICU, and hospital stay), and severity scores (NEWS2, q-SOFA, and CT-COVID). A higher percentage of non-depressed patients were younger than 60 (75%) and were men (85%) (Table 1).

Spearman correlation analysis (Figure 2A) revealed a direct correlation of BDI scores with age ($r = 0.34, p = 0.005$) and D-dimer ($r = 0.35, p = 0.003$). The strongest correlation was between D-dimer versus age ($r = 0.45, p < 0.0001$) and D-dimer versus IL-6 ($r = 0.30, p < 0.01$). The BDI scores, THs, and IL-6 showed no significant difference (Figure 2A).

Regarding the BDI score, heterozygous patients (Thr92Ala) had lower scores than homozygous patients ($p = 0.032$) (Table 1 and Figure 2B).

The overall prevalence of depressive symptoms post-discharge was 41.2% (28 patients). Depressive symptoms were less common in Ala/Thr patients (29.3%) compared to Thr/Thr patients (59.1%) or Ala/Ala patients (60%) ($p = 0.048$) (Figure 3). Logistic regression analysis, adjusted for 15 comorbidities and other covariates, indicated that the Thr/Ala allele was associated with a reduced risk of depressive symptoms compared to the combined Thr/Thr + Ala/Ala genotype (overdominant model) (Table 2).

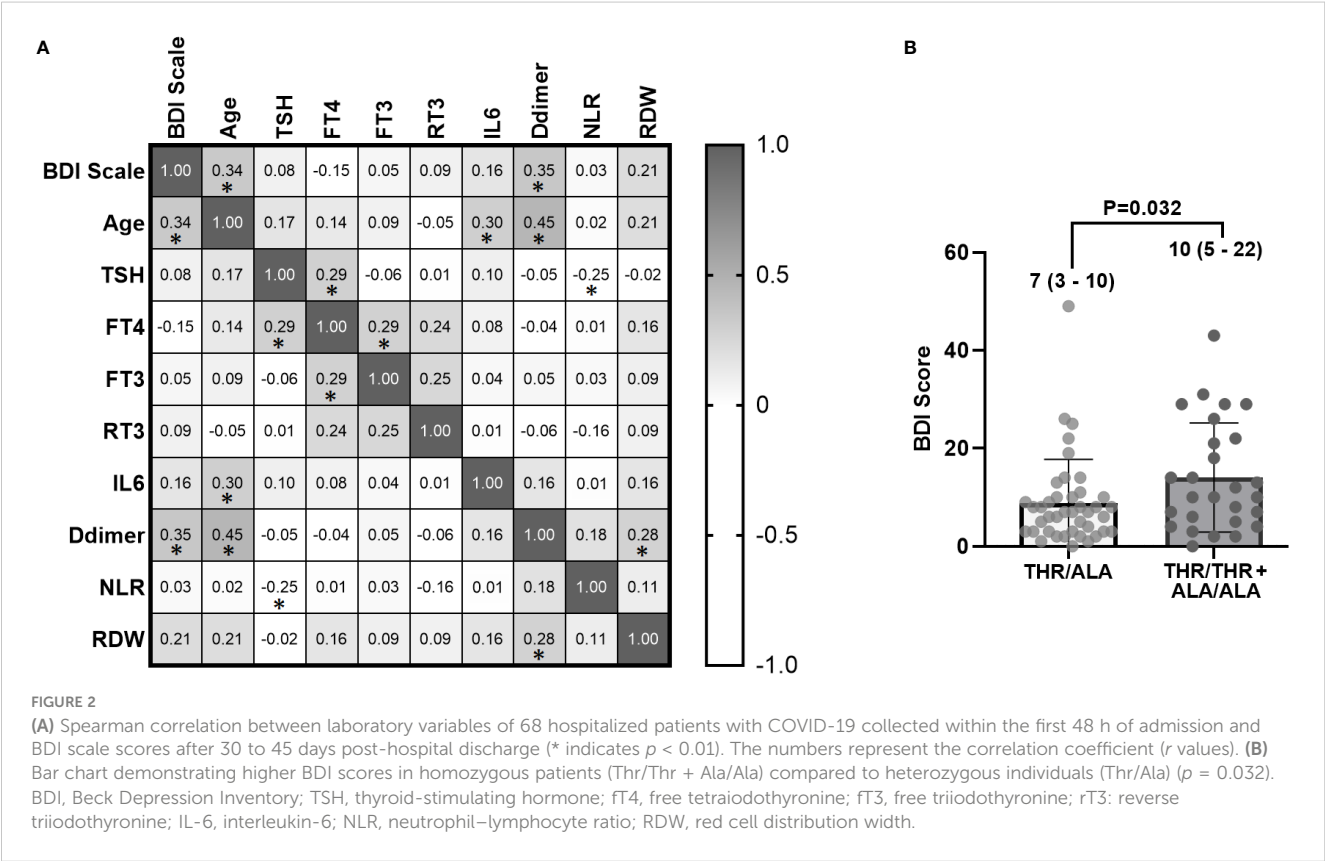
Thyroid function tests, markers of inflammation, tissue damage, and hemochromocytometric parameters are shown in Table 2. There was no significant difference between laboratory parameters of the patient genotypes (Table 3). The only laboratory variable significantly different in patients with depressive symptoms was D-dimer levels, which were higher in these patients ($p < 0.01$).

4 Discussion

To our knowledge, this study is the first of its kind to prospectively analyze the relationship between the Thr92Ala-DIO2 polymorphism and post-COVID-19 depression in hospitalized patients. Our findings indicate that the Thr/Ala genotype correlates with a significantly reduced risk of post-discharge depression, with risk reduction ranging between 70% and 81% as per univariate and multivariate logistic regression analyses adjusted for various covariates.

DIO2, essential for physiological function in the CNS, brown adipose tissue (25), and muscle (26), plays a pivotal role in local triiodothyronine (T3) production, influencing neurological development and function. Active T3 is produced within the brain by DIO2, predominantly by astrocytes, affecting genes associated with neuronal development, myelination, and synaptic transmission (27, 28). Notably, studies on mice that lack DIO2 revealed reduced brain T3 content with mild neurological effects, such as altered emotional behaviors and memory processing. Upregulation of DIO2 has been observed in various neurological disorders, influencing gene expression associated with inflammation and cell death.

The Thr92Ala D2 polymorphism has been associated with decreased TH activity in various end-organ targets. Research conducted *in vitro* and *ex vivo* suggests that the Ala allele is linked to enzyme dysfunction, impacting neurodegenerative mechanisms and oxidative stress within the central nervous system (29). Additionally, this polymorphism has been correlated



Inheritance Models	Genotype	Depressive Symptomatology (n)	Depressive Symptomatology (%)	OR (95% CI)	P value
Overall	TT + TC + CC	28/68	41.2%	-	-
Codominant	TT	13/22	59.1%	0.99 (0.80 – 1.01)	0.048
	TC	12/41	29.3%	0.28 (0.09 – 0.88)	
	CC	3/5	60%	1.02 (0.71 – 2.68)	
Dominant	TT	13/22	59.1%	2.98 (0.98 – 8.84)	0.037
	CC + TC	15/46	32.6%	0.33 (0.11 – 1.02)	
Recessive	TC + TT	25/63	39.7%	0.43 (0.07 – 2.29)	0.374
	CC	3/5	60%	2.28 (0.43 – 13.3)	
Overdominant	TT + CC	16/27	59.2%	3.15 (1.24 – 9.65)	0.014
	TC	12/41	29.3%	0.28 (0.10 – 0.81)	

FIGURE 3

Correlation between DIO2 Thr92Ala polymorphism and depressive symptomatology (chi-square test). CI, confidence interval; OR, odds ratio.

TABLE 2 Blood biochemistry in patients with COVID-19 and their association with Thr92Ala-DIO2 polymorphism and depressive symptomatology ($n = 68$).

Variables (normal range)	Total ($n = 68$)	Thr/Ala ($n = 41$)	Thr/Thr + Ala/Ala ($n = 27$)	p-value	Non-depression ($n = 40$)	Depression ($n = 28$)	p-value
TSH (0.4–5.8 μ IU/mL)	1.0 (0.65–2.25)	1.0 (0.58–2.05)	1.0 (0.82–3)	0.239	1.0 (0.65–1.89)	1.0 (0.64–3.1)	0.401
fT3 (2.0–4.2 pg/mL)	3.0 (2.6–3.6)	3.1 (2.6–3.7)	2.91 (2.3–3.2)	0.184	3.0 (2.59–3.7)	3.0 (2.65–3.47)	0.894
fT4 (0.89–1.72 ng/dL)	1.24 (0.99–1.62)	1.21 (0.98–1.6)	1.28 (1.06–1.58)	0.642	1.25 (0.99–1.62)	1.24 (0.97–1.62)	0.698
rT3 (0.1–0.35 ng/mL)	0.54 (0.31–0.65)	0.58 (0.29–0.68)	0.51 (0.35–0.62)	0.701	0.51 (0.29–0.61)	0.58 (0.35–0.73)	0.144
IL-6 (<3.4 pg/mL)	38.2 (19.4–75.1)	48.3 (18.6–69)	32.8 (19.1–83)	0.943	36.7 (17.8–67)	52.3 (27.2–77.7)	0.215
CRP (<5.0 mg/dL)	82.2 (48–177)	94.4 (51–179)	79.4 (45–146)	0.499	88.9 (48.7–170)	63.3 (45–177)	0.760
Neutrophil (1.9–6.7 10^3 cells/ μ L)	6.74 (5.16–10.5)	7.09 (5.39–12.1)	6.64 (4.95–9.01)	0.445	7.46 (5.35–12.2)	6.68 (4.99–8.16)	0.447
D-dimer (<500 ng/mL)	699 (468–1,422)	696 (470–1,446)	702 (462–1,441)	0.970	643 (384–835)	1,106 (615–2,824)	0.0016
LDH (207–414 U/L)	812 (617–1,033)	807 (617–984)	815 (611–1,115)	0.644	758 (616–896)	911 (617–1,122)	0.258
Albumin (3.5–5.5 g/dL)	3.3 (3–3.6)	3.3 (2.9–3.6)	3.3 (3–3.6)	0.327	3.4 (3.0–3.7)	3.2 (2.9–3.6)	0.106
HbA1c (4%–5.6%)	7.2 (6.6–8.8)	7.4 (6.6–8.8)	7.2 (6.5–9.3)	0.986	7.1 (6.4–8.6)	7.4 (7.0–9.6)	0.111
MCV (82–100 fL)	89.8 (86–92)	89.4 (86–92)	90 (86–92)	0.426	89.7 (86–92)	90 (87–92)	0.889
N/L ratio (1–3)	9.16 (6.4–14)	9.11 (6.2–14.1)	9.4 (6.5–12.3)	0.815	9.3 (6.1–14)	9 (6.6–13.8)	0.894
Creatinine (mg/dL)	1.06 (0.87–1.35)	1.13 (0.89–1.37)	1.00 (0.82–1.27)	0.261	1.06 (0.89–1.3)	0.98 (0.78–1.4)	0.342

Mann–Whitney test was performed for continuous variables. CI, confidence interval; CRP, C-reactive protein; fT3, free triiodothyronine; HbA1c, hemoglobin A1c; IL-6, interleukin 6; IQR, interquartile range; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; N/L ratio, neutrophil–lymphocyte ratio; OR, odds ratio; rT3, reverse triiodothyronine; TSH, thyroid-stimulating hormone.

The bold values correspond to the results assessed with significant p-values ($P < 0.01$).

TABLE 3 Multivariable regression analyses between D2 Thr92Ala polymorphism (Thr/Thr, Thr/Ala, Ala/Ala, and overdominant model) and depressive symptomatology.

				Ala/Thr vs. Ala/Ala + Thr/Thr (Overdominant model)		
				Depression		
				OR	95% CI	p
Model 5	Model 4	Model 1	Depression	0.28	0.10–0.77	0.015
			Age > 60 years	0.27	0.08–0.79	0.019
			Gender (male)	0.29	0.09–0.87	0.030
			Diabetes	0.29	0.10–0.80	0.018
			SAH	0.28	0.10–0.79	0.018
			Obesity	0.29	0.10–0.79	0.017
		Model 1		0.28	0.08–0.91	0.039
		Model 2	TSH	0.30	0.10–0.82	0.022
			Free T3	0.27	0.09–0.75	0.014
			Free T4	0.27	0.09–0.75	0.013
			Reverse T3	0.25	0.08–0.70	0.010
		Model 2		0.22	0.07–0.66	0.009
		Model 3	IL-6	0.27	0.09–0.75	0.013
			CRP	0.29	0.09–0.88	0.031
			D-dimer	0.26	0.08–0.74	0.014
			LDH	0.24	0.08–0.69	0.009
			Albumin	0.30	0.11–0.84	0.024
			Hemoglobin	0.22	0.06–0.66	0.009
		Model 3		0.19	0.05–0.71	0.018

Multivariable regression analyses: Model 1—adjusted for age > 60 years, diabetes, SAH, Systemic Arterial Hypertension, and obesity; Model 2—adjusted for TSH, fT3, fT4, and rT3; Model 3—adjusted for IL6, CRP, Ddimer, Lactate dehydrogenase (LDH), albumin, and hemoglobin. Model 4—adjusted for Models 1 and 3; Model 5—adjusted for all of the above variables. The bold values correspond to the results assessed with significant p-values (P < 0.01).

with various neuropsychiatric conditions, including autism (Marcondes et al., 2021), schizophrenia (30), depression (19, 20), and cognitive impairment (31).

A Lithuanian study involving 168 participants investigated the link between 10 single-nucleotide polymorphisms (SNPs) in DIO1, DIO2, DIO3, and transmembrane TH transporters, specifically the organic anion transporter polypeptide 1C1 (OATP1C1), in relation to post-stroke depressive symptoms and anxiety. Among these SNPs, only the wild-type OATP1C1-rs974453 genotype (GG) showed a significant association with an increased likelihood for depression symptoms (OR = 2.73; 95% CI: 1.04–7.12; *p* = 0.041). In contrast, the Thr92Ala polymorphism did not demonstrate a statistically significant difference, even though it was more prevalent in the Thr/Thr genotype in patients with depression (20). Conversely, a study in Poland indicated that the Ala–Ala genotype of the Thr92Ala polymorphism was more common in healthy individuals compared to those with recurrent depression (7.2% vs. 0.6%, *p* = 0.03, respectively), suggesting its potential as a marker for reduced risk of recurrent depressive disorder (32).

This protection may be explained by the association of Thr92Ala-DIO2 gene expression with endoplasmic reticulum (ER) stress, inflammation, oxidative stress, apoptosis, and mitochondrial dysfunction (33). Disruption of ER homeostasis can lead to the accumulation of misfolded or unfolded proteins in the ER lumen, a condition referred to as ER stress. ER stress is associated with obesity, insulin resistance, type 2 diabetes (34), endothelial dysfunction (35), and low-grade chronic inflammation (36). These conditions have been associated with higher risk and worse prognosis of COVID-19 (37) and depression (38, 39).

Clinical studies have found associations between decreased levels of brain-derived neurotrophic factor (BDNF) and increased inflammatory markers, which are linked to the onset of depressive symptoms and various psychiatric disorders (40). In individuals with depression, one study revealed a correlation between elevated TSH levels, decreased serum BDNF levels, and a lower rise in BDNF during antidepressant treatment (41). A more recent study examining 50 patients undergoing their first episode of psychosis showed that high TSH levels were associated with low peripheral

BDNF and reduced hippocampal volume, suggesting a potential neuroprotective effect of THs on the hippocampus (42).

Animal studies also contribute to our understanding by showing that BDNF has a protective effect against ER stress-induced cell death in brain neurons. This mechanism, which depends on PI3-K activation and inhibits caspase-12, highlights the importance of BDNF in maintaining neuronal integrity under stress (43). The connection between the Thr92Ala-DIO2 gene, ER stress, and BDNF regulation provides a comprehensive perspective on the biological mechanisms that protect against pathological conditions and depressive symptoms.

Research indicates a substantial genetic factor in depression, estimated to contribute approximately 30%–40% to its heritability (44, 45). A recent study found a significant link between the SIRT1 rs12415800 polymorphism, a gene associated with longevity, cellular defense against oxidative stress, and depressive symptoms in university students (46). This association was evident in both codominant ($p = 0.0437$) and overdominant ($p = 0.0147$) genetic models, demonstrating the heterozygous advantage (similar to our study) of this polymorphism against depressive symptoms (47).

Microglial cells, specific types of macrophages in the central nervous system, play a crucial role in neuroinflammation and are increasingly linked to the development of depression. Recent findings suggest a potential link between depression onset and viral infections like SARS-CoV-2, BoDV-1, ZIKV, HIV, and HHV6, which impact various glial cells, including astrocytes, oligodendrocytes, and microglia (48). Transcriptomic analysis [Gene Set Enrichment Analysis (GSEA)] of mice with the Thr92Ala polymorphism revealed increased gene expression related to neuroplasticity, cognition, apoptosis, and neuroinflammation. These results strongly suggest an association between Thr92Ala and neuroinflammation, involving astrocytes as the primary cell type expressing DIO2 in the central nervous system (49).

There are some limitations in this study. Our sample size was relatively small, and the observation time was short; we did not collect healthy people as controls, which may have some influence on the study results; we used mostly self-assessment scales, which may introduce recall bias; and we were unable to measure serum BDNF levels in our patients.

In this prospective study, we present evidence suggesting that possessing heterozygosity of Thr92Ala-DIO2 may have a protective role in preventing the occurrence of depressive symptoms after being discharged from the hospital. Additional research is needed to confirm these findings.

Data availability statement

The data presented in the study have been deposited in the figshare repository with the following accession number: <https://doi.org/10.6084/m9.figshare.25118159.v1>.

Ethics statement

The studies involving humans were approved by Hospital Universitario Lauro Wanderley's Ethics Committee for Human

Research. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DB: Data curation, Investigation, Methodology, Writing – original draft. FEB: Formal analysis, Investigation, Methodology, Software, Writing – original draft. GC: Data curation, Methodology, Writing – review & editing. FLB: Data curation, Methodology, Writing – review & editing. AB: Data curation, Writing – review & editing. HS: Data curation, Methodology, Writing – review & editing. HT: Data curation, Methodology, Writing – review & editing. JR: Data curation, Methodology, Writing – review & editing. CF: Data curation, Writing – review & editing. RC: Conceptualization, Validation, Writing – review & editing. LP: Investigation, Writing – review & editing, Methodology. GV: Conceptualization, Writing – review & editing. HR: Conceptualization, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank all the patients who participated in this study and all the healthcare professionals at the Metropolitan Hospital Dom José Maria Pires for their efforts in taking care of these patients.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1366500/full#supplementary-material>

References

- Peter RS, Nieters A, Kräusslich HG, Brockmann SO, Göpel S, Kindel G, et al. Post-acute sequelae of covid-19 six to 12 months after infection: population based study. *BMJ*. (2022) 379:e071050. doi: 10.1136/BMJ-2022-071050
- Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. (2021) 8:416–27. doi: 10.1016/S2215-0366(21)00084-5
- Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand*. (2017) 135:373–87. doi: 10.1111/ACPS.12698
- Gonda X, Hullam G, Antal P, Eszlari N, Petschner P, Hökfelt TG, et al. Significance of risk polymorphisms for depression depends on stress exposure. *Sci Rep*. (2018) 8:1–10. doi: 10.1038/s41598-018-22221-z
- Zięba A, Matosiuk D, Kaczor AA. The role of genetics in the development and pharmacotherapy of depression and its impact on drug discovery. *Int J Mol Sci*. (2023) 24:2946. doi: 10.3390/IJMS24032946
- Müssig K, Künle A, Säuberlich AL, Weinert C, Ethofer T, Saur R, et al. Thyroid peroxidase antibody positivity is associated with symptomatic distress in patients with Hashimoto's thyroiditis. *Brain Behav Immun*. (2012) 26:559–63. doi: 10.1016/J.BBI.2012.01.006
- Loh HH, Lim LL, Yee A, Loh HS. Association between subclinical hypothyroidism and depression: An updated systematic review and meta-analysis. *BMC Psychiatry*. (2019) 19:1–10. doi: 10.1186/S12888-018-2006-2/FIGURES/5
- Kjellman BF, Ljunggren JG, Beck-Friis J, Wetterberg L. Reverse T3 levels in affective disorders. *Psychiatry Res*. (1983) 10:1–9. doi: 10.1016/0165-1781(83)90022-7
- Kirkegaard C, Faber J. Free thyroxine and 3,3',5'-triiodothyronine levels in cerebrospinal fluid in patients with endogenous depression. *Acta Endocrinol (Copenh)*. (1991) 124:166–72. doi: 10.1530/ACTA.0.1240166
- Jia Y, Zhong S, Wang Y, Liu T, Liao X, Huang L. The correlation between biochemical abnormalities in frontal white matter, hippocampus and serum thyroid hormone levels in first-episode patients with major depressive disorder. *J Affect Disord*. (2015) 180:162–9. doi: 10.1016/J.JAD.2015.04.005
- Ma J, Zhao M, Niu G, Wang Z, Jiang S, Liu Z. Relationship between thyroid hormone and sex hormone levels and non-suicidal self-injury in male adolescents with depression. *Front Psychiatry*. (2022) 13:1071563. doi: 10.3389/FPSYT.2022.1071563
- Estivalet AAF, Leiria LB, Dora JM, Rheinheimer J, Bouças AP, Maia AL, et al. D2 Thr92Ala and PPARγ2 pro12ala polymorphisms interact in the modulation of insulin resistance in type 2 diabetic patients. *Obesity*. (2011) 19:825–32. doi: 10.1038/oby.2010.231
- Dora JM, MaChado WE, Rheinheimer J, Crispim D, Maia AL. Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. *Eur J Endocrinol*. (2010) 163:427–34. doi: 10.1530/EJE-10-0419
- Wang X, Chen K, Zhang C, Wang H, Li J, Wang C, et al. The type 2 deiodinase thr92Ala polymorphism is associated with higher body mass index and fasting glucose levels: A systematic review and meta-analysis. *BioMed Res Int*. (2021) 2021:9914009. doi: 10.1155/2021/9914009
- van der Deure WM, Peeters RP, Uitterlinden AG, Hofman A, Breteler MM, Witteman J, et al. Impact of thyroid function and polymorphisms in the type 2 deiodinase on blood pressure: the Rotterdam Study and the Rotterdam Scan Study. *Clin Endocrinol (Oxf)*. (2009) 71:137–44. doi: 10.1111/J.1365-2265.2008.03447.X
- Kang YE, Kang YM, Park B, Shong M, Yi HS. Type 2 deiodinase Thr92Ala polymorphism is associated with a reduction in bone mineral density: A community-based Korean genome and epidemiology study. *Clin Endocrinol (Oxf)*. (2020) 93:238–47. doi: 10.1111/cen.14206
- Marcondes AAE, Gomez TGB, Ravache TT, Batistuzzo A, Lorena FB, de Paula CS, et al. Assessment of children in the autistic spectrum disorder that carry the Thr92Ala-DIO2 polymorphism. *J Endocrinol Invest*. (2021) 44:1775–82. doi: 10.1007/S40618-020-01497-X
- Taroza S, Rastenytė D, Podlipskytė A, Patamsytė V, Mickuvienė N. Deiodinases, organic anion transporter polypeptide polymorphisms and ischemic stroke outcomes. *J Neurol Sci*. (2019) 407:116457. doi: 10.1016/j.jns.2019.116457
- Galecka E, Talarowska M, Orzechowska A, Górski P, Bienkiewicz M, Szmaj J. Association of the DIO2 gene single nucleotide polymorphisms with recurrent depressive disorder. *Acta Biochim Pol*. (2015) 62:297–302. doi: 10.18388/abp.2014_1002
- Taroza S, Rastenytė D, Burkauskas J, Podlipskytė A, Kazūkauskienė N, Patamsytė V, et al. Deiodinases, organic anion transporter polypeptide polymorphisms and symptoms of anxiety and depression after ischemic stroke. *J Stroke Cerebrovascular Dis*. (2020) 29:105040. doi: 10.1016/j.jstrokecerebrovasdis.2020.105040
- Beltrão FEL, Beltrão DCA, Carvalho G, de Lima Beltrão FE, de Souza Braga Filho J, de Brito Oliveira J, et al. Heterozygote advantage of the type II deiodinase thr92Ala polymorphism on intrahospital mortality of COVID-19. *J Clin Endocrinol Metab*. (2022) 107:E2488–501. doi: 10.1210/CLINEM/DGAC075
- Andrade L, Gorenstein C, Vieira Filho AH, Tung TC, Artes R. Psychometric properties of the Portuguese version of the State-Trait Anxiety Inventory applied to college students: Factor analysis and relation to the Beck Depression Inventory. *Braz J Med Biol Res*. (2001) 34:367–74. doi: 10.1590/S0100-879X2001000300011
- Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from Coronavirus disease 2019 (COVID-19). *Radiology*. (2020) 295:715–21. doi: 10.1148/radiol.2020200370
- De La Vega FM, Lazaruk KD, Rhodes MD, Wenz MH. Assessment of two flexible and compatible SNP genotyping platforms: TaqMan® SNP Genotyping Assays and the SNPlex™ Genotyping System. *Mutat Res - Fundam Mol Mech Mutagenesis*. (2005) 573:111–35. doi: 10.1016/J.MRFMMM.2005.01.008
- Strączkowski M, Nikolajuk A, Stefanowicz M, Matulewicz N, Fernandez-Real JM, Karczewska-Kupczewska M. Adipose tissue and skeletal muscle expression of genes associated with thyroid hormone action in obesity and insulin resistance. *Thyroid* (2022) 32:206–14. doi: 10.1089/THY.2021.0351
- Marsili A, Tang D, Harney JW, Singh P, Zavacki AM, Dentice M, et al. Type II iodothyronine deiodinase provides intracellular 3,5,3'-triiodothyronine to normal and regenerating mouse skeletal muscle. *Am J Physiol Endocrinol Metab*. (2011) 301:818–24. doi: 10.1152/AJPENDO.00292.2011/ASSET/IMAGES/LARGE/ZH10101163430005.JPEG
- Richard S, Flamant F. Regulation of T3 availability in the developing brain: The mouse genetics contribution. *Front Endocrinol (Lausanne)*. (2018) 9:265/BIBTEX. doi: 10.3389/FENDO.2018.00265/BIBTEX
- Salas-Lucia F, Fekete C, Sinkó R, Egri P, Rada K, Ruska Y, et al. Axonal T3 uptake and transport can trigger thyroid hormone signaling in the brain. *Elife*. (2023) 12:e82683. doi: 10.7554/ELIFE.82683
- Butler PW, Smith SM, Linderman JD, Brychta RJ, Alberobello AT, Dubaz OM, et al. The thr92Ala 5' Type 2 deiodinase gene polymorphism is associated with a delayed triiodothyronine secretion in response to the thyrotropin-releasing hormone-stimulation test: A pharmacogenomic study. *Thyroid*. (2010) 20:1407. doi: 10.1089/THY.2010.0244
- Colak A, Akan G, Oncu F, Yanbay H, Acar S, Yesilbursa D, et al. 1508- Association study of the dio2 gene as a susceptibility candidate for schizophrenia in the Turkish population; a case-control study. *Eur Psychiatry*. (2013) 28:1. doi: 10.1016/S0924-9338(13)76526-X
- Wouters HJCM, Van Loon HCM, van der Klauw MM, Elderson MF, Slagter SN, Kobold AM, et al. No effect of the thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. *Thyroid*. (2017) 27:147–55. doi: 10.1089/THY.2016.0199
- Galecka E, Talarowska M, Orzechowska A, Górski P, Szmaj J. Polymorphisms in the type I deiodinase gene and frontal function in recurrent depressive disorder. *Adv Med Sci*. (2016) 61:198–202. doi: 10.1016/J.ADVMS.2015.12.008
- Jo S, Fonseca TL, Bocco BMLC, Fernandes GW, McAninch EA, Bolin AP, et al. Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain. *J Clin Invest*. (2019) 129:230. doi: 10.1172/JCI123176
- Özcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Özdelen E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science*. (2004) 306:457–61. doi: 10.1126/SCIENCE.1103160/SUPPL_FILE/OZCAN.SOM.REV.PDF
- di Pietro N, Marcovecchio ML, di Silvestre S, de Giorgis T, Cordone VGP, Lanuti P, et al. Plasma from pre-pubertal obese children impairs insulin stimulated Nitric Oxide (NO) bioavailability in endothelial cells: Role of ER stress. *Mol Cell Endocrinol*. (2017) 443:52. doi: 10.1016/J.MCE.2017.01.001
- Kim S, Joe Y, Jeong SO, Zheng M, Bak SH, Park SW, et al. Endoplasmic reticulum stress is sufficient for the induction of IL-1β production via activation of the NF-κB and inflammasome pathways. *Innate Immun*. (2014) 20:799–815. doi: 10.1177/1753425913508593
- Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected — obesity, impaired metabolic health and COVID-19. *Nat Rev Endocrinol*. (2021) 17:135–49. doi: 10.1038/s41574-020-00462-1
- Mao J, Hu Y, Ruan L, Ji Y, Lou Z. Role of endoplasmic reticulum stress in depression (Review). *Mol Med Rep*. (2019) 20:4774–80. doi: 10.3892/MMR.2019.10789
- Behnke J, Mann MJ, Scruggs FL, Feige MJ, Hendershot LM. Members of the Hsp70 family recognize distinct types of sequences to execute ER quality control. *Mol Cell*. (2016) 63:739. doi: 10.1016/J.MOLCEL.2016.07.012
- Lima Giacobbo B, Doorduyn J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. *Mol Neurobiol*. (2019) 56:3295. doi: 10.1007/S12035-018-1283-6
- Baek JH, Kang ES, Fava M, Mischooulon D, Nierenberg AA, Lee D, et al. Thyroid stimulating hormone and serum, plasma, and platelet brain-derived neurotrophic factor during a 3-month follow-up in patients with major depressive disorder. *J Affect Disord*. (2014) 169:112–7. doi: 10.1016/J.JAD.2014.08.009
- Toll A, Blanco-Hinojo L, Berge D, Manzano A, El Abidi K, Perez-Solà V, et al. Relationship between thyroid-stimulating hormone, BDNF levels, and hippocampal volume in antipsychotic-naïve first-episode psychosis patients. *Front Psychiatry*. (2023) 14:1301714/BIBTEX. doi: 10.3389/FPSYT.2023.1301714/BIBTEX
- Shimoke K, Utsumi T, Kishi S, Nishimura M, Sasaya H, Kudo M, et al. Prevention of endoplasmic reticulum stress-induced cell death by brain-derived neurotrophic factor in cultured cerebral cortical neurons. *Brain Res*. (2004) 1028:105–11. doi: 10.1016/J.BRAINRES.2004.09.005

44. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet.* (2018) 50:668. doi: 10.1038/S41588-018-0090-3
45. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. *Am J Psychiatry.* (2000) 157:1552–62. doi: 10.1176/APPLAJP.157.10.1552/ASSET/IMAGES/LARGE/Q42F1.JPEG
46. Kilic U, Gok O, Bacaksiz A, Izmirli M, Elibol-Can B, Uysal O. SIRT1 gene polymorphisms affect the protein expression in cardiovascular diseases. *PloS One.* (2014) 9:90428. doi: 10.1371/JOURNAL.PONE.0090428
47. Wang C, Ji L, Ren D, Yuan F, Liu L, Bi Y, et al. Personality traits as mediators in the association between SIRT1 rs12415800 polymorphism and depressive symptoms among Chinese college students. *Front Psychiatry.* (2023) 14:1104664/BIBTEX. doi: 10.3389/FPSYT.2023.1104664/BIBTEX
48. Yu X, Wang S, Wu W, Chang H, Shan P, Yang L, et al. Exploring new mechanism of depression from the effects of virus on nerve cells. *Cells.* (2023) 12:1767. doi: 10.3390/CELLS12131767
49. Lorena FB, Sato JM, Coviello BM, Arnold AJT, Batistuzzo A, Yamanouchi LM, et al. Age worsens the cognitive phenotype in mice carrying the thr92Ala-DIO2 polymorphism. *Metabolites.* (2022) 12:629. doi: 10.3390/METABO12070629/S1



OPEN ACCESS

EDITED BY

Kamyar Asadipooya,
University of Kentucky, United States

REVIEWED BY

Rita Indirli,
University of Milan, Italy
Zhe Zhao,
Max Planck Florida Institute for Neuroscience
(MPFI), United States

*CORRESPONDENCE

Yunfeng Liu

✉ nectarliu@163.com

Yi Zhang

✉ yizhang313@163.com

[†]These authors have contributed equally to this work

RECEIVED 21 November 2023

ACCEPTED 03 June 2024

PUBLISHED 14 June 2024

CITATION

Wu B, Li R, Hao J, Qi Y, Liu B, Wei H, Li Z, Zhang Y and Liu Y (2024) CT semi-quantitative score used as risk factor for hyponatremia in patients with COVID-19: a cross-sectional study.
Front. Endocrinol. 15:1342204.
doi: 10.3389/fendo.2024.1342204

COPYRIGHT

© 2024 Wu, Li, Hao, Qi, Liu, Wei, Li, Zhang and Liu. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](#). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

CT semi-quantitative score used as risk factor for hyponatremia in patients with COVID-19: a cross-sectional study

Baofeng Wu^{1,2†}, Ru Li^{1,2†}, Jinxuan Hao^{1,2}, Yijie Qi^{1,2}, Botao Liu³, Hongxia Wei^{1,2}, Zhe Li^{1,2}, Yi Zhang^{4*} and Yunfeng Liu^{1*}

¹Department of Endocrinology, First Hospital of Shanxi Medical University, Taiyuan, China, ²First Clinical Medical College, Shanxi Medical University, Taiyuan, China, ³Department of Medical Imaging, Shanxi Medical University, Taiyuan, China, ⁴Department of Pharmacology, Shanxi Medical University, Taiyuan, China

Purpose: Chest computed tomography (CT) is used to determine the severity of COVID-19 pneumonia, and pneumonia is associated with hyponatremia. This study aims to explore the predictive value of the semi-quantitative CT visual score for hyponatremia in patients with COVID-19 to provide a reference for clinical practice.

Methods: In this cross-sectional study, 343 patients with RT-PCR confirmed COVID-19, all patients underwent CT, and the severity of lung lesions was scored by radiologists using the semi-quantitative CT visual score. The risk factors of hyponatremia in COVID-19 patients were analyzed and combined with laboratory tests. The thyroid function changes caused by SARS-CoV-2 infection and their interaction with hyponatremia were also analyzed.

Results: In patients with SARS-CoV-2 infection, the total severity score (TSS) of hyponatremia was higher [M(range), 3.5(2.5–5.5) vs 3.0(2.0–4.5) scores, $P=0.001$], implying that patients with hyponatremia had more severe lung lesions. The risk factors of hyponatremia in the multivariate regression model included age, vomiting, neutrophils, platelet, and total severity score. SARS-CoV-2 infection impacted thyroid function, and patients with hyponatremia showed a lower free triiodothyronine (3.1 ± 0.9 vs 3.7 ± 0.9 , $P=0.001$) and thyroid stimulating hormone level [$1.4(0.8–2.4)$ vs $2.2(1.2–3.4)$, $P=0.038$].

Conclusion: Semi-quantitative CT score can be used as a risk factor for hyponatremia in patients with COVID-19. There is a weak positive correlation between serum sodium and free triiodothyronine in patients with SARS-CoV-2 infection.

KEYWORDS

COVID-19, SARS-CoV-2, hyponatremia, computed tomography, free triiodothyronine, pneumonia

1 Introduction

Hyponatremia is a common electrolyte disorder in hospitalized patients, often associated with poor prognosis (1). Severe hyponatremia may cause complications, such as cerebral edema, seizures, and coma. Patients with community-acquired pneumonia (CAP) are more likely to have hyponatremia ($\text{Na}^+ < 135 \text{ mmol/L}$), and hyponatremia is associated with more extended hospital stays, increased hospital costs, and increased mortality (2). The link between COVID-19 and hyponatremia is well known, and multiple studies have described the prevalence of hyponatremia in COVID-19 patients ranging from 20% to 35% (3). COVID-19 causes hyponatremia in patients likely to have the following several aspects: the first is due to the SARS-CoV-2 infection increases interleukin 6 (IL-6) (4), and IL-6 can cross the blood-brain barrier and directly stimulate the supraoptic and paraventricular nuclei cause the syndrome of inappropriate antidiuresis (SIAD) (5); Secondly, SARS-CoV-2 enters host cells through the angiotensin converting enzyme 2 (ACE2), and its binding to ACE2 will down-regulate the activity of ACE2, causing an imbalance between ACE and ACE2, destroying the renin-angiotensin-aldosterone system (RAAS), and leading to the accumulation of angiotensin II (6). Animal studies have found that local application of various components of RAS to the paraventricular nucleus and supraventricular nucleus of the hypothalamus can trigger the release of hypothalamus antidiuretic hormone (ADH), which may also be the cause of hyponatremia in COVID-19 patients (7); Finally, electrolyte disturbances can also be caused by inappropriate use of diuretics and hypotonic fluids in patients with excessive fluid load for treatment.

Most patients with SARS-CoV-2 infection present with pneumonia, and the most common symptoms include fever, cough, dyspnea, and sore throat. Chest CT is an essential and helpful technique for diagnosing and evaluating lung diseases, including pneumonia. CT can detect the signs of pulmonary involvement of COVID-19 and can be used for highly sensitive diagnosis earlier than the reverse transcription-polymerase chain reaction (RT-PCR) test results, which is helpful to quickly and accurately determine the severity of the disease to carry out reasonable management and treatment of patients (8, 9). Many chest CT scoring systems have been developed to assess the severity of lung involvement, and the TSS is widely used (10, 11).

This study explored the association between semi-quantitative CT visual score and endocrine-related factors in patients with SARS-CoV-2 infection and hyponatremia, providing evidence for the vital role of CT score in pneumonia diagnosis, disease severity stratification, and prognosis analysis.

2 Materials and methods

2.1 Study design

This study was a cross-sectional study. Patients admitted to the First Hospital of Shanxi Medical University and diagnosed with COVID-19 from January 1 to January 31, 2023, were included. The

study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Approval number: 2018K002). The patients/participants provided written informed consent to participate in this study.

Inclusion criteria:

1. SARS-CoV-2 infection was positive by RT-PCR 2. Chest CT showed definite pulmonary infection 3. Age ≥ 18 years old

Exclusion criteria:

1. Patients who were missing CT imaging data and laboratory indicators 2. Patients with hypernatremia 3. Patients were readmitted due to COVID-19 and transferred patients

According to inclusion and exclusion criteria, 343 patients were included in the final study (Figure 1). The purpose of this study is to explore the CT semi-quantitative score of COVID-19 patients with hyponatremia prediction effect. Therefore, patients included in the study must demonstrate the presence of SARS-CoV-2 infection and complete data on the underlying laboratory tests and examinations, and those who did not meet these criteria were excluded. Second, given the rarity of hypernatremia in COVID-19 patients (prevalence of 3.7% to 7%) (12, 13), we also excluded patients with hypernatremia because only 15 patients had hypernatremia in this study, which could not meet the statistical requirements.

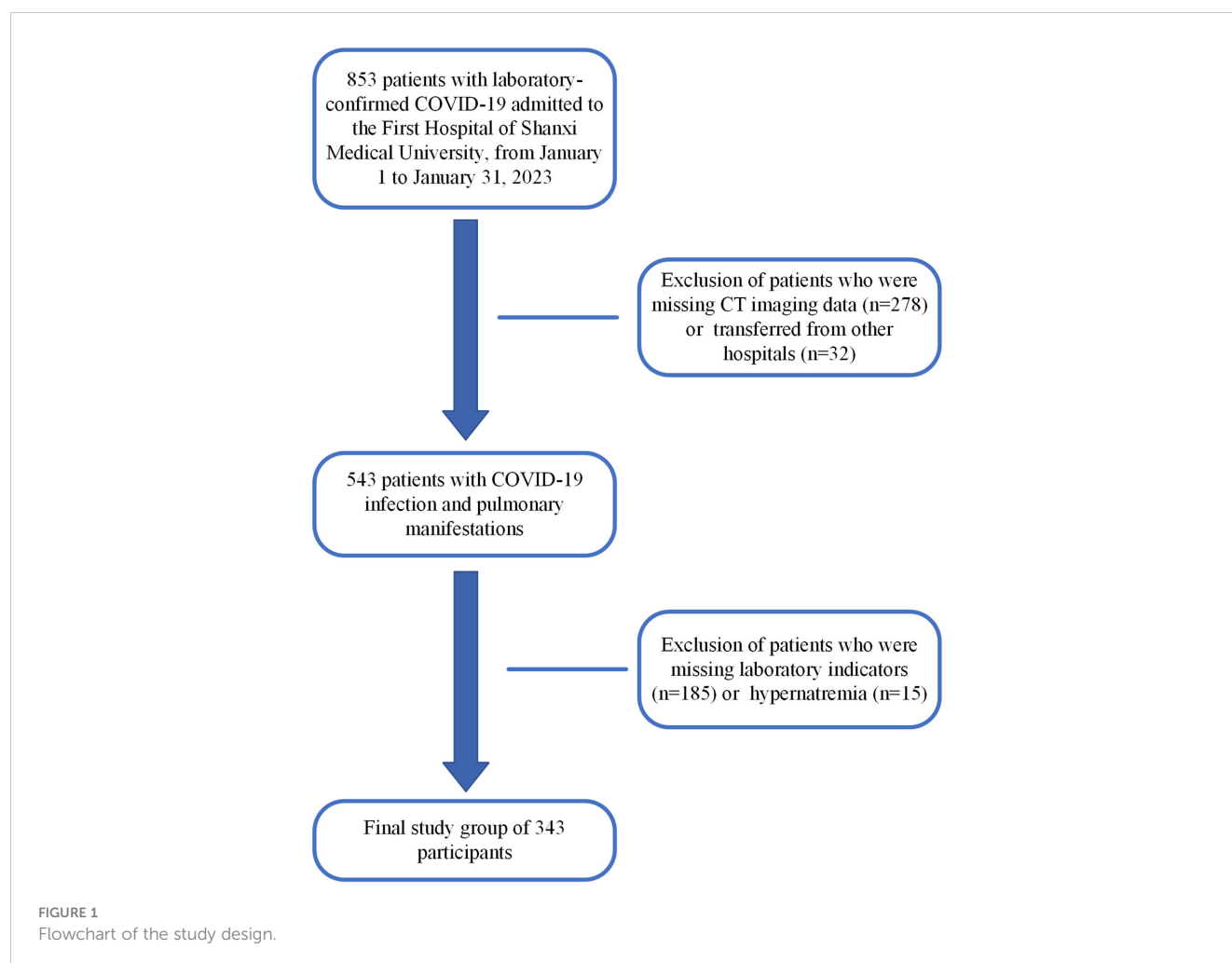
2.2 Definition of covariates

The variables studied included age, sex, vital signs, symptoms, comorbidities, medication at admission, and laboratory parameters. The clinical symptoms we collected included fever, shortness of breath, cough/expectoration, muscle soreness, disturbance of consciousness, poor appetite, vomiting, and diarrhea. Comorbidities collected included diabetes, hypertension, coronary heart disease, cerebral infarction, thyroid dysfunction, and pulmonary disease. Medications on admission included diuretics, ACEI/ARBs, and glucocorticoids. Laboratory indicators included blood cell analysis, liver and kidney function indicators, coagulation indicators, electrolytes, inflammatory indicators, and other indicators. Blood cell analysis is measured by instrumental method (CAL8000), the determination of liver and kidney function by adopting the method of rate method and bromocresol green method, electrolytic determination with ion selective electrode (indirect method), coagulation function is measured by coagulation method and immunoturbidimetric method (ACL TOP 550), BNP and PCT are measured by microparticle chemiluminescence method and thyroid function is measured by electrochemiluminescence method (COBAS 6000).

Hyponatremia was defined as serum sodium less than 135 mmol/L, measured mainly by the indirect ion-selective electrode (ISE) method. Patients were further classified as having mild, moderate, or severe hyponatremia if their serum sodium levels were 130 to < 135 mmol/L, 125 to < 130 mmol/L, and < 125 mmol/L, respectively.

2.3 CT image acquisition and interpretation

All patients underwent a chest CT scan on admission. CT image data were obtained from one of four CT scanners (GE Lightspeed



VCT 64, GE HealthCare, American; Somatom Force, Siemens Healthineers, Germany; IQon Spectral CT, Philips Healthcare, The Netherlands; NeuViz 128 CT, Neusoftmedical, China). The CT scan was performed with the patient supine and at the end of inspiration without administering intravenous contrast material. The scanning range was from the apex to the base of the lung. According to the international recommendations and other studies (14, 15), the parameters used were tube voltage (120kV) and tube current (60–100 mA), which were set by the automatic exposure control system (iDose) program, and the image quality was customized according to the needs of low dose patients. Thoracic VCAR pulmonary function analysis software (AW VolumeShare 7, GE company, American) was used to analyze the image data. The 0.625 mm slice thickness image at the end of deep inspiration was post-processed, and the threshold limit (-1024 to -200 HU) and automatic segmentation technology were used. The heart, trachea, rib, and other lung tissues were segmented to obtain a three-dimensional lung tissue model.

2.4 Semiquantitative CT visual score

In this study, we used the TSS to analyze chest CT findings in hospitalized patients. TSS is a digital scoring system based on visual

evaluation that analyzes the range of lesions in CT images. Two radiologists with years of experience in imaging diagnosis performed scoring. To more clearly express mild and moderate hyponatremia CT score difference, our lung lesions (ground-glass opacity, consolidation, GGO + consolidation) to the following classification: 0:0%; 1:1–10%; 2: 11–20%; 3:21–30%; 4:31–40%; 5:41–50%; 6: >50%. According to these percentages, 0,1,2,3,4,5 and 6 points are given, respectively. The final TSS was the total score of the left and right lungs (range 0–12).

2.5 Statistical analysis

The conformity of the data to a normal distribution was evaluated using skewness, kurtosis tests, and histogram plots. Normally distributed continuous variables are presented as mean and standard deviation ($\pm$ SD); a Student *t*-test was used. Non-normalized variables were presented as medians with interquartile ranges, and a Mann-Whitney *U* test was used. Categorical variables are described as the number (percentage), and Chi-square or Fisher's exact tests were used. Multivariate analysis was carried out using Logistic Regression (Forward Selection: Likelihood Ratio) to determine the significant risk factors of hyponatremia. The

analysis of variance (ANOVA) was used in normal distribution variables, and the Kruskal Wallis test was used in non-normal distribution variables to compare the hyponatremia group (mild/moderate/severe) and the difference between normonatremia group. The data was entered and analyzed using the IBM SPSS 27 system (SPSS Inc., Chicago, IL, USA). A P -value $\leq 5\%$ was taken for statistical significance.

3 Results

3.1 General characteristics of COVID-19 patients

A total of 343 eligible patients were included in the study, 58.6% male. The mean age of the patients was 74.5 ± 13.1 years, and 89.5% were older than 60 years. Cough/expectoration (74.9%), poor appetite (66.2%), and shortness of breath (44.6%) were the most common clinical symptoms observed. Hypertension and diabetes were the most common comorbidities, accounting for 49.0% and 25.9%, respectively. Of the 343 study patients, 43.4% had hyponatremia, whereas 56.6% had normonatremia (Table 1). Among the patients with hyponatremia, the prevalence of mild, moderate, and severe hyponatremia was 53.7%, 16.8%, and 29.5%, respectively (Supplementary Table S1).

Patients in the hyponatremia group were significantly older [M (range), 80.0(70.0–86.5) vs 72.5(65.0–82.8) years old, $P < 0.001$] than those in the normonatremia group. Vomiting (14.1% vs 5.7%, $P=0.008$) and diuretic use (10.1% vs 3.1%, $P=0.008$) in the hyponatremia group were significantly different from those in normonatremia group. The remaining measures of vital signs, symptoms, coexisting conditions, and out-of-hospital medication use did not differ significantly between the two groups (Table 1).

3.2 Laboratory findings and TSS

Among the laboratory indicators in Table 1, the median (IQR) findings of complete blood count (white blood cell/platelet/hemoglobin/neutrophil), renal function indexes (BUN, SCr), ALT, potassium, coagulation indicators (PT, APTT, and FDP), and BNP were within normal limits. Compared with the normonatremia group, the white blood cells and neutrophils in the hyponatremia group increased, while the platelets and lymphocytes decreased, and the difference was statistically significant (all $P < 0.05$, Table 1). Compared with the normonatremia group, the median eGFR and chlorine in the hyponatremia group were lower than the lower limit of normal, and the difference was statistically significant (all $P < 0.05$, Table 1). The median blood glucose, D dimer, and PCT in the hyponatremia group were increased, which were higher than the upper limit of normal, and the difference was statistically significant (all $P < 0.05$, Table 1).

Excellent agreement was achieved between the two radiologists in the assessment of lung lesions, with an average measurement intraclass correlation coefficient (ICC) of 0.953 (95% CI, 0.942–0.962; $P < 0.001$) (Supplementary Table S2). Thus indicating a high

reliability of the semi-quantitative method, in the following analysis, the average of the CT scores of the two radiologists was selected instead of using the scores of radiologist 1 or radiologist 2. For TSS, the hyponatremia group showed higher scores than the normonatremia group [M(range), 3.5(2.5–5.5) vs 3.0(2.0–4.5) scores, $P=0.001$] (Table 1), indicating more severe lung lesions. The hyponatremia was further divided into mild, moderate, and severe groups, and the difference in CT scores between different degrees of hyponatremia group and normonatremia group was analyzed. The results showed that the difference between the normonatremia and mild hyponatremia groups ($P=0.001$) and the normonatremia and moderate hyponatremia groups ($P=0.023$) were significant (Figure 2).

3.3 Risk factors for hyponatremia in patients with SARS-CoV-2 infection

Univariate and multivariate logistic regression analyses were performed to explore the risk factors of hyponatremia in patients with SARS-CoV-2 infection, combined with the statistics of the difference between the normonatremia group and the hyponatremia group. By univariate logistic regression analysis, statistically significant risk factors for hyponatremia included age, vomiting, diuretics, platelets, lymphocytes, neutrophils, NLR, eGFR, APTT, BNP, PCT, and TSS, as shown in Table 2.

Based on our clinical observations, fluid loss due to diarrhea/vomiting and medications such as diuretics, ACEI/ARBs, or glucocorticoids can cause electrolyte disturbances. After excluding the variables with higher degree of collinearity, multivariate logistic regression analysis was performed, and the results showed that (Table 2) age (OR=1.039, 95%CI 1.018–1.061, $P < 0.001$), vomiting (OR=2.920, 95%CI 1.233–6.913, $P=0.015$), neutrophil count (OR=1.167, 95%CI 1.079–1.263, $P < 0.001$), TSS score (OR=1.203, 95%CI 1.069–1.354, $P=0.002$), and platelet count (OR=0.995, 95%CI 0.991–0.998, $P=0.002$) were independent risk factors for hyponatremia in COVID-19 patients.

3.4 The thyroid function between normonatremia group and hyponatremia group

To explore the role of endocrine-related factors in developing hyponatremia in COVID-19 patients, we performed a subgroup analysis of 104 patients with available thyroid function data. The results showed (Table 3) that the levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were within the normal range. However, the levels of FT3, FT4, and TSH in the hyponatremia group were lower than those in the normonatremia group, and the difference in FT3 (3.1 ± 0.9 vs 3.7 ± 0.9 , $P=0.001$) and TSH [M (range), 1.4 (0.8–2.4) vs 2.2 (1.2–3.4) uIU/ml, $P=0.038$] between the two groups were statistically significant. The result may indicate that SARS-CoV-2 infection affects pituitary and thyroid function differently.

TABLE 1 Demographic and clinical characteristics of the patients.

	Normonatremia (<i>n</i> =194)	Hyponatremia (<i>n</i> =149)	<i>P</i> - value
Demographic characteristics			
Age (years)	72.5 (65.0–82.8)	80.0 (70.0–86.5)	<0.001
Male, <i>n</i> (%)	110.0 (56.7)	91.0 (61.1)	0.415
Body mass index (kg/m ²)	23.9 (21.1–26.8)	24.2 (21.3–26.7)	0.769
Vital signs			
Body temperature (°C)	36.5 (36.3–36.8)	36.6 (36.3–37.0)	0.087
Pulse (Times/min)	80.0 (76.0–90.0)	80.0 (73.5–90.5)	0.430
SBP (mmHg)	130.0 (118.0–139.8)	132.0 (118.0–144.0)	0.325
DBP (mmHg)	76.0 (70.0–82.0)	76.0 (69.0–82.5)	0.839
Symptoms			
Fever, <i>n</i> (%)	28.0 (14.4)	31.0 (20.8)	0.121
Shortness of breath, <i>n</i> (%)	93.0 (47.9)	60.0 (40.3)	0.157
Cough/ Expectoration, <i>n</i> (%)	153.0 (78.9)	104.0 (69.8)	0.055
Muscle soreness, <i>n</i> (%)	26.0 (13.4)	14.0 (9.4)	0.252
Disturbance of consciousness, <i>n</i> (%)	12.0 (6.2)	16.0 (10.7)	0.127
Poor appetite, <i>n</i> (%)	124.0 (63.9)	103.0 (69.1)	0.312
Vomiting, <i>n</i> (%)	11.0 (5.7)	21.0 (14.1)	0.008
Diarrhea, <i>n</i> (%)	6.0 (3.1)	6.0 (4.0)	0.641
Comorbidities			
Diabetes, <i>n</i> (%)	45.0 (23.2)	44.0 (29.5)	0.185
Hypertension, <i>n</i> (%)	97.0 (50.0)	71.0 (47.7)	0.666
Coronary heart disease, <i>n</i> (%)	31.0 (16.0)	16.0 (10.7)	0.162
Cerebral infarction, <i>n</i> (%)	28.0 (14.4)	22.0 (14.8)	0.931
Thyroid dysfunction, <i>n</i> (%)	7.0 (3.6)	4.0 (2.7)	0.863
Pulmonary disease, <i>n</i> (%)	5.0 (2.6)	9.0 (6.0)	0.108
Medication at admission			
Diuretics, <i>n</i> (%)	6.0 (3.1)	15.0 (10.1)	0.008
ACEI/ARBs, <i>n</i> (%)	15.0 (7.7)	17.0 (11.4)	0.245

(Continued)

TABLE 1 Continued

	Normonatremia (<i>n</i> =194)	Hyponatremia (<i>n</i> =149)	<i>P</i> - value
Medication at admission			
Glucocorticoids, <i>n</i> (%)	15.0 (7.7)	8.0 (5.4)	0.386
Laboratory tests			
Leukocyte (×10 ⁹ /L)	5.7 (4.1–7.8)	6.2 (4.8–9.9)	0.008
Hemoglobin (g/L)	137.0 (124.0–148.0)	134.0 (121.5–144.0)	0.186
Platelets (×10 ⁹ /L)	194.0 (142.0–246.0)	173.0 (124.5–229.5)	0.016
Lymphocytes (×10 ⁹ /L)	1.0 (0.7–1.4)	0.8 (0.5–1.1)	<0.001
Neutrophils (×10 ⁹ /L)	3.8 (2.4–6.5)	4.7 (3.3–7.9)	<0.001
NLR	3.8 (2.5–6.8)	7.3 (3.5–12.9)	<0.001
Blood glucose (mmol/L)	6.7 (5.8–8.8)	7.0 (6.2–9.2)	0.058
ALT (U/L)	20.5 (13.0–35.3)	27.0 (18.0–38.5)	0.022
AST (U/L)	27.0 (21.0–41.0)	37.0 (24.0–57.0)	<0.001
Albumin (g/L)	35.8 (33.0–39.3)	34.5 (31.8–38.1)	0.028
BUN (mmol/L)	5.3 (4.0–7.3)	5.5 (4.1–7.9)	0.558
SCr (μmol/L)	67.0 (57.0–81.6)	71.0 (56.0–88.5)	0.466
eGFR (mL/ min/1.73m ²)	91.5 (75.7–100.1)	85.2 (68.9–95.0)	0.004
Potassium (mmol/L)	3.9 (3.6–4.3)	3.9 (3.5–4.2)	0.197
Chlorine (mmol/L)	102.7 (100.4–104.8)	93.8 (87.2–98.1)	<0.001
PT (s)	13.6 (12.8–14.4)	13.4 (12.7–14.3)	0.392
APTT (s)	31.6 (29.3–33.7)	32.3 (29.9–35.9)	0.035
FDP (ug/ml)	4.7 (1.8–163.5)	4.4 (1.9–133.5)	0.504
D dimer (mg/L)	2.2 (0.3–4.5)	1.8 (0.3–4.4)	0.639
PCT (ng/ml)	0.26 (0.16–0.35)	0.29 (0.20–0.45)	0.011
BNP (ng/L)	52.6 (26.8–122.8)	109.0 (48.0–270.9)	<0.001
hs-cTnT (pg/ml)	9.5 (4.4–19.6)	13.5 (7.3–35.5)	<0.001
CT assessment			
TSS (scores)	3.0 (2.0–4.5)	3.5 (2.5–5.5)	0.001

Values are expressed as mean (± standard deviation), median (interquartile range), or number (percentage). Serum creatinine (SCr) measurements were used to calculate the estimated Glomerular Filtration Rate (eGFR) by using the 2021 Chronic Kidney Disease Epidemiology Collaboration (2021 CKD-EPI) Creatinine equation (16). SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NLR, neutrophil to lymphocyte ratio; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrinogen degradation products; PCT, procalcitonin; BNP, brain natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; TSS, total severity score. A P-value <0.05 was considered statistically significant, shown in bold.

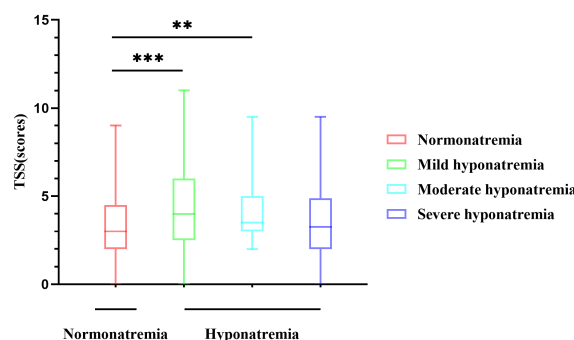


FIGURE 2

Differences in CT scores of different degrees of hyponatremia. The difference between the normonatremia and mild hyponatremia groups, and the normonatremia and moderate hyponatremia groups were significant. ** $P < 0.01$, *** $P < 0.001$.

We performed a correlation analysis further to explore the relationship between FT3 and serum sodium. Spearman correlation analysis showed that there was a positive correlation between FT3 and serum sodium ($r_s = 0.358$, $P < 0.001$) (Table 4). The higher the level of FT3, the higher the serum sodium of patients, but this correlation was weak.

4 Discussion

Hyponatremia is a common electrolyte disorder associated with high morbidity and mortality, about 30% in hospitalized patients, and the incidence is higher in intensive care units (17). Compared to patients with pneumonia, COVID-19 patients with a significantly higher risk of hyponatremia (3, 18). Therefore, active prevention and treatment of hyponatremia greatly help the prognosis of the disease. Frontera and colleagues found that among patients with COVID-19, moderate ($\text{Na } 121\text{--}129 \text{ mEq/L}$) and severe ($\text{Na} \leq 120 \text{ mEq/L}$) hyponatremia accounted for 7% and 1% of the study population, respectively (19). In our study, which included only patients with COVID-19, the incidence of hyponatremia was 43.4%. The prevalence of mild, moderate, and severe hyponatremia was 23.3%, 7.3%, and 12.8%, respectively. The higher incidence of hyponatremia may be related to the advanced age of patients and more comorbidities, and these factors are often associated with poor prognosis. Secondly, because our data came from a large tertiary general hospital, there were more critically ill patients, so the incidence of hyponatremia in our study was high.

In this study, older age, vomiting, increased neutrophil count, and higher TSS score were associated with a higher risk of hyponatremia in COVID-19 patients. Among patients with SARS-CoV-2 infection, older age, and more coexisting conditions are associated with more severe disease, and these same factors are present in patients with hyponatremia. The study by Muhammad Anees et al. found that an elevated NLR was a risk factor for hyponatremia in hospitalized patients with COVID-19 (20). Although NLR was not proven to be a risk factor for the development of hyponatremia in our study by multivariate logistic regression, neutrophil count was proved to be a risk factor

for the development of hyponatremia in COVID-19 patients by univariate or multivariate logistic regression.

The increase in platelet count can reduce the risk of hyponatremia, but the reduction effect is weak. Thrombocytopenia is another feature of SARS-CoV-2 infection, and in a retrospective study of 1,476 hospitalized COVID-19 patients, 20.7% were found to have thrombocytopenia, and thrombocytopenia was associated with increased mortality (21). We found that thrombocytopenia was more in the hyponatremia group, and the difference was statistically significant compared with the normonatremia group. The causes of thrombocytopenia were related to the direct effect of the virus on bone marrow cells and the formation of autoantibodies by platelets and their participation in immune regulation (22, 23).

ADH is generally produced by the supraoptic and paraventricular hypothalamic nuclei, stored and released from the posterior pituitary. ADH can also be derived from non-pituitary sources, and excessive release of the hormone from other sites results in SIAD. SIAD can be induced by various factors, including tumors, infections such as pneumonia and meningitis, and neurological diseases such as stroke (24). The effect of SIAD on hyponatremia in community-acquired pneumonia has been confirmed by studies (25), and SIAD is considered the leading cause of hyponatremia in COVID-19 patients. IL-6 is one of the most critical cytokines in inflammatory syndrome, causing pathological changes after SARS-CoV-2 infection (26). Elevated IL-6 levels can induce ADH secretion by directly stimulating the hypothalamus and inducing alveolar basement membrane damage and pulmonary hypoxia (27). Second, after SARS-CoV-2 infection, activated immune cells (mainly T and B lymphocytes) and released proinflammatory cytokines stimulate immune cells to release stored ADH (28).

In the study by A Berni et al., IL-6 was elevated in 17 of 29 patients with SARS-CoV-2 infection and inversely correlated with serum sodium concentration (29). In our study, IL-6 was also elevated in the hyponatremia group, and the difference was statistically significant compared with the normonatremia group. Furthermore, in the linear analysis, we also found a weak negative correlation between IL-6 and serum sodium (Supplementary Tables S3, S4). This result of our study may further support the idea of a nonosmotic release of ADH associated with IL-6.

TABLE 2 Logistic regression analysis to predict the indicators of hyponatremia in patients with COVID-19.

	Univariate model		Multivariate model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Demographic characteristics				
Age (years)	1.036 (1.017–1.056)	<0.001	1.039 (1.018–1.061)	<0.001
Symptoms				
Vomiting	2.729 (1.272–5.858)	0.010	2.920 (1.233–6.913)	0.015
Diarrhea	1.315 (0.415–4.162)	0.642		
Medication at admission				
Diuretics	3.507 (1.327–9.274)	0.011		
ACEI/ARBs	1.537 (0.741–3.189)	0.248		
Glucocorticoids	0.677 (0.279–1.642)	0.388		
Laboratory parameters				
Platelets ($\times 10^9/L$)	0.997 (0.994–0.999)	0.016	0.995 (0.991–0.998)	0.002
Lymphocytes ($\times 10^9/L$)	0.494 (0.329–0.749)	<0.001		
Neutrophils ($\times 10^9/L$)	1.038 (1.013–1.171)	0.001	1.167 (1.079–1.263)	<0.001
NLR	1.053 (1.024–1.083)	<0.001		
ALT (mmol/L)	1.000 (0.996–1.004)	0.848		
AST (mmol/L)	1.002 (0.999–1.005)	0.196		
Albumin	0.968 (0.928–1.009)	0.124		
eGFR (mL/min/1.73m ²)	0.990 (0.981–1.000)	0.039		
APTT (s)	1.036 (0.999–1.075)	0.058		
PCT (ng/ml)	1.062 (1.003–1.125)	0.040		
BNP (ng/L)	1.001 (1.000–1.002)	0.007		
hs-cTnT (pg/ml)	1.001 (0.999–1.003)	0.226		
CT assessment				
TSS (scores)	1.220 (1.094–1.361)	<0.001	1.203 (1.069–1.354)	0.002

OR, odds ratio; CI, confidence intervals; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; PCT, procalcitonin; BNP, brain natriuretic peptide; TSS, total severity score.

A P-value <0.05 was considered statistically significant, shown in bold.

With the rapid spread of COVID-19 worldwide, many scoring systems for lung assessment have been released. Chest CT severity score, total severity score, modified total severity score, and other scoring methods have excellent reliability in clinical assessment (11, 30). Peijie Lyu and colleagues found that qualitative or quantitative chest CT measures can assess the clinical severity of COVID-19 pneumonia (31). Miklos Szabo et al. found that the chest CT scoring system (CCTS) and specific chest CT patterns can predict ventilation requirements and mortality in COVID-19 (32). In this study, we used the TSS semi-quantitative method to assess the severity of lung lesions in patients with COVID-19 and then correlate it with hyponatremia. Because our study included a small number of patients with severe or critical lung illness, we modified the CT score of the lung to make it easier to identify mild and moderate pulmonary infections and to explore their effect on

hyponatremia. The results showed that there was a significant difference in total severity score between the normonatremia group and the hyponatremia group, which suggested that CT score may be a risk factor for hyponatremia, and the results of multivariate logistic regression also proved this, the higher the TSS score, the higher the risk of hyponatremia.

CT score can predict the severity of pneumonia after SARS-CoV-2 infection (31–33), and hyponatremia can be caused by SARS-CoV-2 infection (34, 35). Many studies have confirmed these conclusions. To the best of our knowledge, this study is the first to correlate CT score with hyponatremia, and further exploration showed a weak inverse association between TSS and serum sodium (Supplementary Table S5), suggesting that not only can CT score predict the risk of hyponatremia, but it also seems to predict the severity of hyponatremia. Of course, we still need to do

TABLE 3 Comparison of thyroid function between Normonatremia group and hyponatremia group.

	Normonatremia (n=50)	Hyponatremia (n=54)	P-value
Thyroid function			
FT3 (pmol/L)	3.7 ± 0.9	3.1 ± 0.9	0.001
FT4 (pmol/L)	16.9 (15.2–18.8)	15.7 (13.2–21.1)	0.507
FT3/FT4	0.23 (0.18–0.25)	0.21 (0.16–0.27)	0.486
TSH (uIU/ml)	2.2 (1.2–3.4)	1.4 (0.8–2.4)	0.038
CT assessment			
TSS	2.3 (2.0–4.0)	2.8 (2.0–3.6)	0.172

Values are expressed as mean (± standard deviation) or median (interquartile range). FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TSS, total severity score.

A P-value <0.05 was considered statistically significant, shown in bold.

much validation. Given the widespread and convenient use of chest CT examination in clinical practice, our results are encouraging, which means that CT score can not only predict the occurrence of hyponatremia after SARS-CoV-2 infection but also provide new ideas for evaluating the association between other lung infections and hyponatremia. Although derived from inpatients, our findings may also be helpful in the outpatient setting since chest CT is routinely performed based on lung lesions. CT scores can predict the development of hyponatremia before serologic tests, which may facilitate early intervention in the outpatient setting. Multiple studies have reported impaired thyroid function in COVID-19 patients, including decreased TSH and T3 levels, decreased TSH levels alone, decreased TSH and increased T4 levels, and decreased TSH and FT4 (36–39). The causes of thyroid dysfunction may be related to a direct effect of COVID-19 on thyroid follicular cells or to disturbances in immune function (40, 41). Our study found that TSH and FT3 in patients with hyponatremia were lower than those with normal serum sodium. Similarly, W Gao et al. found that FT3 concentration was significantly lower in patients with severe COVID-19 than in non-severe patients, and FT3 reduction could be used as an independent predictor of all-cause mortality in patients with severe COVID-19 (42). We considered that the reasons for the lower TSH and FT3 in the hyponatremia group were as follows (1): After SARS-CoV-2 infection, the pituitary cells of patients were damaged (43), resulting in the increased release of ADH and the decreased secretion of TSH. The increased release of ADH can cause dilute hyponatremia, while the decreased secretion of TSH can cause a decrease in FT4 and FT3 (2). Cytokine IL-6 is involved in SARS-CoV-2-related cytokine storm (44). Elevated IL-6

can cause the non-osmotic release of ADH and increase the occurrence of hyponatremia. McGonagle et al. found that increased IL-6 and TNF- α were associated with decreased FT3 levels in patients with severe COVID-19 (45). In patients with SARS-CoV-2 infection, elevated IL-6 is associated with subacute thyroiditis, Graves' disease, and Hashimoto's thyroiditis (46), while abnormalities of the hypothalamic-pituitary-thyroid axis can cause a series of changes in TSH and thyroid hormones. Hyponatremia and low FT3 together affect the severity and prognosis of the disease (3). The patients in our hyponatremia group had a poorer general condition (Supplementary Table S6), were at higher risk for multiorgan dysfunction, and were more likely to be treated with glucocorticoids according to guideline recommendations. In contrast, the administration of glucocorticoids decreases TSH levels and inhibits the conversion of T4 to T3 while stimulating the conversion of T4 to rT3 (47, 48), the changes similar to those observed in non-thyroidal illness syndrome. Decreases in TSH and T3 are common, and the degree of decrease in T3 correlates with disease severity. Although the results of these studies were based on patients with SARS-CoV-2 infection, it also suggests that we should be aware of thyroid abnormalities in other lung lesions.

Our study also has several additional limitations: First, we did not observe the dynamic evolution of CT scores and hyponatremia in this cross-sectional study, and the lack of a certain follow-up period may make our conclusions partial. Second, the semi-quantitative CT score used in this study is subject to error and unvalidated, as well as the lack of specific serologic measures of specificity (e.g., ADH), which could attenuate the association between CT score and hyponatremia. Third, this study lacked a study of patients with hypernatremia because hypernatremia may be associated with worse outcomes (ICU admission, intubation, death). Finally, there were no statistics on vaccination status, such as the occurrence of autoimmune thyroid disease after COVID-19 vaccination, in some studies, so it is difficult to rule out the effect of this confounding factor.

In conclusion, in this study, for the first time, the semi-quantitative CT visual score was associated with hyponatremia, and the endocrine factor (thyroid function) was analyzed to clarify the relationship further. It was found that the CT score level can be used to evaluate the occurrence of hyponatremia, which can achieve early detection, prediction, and intervention in clinical practice. It is helpful to reduce the occurrence of clinical complications. Although our study population was derived from patients with SARS-CoV-2 infection, it provides a new perspective for analyzing patients with other lung lesions or endocrine abnormalities.

5 Conclusion

In our study, CT semi-quantitative score was associated with hyponatremia for the first time, and the endocrine factor (thyroid function) was analyzed to clarify further the association, and high TSS was found to be a risk factor for hyponatremia. Although our study population was derived from patients with SARS-CoV-2 infection, it provides a new perspective for analyzing patients with other lung lesions or endocrine abnormalities. The haze

TABLE 4 Correlation between FT3 and serum sodium.

	Correlation coefficient(<i>r</i>)	Spearman <i>P</i> -value	95% CI	
			Low	High
FT3-Serum sodium	0.358	<0.001	0.172	0.519

CI, confidence intervals; FT3, free triiodothyronine.

brought by COVID-19 has gradually dissipated, but new variants still exist, and the research on long COVID-19 is in the early stages. We hope our research can provide a reference for disease prevention, diagnosis, and treatment.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Hospital of Shanxi Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BW: Visualization, Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. RL: Formal analysis, Data curation, Writing – review & editing, Writing – original draft, Methodology, Investigation. JH: Writing – review & editing, Visualization, Formal analysis, Data curation. YQ: Writing – review & editing, Visualization, Formal analysis, Data curation. BL: Writing – review & editing, Software, Formal analysis, Data curation. HW: Writing – review & editing, Software, Formal analysis, Data curation. ZL: Writing – review & editing, Software, Formal analysis, Data curation. YZ: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. YL: Writing

– review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (Grant numbers 81973378 and 82073909), Shanxi Scholarship Council of China (Grant number:2020-0172), the Shanxi Provincial Central Leading Local Science and Technology Development Fund Project (Grant number: YDZJSX2022A059), Four “Batches” Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province (Grant number:2023XM022).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1342204/full#supplementary-material>

References

1. Müller M, Schefold JC, Guignard V, Exadaktylos AK, Pfortmueller CA. Hyponatraemia is independently associated with in-hospital mortality in patients with pneumonia. *Eur J Intern Med.* (2018) 54:46–52. doi: 10.1016/j.ejim.2018.04.008
2. Potasso L, Sailer CO, Blum CA, Cesana-Nigro N, Schuetz P, Mueller B, et al. Mild to moderate hyponatremia at discharge is associated with increased risk of recurrence in patients with community-acquired pneumonia. *Eur J Intern Med.* (2020) 75:44–9. doi: 10.1016/j.ejim.2019.12.009
3. Tzoulis P, Grossman AB, Baldeweg SE, Bouloux P, Kaltsas G. Management of endocrine disease: dysnatraemia in covid-19: prevalence, prognostic impact, pathophysiology, and management. *Eur J Endocrinol.* (2021) 185:R103–R11. doi: 10.1530/EJE-21-0281
4. Atila C, Monnerat S, Bingisser R, Siegemund M, Lampart M, Rueegg M, et al. Inverse relationship between il-6 and sodium levels in patients with covid-19 and other respiratory tract infections: data from the coviva study. *Endocr Connect.* (2022) 11: e220171. doi: 10.1530/EC-22-0171
5. Palin K, Moreau ML, Sauvans J, Orel H, Nadjar A, Duvoid-Guillou A, et al. Interleukin-6 activates arginine vasopressin neurons in the supraoptic nucleus during immune challenge in rats. *Am J Physiol Endocrinol Metab.* (2009) 296:E1289–E99. doi: 10.1152/ajpendo.90489.2008
6. Govender N, Khaliq O, Moodley J, Naicker T. Unravelling the mechanistic role of ace2 and tmprss2 in hypertension: A risk factor for covid-19. *Curr Hypertens Rev.* (2022) 18:130–7. doi: 10.2174/1573402118666220816090809
7. Zini S, Fournie-Zaluski MC, Chauvel E, Roques BP, Corvol P, Llorens-Cortes C. Identification of metabolic pathways of brain angiotensin ii and iii using specific aminopeptidase inhibitors: predominant role of angiotensin iii in the control of vasopressin release. *Proc Natl Acad Sci U.S.A.* (1996) 93:11968–73. doi: 10.1073/pnas.93.21.11968
8. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating covid-19 from non-covid-19 viral pneumonia at chest ct. *Radiology.* (2020) 296:E46–54. doi: 10.1148/radiol.2020200823
9. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the covid-19 pandemic: A multinational consensus statement from the fleischner society. *Radiology.* (2020) 296:172–80. doi: 10.1148/radiol.2020201365

10. Francone M, Iafra F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest ct score in covid-19 patients: correlation with disease severity and short-term prognosis. *Eur Radiol.* (2020) 30:6808–17. doi: 10.1007/s00330-020-07033-y
11. Elmokadem AH, Mounir AM, Ramadan ZA, Elsedeq M, Saleh GA. Comparison of chest ct severity scoring systems for covid-19. *Eur Radiol.* (2022) 32:3501–12. doi: 10.1007/s00330-021-08432-5
12. Ruiz-Sánchez JG, Núñez-Gil IJ, Cuesta M, Rubio MA, Maroun-Eid C, Arroyo-Espiguero R, et al. Prognostic impact of hyponatremia and hypernatremia in covid-19 pneumonia. A hope-covid-19 (Health outcome predictive evaluation for covid-19) registry analysis. *Front Endocrinol (Lausanne).* (2020) 11:599255. doi: 10.3389/fendo.2020.599255
13. Hirsch JS, Uppal NN, Sharma P, Khanin Y, Shah HH, Malieckal DA, et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with covid-19. *Nephrol Dial Transplant.* (2021) 36:1135–8. doi: 10.1093/ndt/gfab067
14. Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, et al. Chest ct features of covid-19 in rome, Italy. *Radiology.* (2020) 296:E79–85. doi: 10.1148/radiol.2020201237
15. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, et al. Chest ct findings in patients with coronavirus disease 2019 and its relationship with clinical features. *Invest Radiol.* (2020) 55:257–61. doi: 10.1097/RLI.0000000000000670
16. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A unifying approach for gfr estimation: recommendations of the nkf-asn task force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis.* (2022) 79:268–88. doi: 10.1053/j.ajkd.2021.08.003
17. Rondon-Berrios H, Agaba EI, Tzamaloukas AH. Hyponatremia: pathophysiology, classification, manifestations and management. *Int Urol Nephrol.* (2014) 46:2153–65. doi: 10.1007/s11255-014-0839-2
18. Gustafson BA-O, Zhao Y, Milkovits AE, Kamrda ME. Incidence of hyponatremia among critically ill patients with and without covid-19 infection at a community teaching hospital. *J. Intensive Care Med.* (2023) 38:911–6. doi: 10.1177/08850666231170760
19. Frontera JA, Valdes E, Huang J, Lewis A, Lord AS, Zhou T, et al. Prevalence and impact of hyponatremia in patients with coronavirus disease 2019 in new york city. *Crit Care Med.* (2020) 48:e1211–e7. doi: 10.1097/CCM.00000000000004605
20. Anees M, Raza M, Farooq O, Mumtaz A. Risk factors for hyponatremia in covid-19 hospitalised patients. *Pak J Med Sci.* (2023) 39:274–9. doi: 10.12669/pjms.39.1.5466
21. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with covid-19. *J Thromb Haemost.* (2020) 18:1469–72. doi: 10.1111/jth.14848
22. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in covid-19 patients. *Ann Hematol.* (2020) 99:1205–8. doi: 10.1007/s00277-020-04019-0
23. Nardi M, Tomlinson S, Greco MA, Karparkin S. Complement-independent, peroxide-induced antibody lysis of platelets in hiv-1-related immune thrombocytopenia. *Cell.* (2001) 106:551–61. doi: 10.1016/s0092-8674(01)00477-9
24. Ayat P, Alam S, Capric V, Chen J, McFarlane SI. Syndrome of inappropriate secretion of antidiuretic hormone (Siadh) with severe hyponatremia as the initial and sole presentation of covid-19 infection: A case report and pathophysiologic insights. *Cureus.* (2023) 15:e34161. doi: 10.7759/cureus.34161
25. Cuesta M, Slattery D, Goulden EL, Gupta S, Tatro E, Sherlock M, et al. Hyponatraemia in patients with community-acquired pneumonia; prevalence and aetiology, and natural history of siad. *Clin Endocrinol (Oxf).* (2019) 90:744–52. doi: 10.1111/cen.13937
26. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. Covid-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
27. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (Covid-19) in wuhan, China. *Clin Infect Dis.* (2020) 71:762–8. doi: 10.1093/cid/ciaa248
28. Scroggins SM, Sharp LE, Lund JM, Devor EJ, Warrier A, Hamilton WS, et al. Abstract P132: differential and sex dependent expression of vasopressin receptors by B cells, nk cells, and dendritic cells. *Hypertension.* (2019) 74:AP132–AP. doi: 10.1161/hyp.74.suppl_1.P132
29. Berni A, Malandrino D, Parenti G, Maggi M, Poggesi L, Peri A. Hyponatremia, il-6, and sars-cov-2 (Covid-19) infection: may all fit together? *J Endocrinol Invest.* (2020) 43:1137–9. doi: 10.1007/s40618-020-01301-w
30. Guan X, Yao L, Tan Y, Shen Z, Zheng H, Zhou H, et al. Quantitative and semi-quantitative ct assessments of lung lesion burden in covid-19 pneumonia. *Sci Rep.* (2021) 11:5148. doi: 10.1038/s41598-021-84561-7
31. Lyu P, Liu X, Zhang R, Shi L, Gao J. The performance of chest ct in evaluating the clinical severity of covid-19 pneumonia: identifying critical cases based on ct characteristics. *Invest Radiol.* (2020) 55:412–21. doi: 10.1097/RLI.0000000000000689
32. Szabó M, Kardos Z, Kostyál L, Tamáska P, Oláh C, Csányi E, et al. The importance of chest ct severity score and lung ct patterns in risk assessment in covid-19-associated pneumonia: A comparative study. *Front Med (Lausanne).* (2023) 10:1125530. doi: 10.3389/fmed.2023.1125530
33. Hazem M, Ali SI, AlAlwan QM, Al Jabr IK, Alshehri SAF, AlAlwan MQ, et al. Diagnostic performance of the radiological society of north america consensus statement for reporting covid-19 chest ct findings: A revisit. *J Clin Med.* (2023) 12:5180. doi: 10.3390/jcm12165180
34. Pazos-Guerra M, Ruiz-Sánchez JG, Pérez-Candel X, López-Navado C, Hernández-Olmeda F, Cuesta-Hernández M, et al. Inappropriate therapy of euvoletic hyponatremia, the most frequent type of hyponatremia in sars-cov-2 infection, is associated with increased mortality in covid-19 patients. *Front Endocrinol (Lausanne).* (2023) 14:1227059. doi: 10.3389/fendo.2023.1227059
35. Ayus JC, Kalantar-Zadeh K, Tantisattamo E, Rhee CM, Negri AL. Is hyponatremia a novel marker of inflammation in patients with covid-19? *Nephrol Dial Transplant.* (2023) 38:1921–4. doi: 10.1093/ndt/gfad111
36. Fröhlich E, Wahl R. Physiological role and use of thyroid hormone metabolites - potential utility in covid-19 patients. *Front Endocrinol (Lausanne).* (2021) 12:587518. doi: 10.3389/fendo.2021.587518
37. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with covid-19. *J Clin Endocrinol Metab.* (2021) 106:e926–e35. doi: 10.1210/clinem/dgaa813
38. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. Sars-cov-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol.* (2020) 8:739–41. doi: 10.1016/S2213-8587(20)30266-7
39. Khoo B, Tan T, Clarke SA, Mills EG, Patel B, Modi M, et al. Thyroid Function before, During, and after Covid-19. *J Clin Endocrinol Metab.* (2021) 106:e803–e11. doi: 10.1210/clinem/dgaa830
40. Wei L, Sun S, Xu C-H, Zhang J, Xu Y, Zhu H, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol.* (2007) 38:95–102. doi: 10.1016/j.humpath.2006.06.011
41. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. Sars-cov-2 infection: the role of cytokines in covid-19 disease. *Cytokine Growth Factor Rev.* (2020) 54:62–75. doi: 10.1016/j.cytogfr.2020.06.001
42. Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concentrations in severely or critically ill patients with covid-19. *J Endocrinol Invest.* (2021) 44:1031–40. doi: 10.1007/s40618-020-01460-w
43. Wang W, Su X, Ding Y, Fan W, Zhou W, Su J, et al. Thyroid function abnormalities in covid-19 patients. *Front Endocrinol (Lausanne).* (2020) 11:623792. doi: 10.3389/fendo.2020.623792
44. Piekarska A, Góral M, Kozula M, Jawiarczyk-Przybyłowska A, Zawadzka K, Bolanowski M. The influence of sars-cov-2 infection on the thyroid gland. *Biomedicine.* (2023) 11:614. doi: 10.3390/biomedicine11020614
45. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in covid-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev.* (2020) 19:102537. doi: 10.1016/j.autrev.2020.102537
46. Mohammadi B, Dua K, Saghafi M, Singh SK, Heydarifard Z, Zandi M. Covid-19-induced autoimmune thyroiditis: exploring molecular mechanisms. *J Med Virol.* (2023) 95:e29001. doi: 10.1002/jmv.29001
47. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with covid-19: A retrospective study. *Thyroid.* (2021) 31:8–11. doi: 10.1089/thy.2020.0363
48. Van den Berghe G. Non-thyroidal illness in the icu: A syndrome with different faces. *Thyroid.* (2014) 24:1456–65. doi: 10.1089/thy.2014.0201



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Tarik A. A. Elhadd,
Hamad Medical Corporation, Qatar
Anello Marcello Poma,
University of Pisa, Italy

*CORRESPONDENCE

Ke Hu
✉ huke-rmhospital@163.com

[†]These authors have contributed
equally to this work and share
first authorship

RECEIVED 04 April 2024

ACCEPTED 03 July 2024

PUBLISHED 16 July 2024

CITATION

Zhang Q, Zhang Z, Liu X, Wang Y, Chen H,
Hao Y, Zha S, Zhang J, He Y, Zhou B and
Hu K (2024) Thyroid dysfunction in the wake
of Omicron: understanding its role in
COVID-19 severity and mortality.
Front. Endocrinol. 15:1412320.
doi: 10.3389/fendo.2024.1412320

COPYRIGHT

© 2024 Zhang, Zhang, Liu, Wang, Chen, Hao,
Zha, Zhang, He, Zhou and Hu. This is an open-
access article distributed under the terms of
the [Creative Commons Attribution License](#)
(CC BY). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Thyroid dysfunction in the wake of Omicron: understanding its role in COVID-19 severity and mortality

Qingfeng Zhang[†], Zongyue Zhang[†], Xu Liu, Yixuan Wang,
Hao Chen, Yueying Hao, Shiqian Zha, Jingyi Zhang, Yang He,
Beini Zhou and Ke Hu *

Department of Respiratory and Critical Care Medicine, Renmin Hospital of Wuhan University,
Wuhan, China

Purpose: SARS-CoV-2 can invade the thyroid gland. This study was to delineate the risk of thyroid dysfunction amidst the prevalence of the Omicron variant, and to investigate the correlation between thyroid function and Coronavirus disease 2019 (COVID-19) outcomes. The study also aimed to ascertain whether thyroid dysfunction persisted during COVID-19 recovery phase.

Methods: This was a retrospective cohort study. COVID-19 patients from the Renmin Hospital of Wuhan University, China during the epidemic of Omicron variants were included, and their thyroid function were analyzed in groups.

Results: A history of thyroid disease was not associated with COVID-19 outcomes. COVID-19 can lead to a bimodal distribution of thyroid dysfunction. The severity of COVID-19 was inversely proportional to the levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4), leading to a higher prevalence of thyroid dysfunction. Severe COVID-19 was a risk factor for euthyroid sick syndrome (ESS) (OR=22.5, 95% CI, 12.1 - 45.6). Neutrophil to lymphocyte ratio mediated the association between severe COVID-19 and ESS (mediation effect ratio = 41.3%, $p < 0.001$). ESS and decreased indicators of thyroid function were associated with COVID-19 mortality, while high levels of FT3 and FT4 exhibited a protective effect against death. This effect was more significant in women ($p < 0.05$). During the recovery period, hyperthyroidism was quite uncommon, while a small percentage of individuals (7.7%) continued to exhibit hypothyroidism.

Conclusion: COVID-19 severity was linked to thyroid dysfunction. Severe COVID-19 increased the risk of ESS, which was associated with COVID-19 mortality. Post-recovery, hyperthyroidism was rare, but some individuals continued to have hypothyroidism.

KEYWORDS

COVID-19, thyroid dysfunction, hypothyroidism, hyperthyroidism, Omicron variant, euthyroid sick syndrome

Introduction

SARS-CoV-2 is the causative agent in COVID-19 (1). The virus's envelope contains a spike glycoprotein that interacts with the angiotensin-converting enzyme 2 (ACE2) with high specificity and affinity (2). ACE2, a transmembrane protein is found in various organs, including the endocrine system, potentially facilitating the transmission of the virus to these organs. Within the endocrine system, ACE2 is most abundantly present in the testicles, followed by the thyroid and the hypothalamus. The presence of ACE2 in the thyroid renders it a viable target for viral entry (3). Autopsy samples procured from the thyroid gland post-mortem have demonstrated that SARS-CoV-2 can directly infect the thyroid gland, the direct viral insult combined with an intense immune response may trigger or worsen thyroid conditions in predisposed individuals (4, 5).

Thyroid hormones play a pivotal role in regulating the immune system (6). Consequently, COVID-19 could potentially influence thyroid function, and in turn, the state of thyroid function could impact the prognosis of COVID-19.

Existing perspectives suggest that abnormal thyroid function can manifest during the active phase of COVID-19 and persist into the convalescence phase (7). ESS is most prevalent among COVID-19 patients (3) and has been identified as an independent risk factor for disease severity (8). Furthermore, a reduction in FT3 levels has been independently associated with all-cause mortality in patients with severe or critical COVID-19 (9). However, most of the existing research data were collected during the initial phase of the pandemic, when the SARS-CoV-2 variants of concern (VOC) were not yet widespread. Due to the limited sample size, there is a lack of comprehensive studies describing the relationship between COVID-19 and thyroid function. Furthermore, while it is known that both high and low levels of thyroid hormone can be detrimental, no previous studies have explored the non-linear relationship between these hormone levels and the outcomes of COVID-19.

From late 2022 to early 2023, China experienced a pandemic of Omicron variants. Therefore, the aim of this study is to construct a comprehensive map of COVID-19 and thyroid function in a large retrospective cohort during the Omicron variants epidemic.

Materials and methods

Subjects and study design

Our study included 1505 patients admitted to Renmin Hospital of Wuhan University in China from December 15, 2022, to January 25, 2023. All individuals had access to serum FT3, FT4, and TSH concentrations, and were diagnosed with COVID-19. Among them, 111 had pre-existing thyroid conditions, while the remaining 1394 did not. COVID-19 outcomes were compared between these two groups. The 1394 patients without thyroid disease were further categorized into four severity groups (mild, moderate, severe, critical) and two outcome groups (survival, death). Thyroid function and diagnostic categories were compared across these groups. For the longitudinal analysis of thyroid function, we

examined the patient records in our study for any thyroid function tests conducted prior to their COVID-19 diagnosis ('Before COVID-19') and any follow-up thyroid function tests conducted after their initial hospital admission for COVID-19 ('After COVID-19'). The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University, and informed consent was exempted due to its retrospective nature.

COVID-19 diagnosis and severity

A COVID-19 diagnosis is confirmed through a real-time reverse transcriptase polymerase chain reaction (RT-PCR) test, using a nasopharyngeal swab. The severity of the disease is classified into four categories: Mild disease: Characterized by mild clinical symptoms without any evidence of pneumonia on imaging. Moderate disease: Defined by the presence of fever and respiratory symptoms, with imaging revealing signs of pneumonia. Severe disease: Diagnosed if any of the following conditions are met: respiratory rate $\geq 30/\text{min}$, $\text{SpO}_2 \leq 93\%$ at rest, and $>50\%$ progression in 48 hours on imaging. Critical disease: Identified by the occurrence of respiratory failure necessitating mechanical ventilation, shock, or the requirement for admission to an intensive care unit (10).

Thyroid diagnostic categories

All samples were analyzed using the ADVIA 2400 Automatic Biochemical Analyzer from Siemens, Germany. The reagents for the serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) tests were all products of Siemens. Normal ranges are as follows: TSH (0.55-4.78 mIU/L), T3 (2.3-4.2 pg/mL), and T4 (0.89-1.76 ng/dL). Overt hyperthyroidism is defined as a subnormal serum TSH with elevated FT3 and/or FT4. Subclinical hyperthyroidism is defined as a subnormal TSH with normal FT3 and FT4 (11). Overt hypothyroidism is defined as TSH above the reference range and FT3 and/or FT4 below the reference range. Subclinical hypothyroidism is defined by TSH above the reference range and both FT3, FT4 within the normal range (12). Euthyroid sick syndrome (ESS) is characterized by a decreased FT3 and/or FT4 without an increased TSH (8). Euthyroid hyperthyroxinemia/TSH-mediated hyperthyroidism are defined by TSH within or above the reference range and FT3 and/or FT4 above the normal range (11). TSH, FT3, and FT4 are all within the normal range defined as euthyroid.

Statistical analysis

Continuous variables were expressed as median (IQR) and were compared using the Mann-Whitney U test for two-group comparisons and Kruskal-Wallis test for comparisons among four groups. Categorical variables were presented as absolute values (n) or percentages (%) and were analyzed using the chi-square test.

Multivariate logistic regression analyses were conducted to explore the relationships among thyroid disease and outcomes of COVID-19, the severity of COVID-19 and ESS, as well as ESS and mortality. Causal mediation analysis was conducted to examine the relationships between severe/critical COVID-19 and ESS, as well as between severe/critical COVID-19 and mortality. Restricted cubic spline (RCS) analyses were performed to investigate the nonlinear relationships between levels of TSH, FT3, and FT4, and the risk of mortality, separately for males and females. Wilcoxon paired rank sum tests and Friedman test were used for pairwise comparison of TSH, FT3, FT4 in the longitudinal data set. All statistical analyses were performed using R software version 4.3.0 (<http://www.r-project.org>), and double-sided $P < 0.05$ was defined as statistical significance.

Results

Association between thyroid disease and COVID-19

In the cohort, patients had preexisting thyroid disease had a higher proportion of women compared to the group without thyroid disease (80.2% vs 45.0%). However, no significant disparities were observed in the COVID-19 severity and mortality rates between these two groups (Table 1). A multivariate logistic regression analysis revealed that age was risk factor for severe COVID-19 and mortality, while female gender appeared to be a protective factor. A history of thyroid disease, both hyperthyroidism and thyroidectomy/hypothyroidism, did not exhibit any association with the COVID-19 outcomes (Table 2).

Association between COVID-19 severity and thyroid dysfunction

As COVID-19 severity increased, there were corresponding rises in infection indicators like white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), serum amyloid A (SAA), and inflammatory mediators such as interleukin-6 (IL-6) and interleukin-10 (IL-10). Additionally, there was an observed dysfunction in humoral immunity, as indicated by elevated levels of immunoglobulin E (IgE). Conversely, cellular immune function tended to decrease with the severity, as evidenced by lower counts of CD3, CD4, and CD8 T cells. Furthermore, there was a noted decrease in the levels of FT3, FT4, and TSH (Table 3).

Out of the total patients, 687 (49.3%) were euthyroid and 430 (30.8%) were diagnosed with ESS. As COVID-19 severity increased, there was a corresponding increase in the proportions of patients with subclinical hyperthyroidism, hypothyroidism and ESS. Specifically, the prevalence of hypothyroidism was 2.5% in mild cases, 5.0% in moderate cases, 6.5% in severe cases, and 8.7% in critical cases ($p=0.049$). Similarly, the prevalence of ESS was 4.3% in mild cases, 24.4% in moderate cases, 57.3% in severe cases, and 80% in critical cases ($p<0.001$). Interestingly, the proportions of patients

with subclinical hypothyroidism decreased with COVID-19 severity. However, the proportions of hyperthyroidism and euthyroid hyperthyroxinemia/TSH-mediated hyperthyroidism were minimal and remained consistent across all severity groups (Table 4).

After adjusting for age and sex, the severity of COVID-19 was identified as a risk factor for ESS. Specifically, patients with severe COVID-19 were found to be 22.5 times (95% CI, 12.1 – 45.6) more likely to manifest ESS than those with mild COVID-19 (Table 5).

A mediation analysis was performed to explore the potential mediating role of laboratory findings in the relationship between severe/critical COVID-19 and ESS. As depicted in Figure 1A, the NLR was found to significantly mediate this relationship, accounting for 41.3% of the effect ($p < 0.001$). However, no significant mediating effects were detected for IL-6, CD3, and IgE (all $p > 0.05$).

Association between thyroid dysfunction and COVID-19 mortality

As shown in the right section of Table 3, the group of COVID-19 patients who did not survive exhibited higher infection indicators and increased levels of inflammatory mediators compared to the group who survived. Furthermore, the non-survival group displayed compromised cellular immune function and diminished thyroid function. However, no significant differences were noted in the humoral immune function between the two groups, except for a mild increase in IgG levels in the non-survival group.

The group of patients who did not survive had a lower proportion of euthyroidism (8.2% vs 51.6%, $p<0.001$) and a higher incidence of ESS (79.5% vs 28.2%, $p<0.001$) compared to the group who survived. Interestingly, the survival group had a higher proportion of subclinical hyperthyroidism (7.6% vs 1.4%,

TABLE 1 Comparative clinical characteristics of groups without and with a history of thyroid disease*.

Variables	Without thyroid disease (n = 1394)	Thyroid disease (n = 111)	P value
Age, year	67 (55, 76)	64 (55, 72)	0.308
Female, n (%)	627 (45.0)	89 (80.2)	< 0.001
COVID-19 severity			
Mild, n (%)	278 (19.9)	20 (18.0)	0.240
Moderate, n (%)	753 (54.0)	70 (63.1)	
Severe, n (%)	248 (17.8)	16 (14.4)	
Critical, n (%)	115 (8.2)	5 (4.5)	
Death, n (%)	73 (5.2)	3 (2.7)	0.241

*Categorical data shown as number (percentage). Continuous variables displayed as median (interquartile range). COVID-19, coronavirus disease 2019.

TABLE 2 Multivariate logistic regression analysis for risk of severe/critical COVID-19 and death.

Variables	Severe/critical COVID-19		Death	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.06 (1.05 - 1.07)	< 0.001	1.06 (1.04 - 1.08)	< 0.001
Female	0.52 (0.40 - 0.68)	< 0.001	0.55 (0.32 - 0.93)	0.025
Thyroid disease	0.89 (0.50 - 1.50)	0.659	0.68 (0.15 - 2.05)	0.534
Undergone thyroidectomy or hypothyroidism	0.82 (0.43 - 1.46)	0.514	0.87 (0.19 - 2.65)	0.830
Hyperthyroidism	1.24 (0.35 - 3.82)	0.718	NA	0.982

OR, odds ratio; CI, confidence interval; NA, not available.

TABLE 3 Demographic characteristics and laboratory findings across various severity levels and outcomes of COVID-19*.

Variables	Total	COVID-19 severity					Survival status		
		Mild (n = 278)	Moderate (n = 753)	Severe (n = 248)	Critical (n = 115)	P value	Survival (n = 1321)	Death (n = 73)	P value
Age, year	1394	53 (37, 65)	66 (56, 74)	74 (66, 82)	78 (68, 84)	< 0.001	66 (54, 75)	79 (68, 84)	< 0.001
Female, n (%)	1394	137 (49.3)	369 (49.0)	79 (31.9)	42 (36.5)	< 0.001	604 (46)	23 (32)	0.017
FT3, pg/mL	1394	3.09 (2.74, 3.51)	2.69 (2.29, 3.09)	2.12 (1.80, 2.46)	1.79 (1.40, 2.08)	< 0.001	2.65 (2.17, 3.11)	1.85 (1.35, 2.14)	< 0.001
FT4, ng/dL	1394	1.21 (1.08, 1.34)	1.18 (1.04, 1.33)	1.19 (1.08, 1.36)	1.07 (0.91, 1.25)	< 0.001	1.19 (1.05, 1.33)	1.10 (0.94, 1.29)	0.006
TSH, uIU/mL	1394	1.636 (1.069, 2.689)	1.588 (0.838, 2.751)	0.876 (0.422, 2.154)	0.696 (0.387, 1.959)	< 0.001	1.472 (0.735, 2.680)	0.696 (0.337, 1.682)	< 0.001
WBC, 10 ⁹ /L	1389	5.52 (4.23, 6.87)	5.60 (4.19, 7.45)	6.89 (4.46, 9.48)	8.81 (5.86, 12.65)	< 0.001	5.76 (4.26, 7.64)	9.14 (5.70, 12.73)	< 0.001
N, 10 ⁹ /L	1386	3.19 (2.40, 4.53)	3.70 (2.54, 5.15)	5.15 (3.23, 7.83)	6.84 (4.36, 11.02)	< 0.001	3.79 (2.61, 5.54)	7.75 (4.25, 11.17)	< 0.001
L, 10 ⁹ /L	1385	1.42 (0.99, 1.86)	1.14 (0.79, 1.55)	0.80 (0.53, 1.18)	0.62 (0.38, 0.89)	< 0.001	1.12 (0.74, 1.56)	0.62 (0.37, 0.83)	< 0.001
NLR	1382	2.33 (1.51, 3.84)	3.16 (2.01, 5.09)	5.94 (3.81, 10.98)	12.78 (6.06, 22.17)	< 0.001	3.36 (2.03, 6)	13.41 (6, 23.92)	< 0.001
CRP, mg/L	968	1.32 (0.50, 8.04)	8.49 (0.71, 31.14)	34.18 (9.37, 75.25)	79.04 (36.22, 120.99)	< 0.001	10.57 (1.07, 42.32)	88.61 (36.28, 141.33)	< 0.001
SAA, mg/L	464	5.60 (5, 27.67)	34.95 (5, 160.78)	152.67 (40.71, 300)	295.42 (100.14, 300)	< 0.001	58.83 (7.31, 248.87)	290.22 (88.66, 300)	< 0.001
ESR, mm/h	111	11 (8, 18)	27 (19, 43)	36 (22, 52)	40 (21, 70)	0.003	27 (18, 48)	36 (18, 66)	0.487
IL-2, pg/mL	222	2.60 (2.35, 2.93)	2.71 (2.43, 3.22)	2.89 (2.30, 3.35)	2.79 (2.42, 3.48)	0.690	2.73 (2.39, 3.22)	2.81 (2.47, 3.62)	0.219
IL-4, pg/mL	222	5.39 (4.71, 5.64)	4.80 (4.38, 5.24)	4.77 (4.35, 5.18)	4.85 (4.53, 5.33)	0.267	4.82 (4.42, 5.27)	4.65 (4.12, 5.29)	0.566
IL-6, pg/mL	224	12.39 (8.21, 25.40)	12.00 (6.07, 35.24)	17.25 (8.40, 54.12)	64.79 (22.15, 186.20)	< 0.001	14.06 (7.31, 45.33)	70.41 (27.15, 269.50)	< 0.001
IL-10, pg/mL	223	5.00 (4.43, 5.17)	5.35 (4.07, 7.45)	5.83 (4.67, 7.91)	8.83 (5.62, 14.21)	< 0.001	5.45 (4.43, 7.66)	9.49 (5.58, 15.89)	0.001
TNF, pg/mL	222	3.45 (2.97, 3.97)	3.60 (2.87, 4.87)	3.30 (2.85, 4.39)	3.12 (2.65, 4.29)	0.488	3.44 (2.84, 4.54)	3.07 (2.63, 4.31)	0.354
IFN, pg/mL	223	2.62 (2.44, 4.47)	2.77 (2.25, 4.04)	2.82 (2.41, 3.97)	2.94 (2.29, 4.58)	0.870	2.76 (2.31, 4.09)	3.19 (2.29, 4.41)	0.386
IL-17, pg/mL	200	2.54 (1.87, 3.69)	2.68 (2.15, 3.89)	2.81 (1.90, 4.66)	2.99 (2.14, 4.70)	0.736	2.68 (2.01, 4.27)	3.37 (2.43, 4.47)	0.262
CD3, n/uL	189	856 (612, 902)	655 (411, 1023)	470 (252, 614)	286 (160, 476)	< 0.001	598 (357, 942)	245 (143, 400)	< 0.001
CD4, n/uL	188	531 (352, 616)	383 (239, 593)	237 (140, 406)	156 (95, 242)	< 0.001	353 (190, 578)	145 (82, 214)	< 0.001
CD8, n/uL	188	276 (196, 413)	234 (142, 389)	156 (93, 304)	102 (65, 155)	< 0.001	202 (132, 353)	89 (62, 148)	< 0.001

(Continued)

TABLE 3 Continued

Variables	Total	COVID-19 severity					Survival status		
		Mild (n = 278)	Moderate (n = 753)	Severe (n = 248)	Critical (n = 115)	P value	Survival (n = 1321)	Death (n = 73)	P value
CD4/CD8	187	1.53 (1.28, 2.11)	1.60 (1.03, 2.40)	1.61 (1.10, 2.36)	1.64 (0.93, 2.81)	0.986	1.61 (1.03, 2.37)	1.42 (0.93, 2.55)	0.722
CD19, n/uL	188	118 (61, 240)	99 (57, 219)	91 (47, 193)	83 (41, 140)	0.350	97 (56, 215)	68 (41, 137)	0.090
CD16+CD56, n/uL	188	163 (81, 208)	134 (86, 227)	110 (69, 202)	102 (55, 169)	0.065	129 (82, 209)	101 (40, 179)	0.041
IgG, g/L	154	10.19 (7.60, 12.13)	10.40 (8.67, 13.15)	12.05 (9.51, 14.98)	12.10 (9.04, 14.55)	0.126	10.60 (8.67, 13.50)	13.00 (11.85, 14.40)	0.019
IgM, g/L	155	0.95 (0.76, 1.64)	0.95 (0.68, 1.18)	0.64 (0.53, 1.02)	0.96 (0.70, 1.30)	0.035	0.85 (0.63, 1.21)	0.96 (0.71, 1.30)	0.378
IgA, g/L	155	2.12 (1.11, 2.78)	2.15 (1.55, 2.70)	2.92 (1.93, 3.52)	1.69 (1.22, 2.54)	0.023	2.23 (1.55, 2.88)	1.58 (1.18, 2.50)	0.179
IgE, IU/mL	156	25.9 (18.4, 93.7)	40.4 (18.4, 116.0)	130 (29.6, 678.0)	73.3 (22.1, 252.0)	0.012	52.7 (18.4, 176.0)	67.7 (18.4, 246.0)	0.834
C3, g/L	154	0.801 (0.758, 0.967)	0.854 (0.710, 1.040)	0.887 (0.710, 1.123)	0.788 (0.612, 0.897)	0.261	0.852 (0.705, 1.040)	0.780 (0.590, 0.955)	0.169
C4, g/L	153	0.199 (0.174, 0.229)	0.226 (0.184, 0.293)	0.236 (0.181, 0.338)	0.211 (0.159, 0.250)	0.147	0.226 (0.179, 0.293)	0.208 (0.151, 0.235)	0.113

*Categorical data shown as number (percentage). Continuous variables displayed as median (interquartile range). COVID-19, coronavirus disease 2019; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell; N, neutrophil; L, lymphocyte; NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein; SAA, serum amyloid A; ESR, erythrocyte sedimentation rate; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; TNF, tumor necrosis factor; IFN, interferon; IL-17, interleukin-17; CD3, cluster of differentiation 3; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CD19, cluster of differentiation 19; CD16, cluster of differentiation 16; CD56, cluster of differentiation 56; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; IgE, immunoglobulin E; C3, complement component 3; C4, complement component 4.

p=0.047). No significant differences were observed in other types of thyroid dysfunction between the two groups (Table 4).

After adjusting for age and sex, ESS was identified as a risk factor for COVID-19 mortality (OR = 7.30, 95% CI, 4.10 – 13.8) (Table 5). As depicted in Figure 1B, ESS was found to significantly mediate the relationship between severe/critical COVID-19 and death, accounting for 14.4% of the effect (p = 0.002).

To investigated the relationship between thyroid function indicators and mortality due to COVID-19, RCS nonlinear correlation curves were constructed separately for male and female populations. These curves reflected the individual correlations between TSH, FT3, FT4, and COVID-19 mortality. In both male and female populations, decreased levels of TSH, FT3, and FT4 (though FT4 was not significant in women) were associated with an increased risk of death from COVID-19. Interestingly, high levels of FT3 were found to have a protective effect against death in both male and female populations, as well as high levels of FT4 in women (Figure 2).

Thyroid function across different time points

Of 1394 patients without prior thyroid disease, thyroid function tests were available for 411 patients before COVID-19 and for 234 survivors during their convalescence. As depicted in the left section (A, C, E) of Figure 3, both TSH and FT3 levels at the time of COVID-19 admission were significantly lower than their respective baseline values, while FT4 levels were significantly higher (all p

<0.05). Conversely, the right section (B, D, F) of Figure 3 shows that during the recovery period, both TSH and FT3 levels were significantly higher than those at admission, while FT4 levels were significantly lower (all p <0.05).

During the recovery phase from COVID-19, with a median follow-up of 47 days (ranging from 21 to 98 days), the majority of survivors (70.1%) exhibited euthyroidism. Hyperthyroxinemia and subclinical hyperthyroidism were very rare, with no cases of overt hyperthyroidism observed. However, a small proportion of patients still exhibited ESS (6.8%), hypothyroidism (7.7%), and subclinical hypothyroidism (12.4%) (Table 6).

A subset of 164 patients with complete sets of T3, T4, and TSH measurements taken at three distinct time points: before, during, and after COVID-19. These trends were visually represented in Figure 4. The data showed that both FT3 and TSH levels initially decreased upon admission, but eventually returned to their baseline levels during the recovery phase. In contrast, FT4 levels remained relatively stable, with no significant change observed (p = 0.639).

Discussion

In this study, we found that a prior history of thyroid disease, encompassing both hyperthyroidism and thyroidectomy/hypothyroidism, did not impact the prognosis of COVID-19 during the Omicron variant outbreak. A previous retrospective cohort study involving 3703 COVID-19 patients revealed that 6.8% had pre-existing hypothyroidism. This condition was not associated with an increased risk of hospitalization or mortality (13). But, a

TABLE 4 Thyroid diagnostic categories across various severity levels and outcomes of COVID-19*.

Variables	Total (1394)	COVID-19 severity					Survival status		
		Mild (n = 278)	Moderate (n = 753)	Severe (n = 248)	Critical (n = 115)	P value	Survival (n = 1321)	Death (n = 73)	P value
Euthyroid	687 (49.3)	227 (81.7)	408 (54.2)	47 (19.0)	5 (4.3)	< 0.001	681 (51.6)	6 (8.2)	< 0.001
Hyperthyroid	15 (1.1)	2 (0.7)	8 (1.1)	3 (1.2)	2 (1.7)	0.772	14 (1.1)	1 (1.4)	0.556
Subclinical hyperthyroid	101 (7.2)	17 (6.1)	50 (6.6)	30 (12.1)	4 (3.5)	0.007	100 (7.6)	1 (1.4)	0.047
Hypothyroid	71 (5.1)	7 (2.5)	38 (5.0)	16 (6.5)	10 (8.7)	0.049	65 (4.9)	6 (8.2)	0.264
Subclinical hypothyroid	70 (5.0)	9 (3.2)	52 (6.9)	7 (2.8)	2 (1.7)	0.006	69 (5.2)	1 (1.4)	0.175
ESS	430 (30.8)	12 (4.3)	184 (24.4)	142 (57.3)	92 (80)	< 0.001	372 (28.2)	58 (79.5)	< 0.001
Euthyroid hyperthyroxinemia/ TSH- mediated hyperthyroidism	20 (1.4)	4 (1.4)	13 (1.7)	3 (1.2)	0 (0)	0.662	20 (1.5)	0 (0)	0.620

*Categorical data shown as number (percentage).
COVID-19, coronavirus disease 2019; ESS, euthyroid sick syndrome; TSH, thyroid-stimulating hormone.

recent study has identified the absence of a history of hyperthyroidism as a protective factor against COVID-19 mortality (14). It's crucial to underscore that in our cohort, among those with a history of thyroid disease, a mere 16 individuals (14.4%) had hyperthyroidism, while the majority 95 individuals (85.6%) had undergone thyroidectomy or were hypothyroidism (not reflected in the tables). Therefore, the conclusions of this study align with those of previous research.

We underscored that COVID-19 severity was inversely related to the plasma levels of TSH, FT3, and FT4, thereby increasing the risk of hypothyroidism and ESS. A meta-analysis encompassing 565 samples from 6 studies revealed that the severe COVID-19 group exhibited significantly lower TSH and FT3 levels compared to the mild group. However, no significant differences were observed in FT4 levels between the groups (15). The variations in FT4 levels observed in our study can be attributed to a more detailed classification of COVID-19 severity. Notably, only the decrease in FT4 levels in critically ill patients reached statistical significance. A recent meta-analysis found that among COVID-19 patients, ESS was the most prevalent thyroid disease with a pooled prevalence of 26%, followed by thyrotoxicosis and hypothyroidism, with pooled prevalences of 10% and 3%, respectively (3). In contrast, our study observed a different pattern. ESS had an incidence of 30.8%, and hypothyroidism was more prevalent than in the meta-analysis. The rate of hyperthyroidism was notably lower at 1.1%. This discrepancy in the prevalence of hyperthyroidism and hypothyroidism may be a characteristic of the Omicron variant infection. Further exploration revealed that COVID-19 severity independently contributes to the risk of ESS. Interestingly, the impact of severe COVID-19 on ESS appeared to be partially mediated through the NLR (mediation effect ratio = 41.3%). Studies have shown that neutrophils exhibited continuous basal hyperactivation in the peripheral circulating blood of COVID-19

patients, which was associated with vascular endothelial injury (16). Neutrophils played a crucial role in the progression of COVID-19 through various mechanisms, including cytokine storms, tissue injury, and thrombotic events (17). In infected thyroid tissues, infiltrates of innate immune cells (macrophages and polymorphonuclear neutrophils) were prevalent (5). In fact, a high NLR was associated with severe COVID-19 and poor prognosis (18). In the context of SARS-CoV-2 infection, it's currently understood that the immune system may become hyperactive, potentially leading to the development and

TABLE 5 Multivariate logistic regression analysis for risk of ESS and death.

Variables	OR (95% CI)	P value
Multivariate logistic regression for ESS		
Age	1.01 (1.00 - 1.02)	0.006
Female	0.82 (0.63 - 1.07)	0.143
COVID-19 severity		< 0.001
Mild	reference	
Moderate	6.16 (3.46 - 12.0)	
Severe	22.5 (12.1 - 45.6)	
Critical	66.8 (32.2 - 150)	
Multivariate logistic regression for Death		
Age	1.04 (1.02 - 1.06)	< 0.001
Female	0.70 (0.41 - 1.18)	0.188
ESS	7.30 (4.10 - 13.8)	< 0.001

OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ESS, euthyroid sick syndrome.

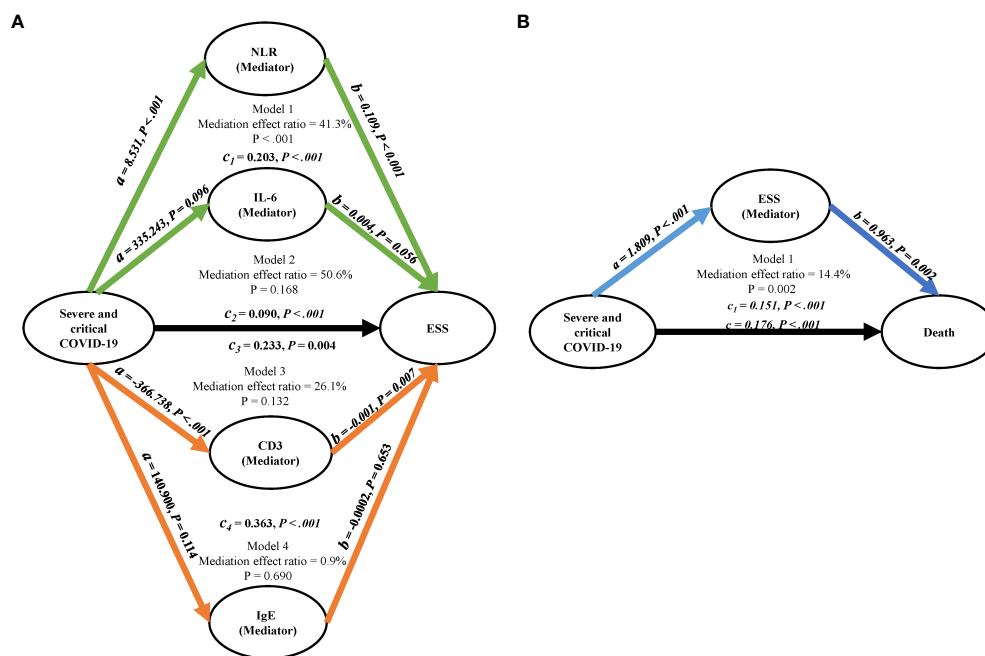


FIGURE 1

Mediation analysis diagrams. (A) Represents the mediation factors NLR, IL-6, CD3, and IgE in the relationship between severe/critical COVID-19 and ESS. (B) Illustrates ESS as the mediating factor in the relationship between severe/critical COVID-19 and death; Adjusted for age and gender. COVID-19, coronavirus disease 2019; NLR, neutrophil to lymphocyte ratio; CD3, cluster of differentiation 3; IgE, immunoglobulin E; ESS, euthyroid sick syndrome.

progression of autoimmune thyroid diseases. This phenomenon might be attributed to abnormal responses of T-cell subtypes, the presence of autoantibodies, and an overproduction of inflammatory cytokines, specifically IL-6, IFN- γ , and TNF- α (19). Our study did observe an increase in the level of inflammatory factors, depletion of

cellular immunity, and disorder of humoral immunity with the severity of COVID-19. However, these findings may be limited by the number of patients tested. The roles of IL-6, CD3, and IgE as mediating factors of severe COVID-19 and ESS were not found to be significant.

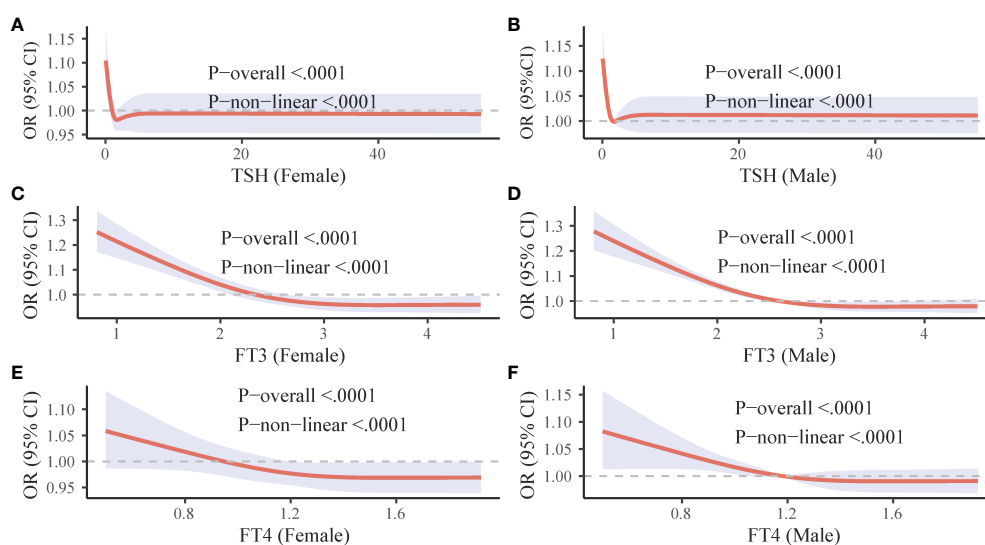
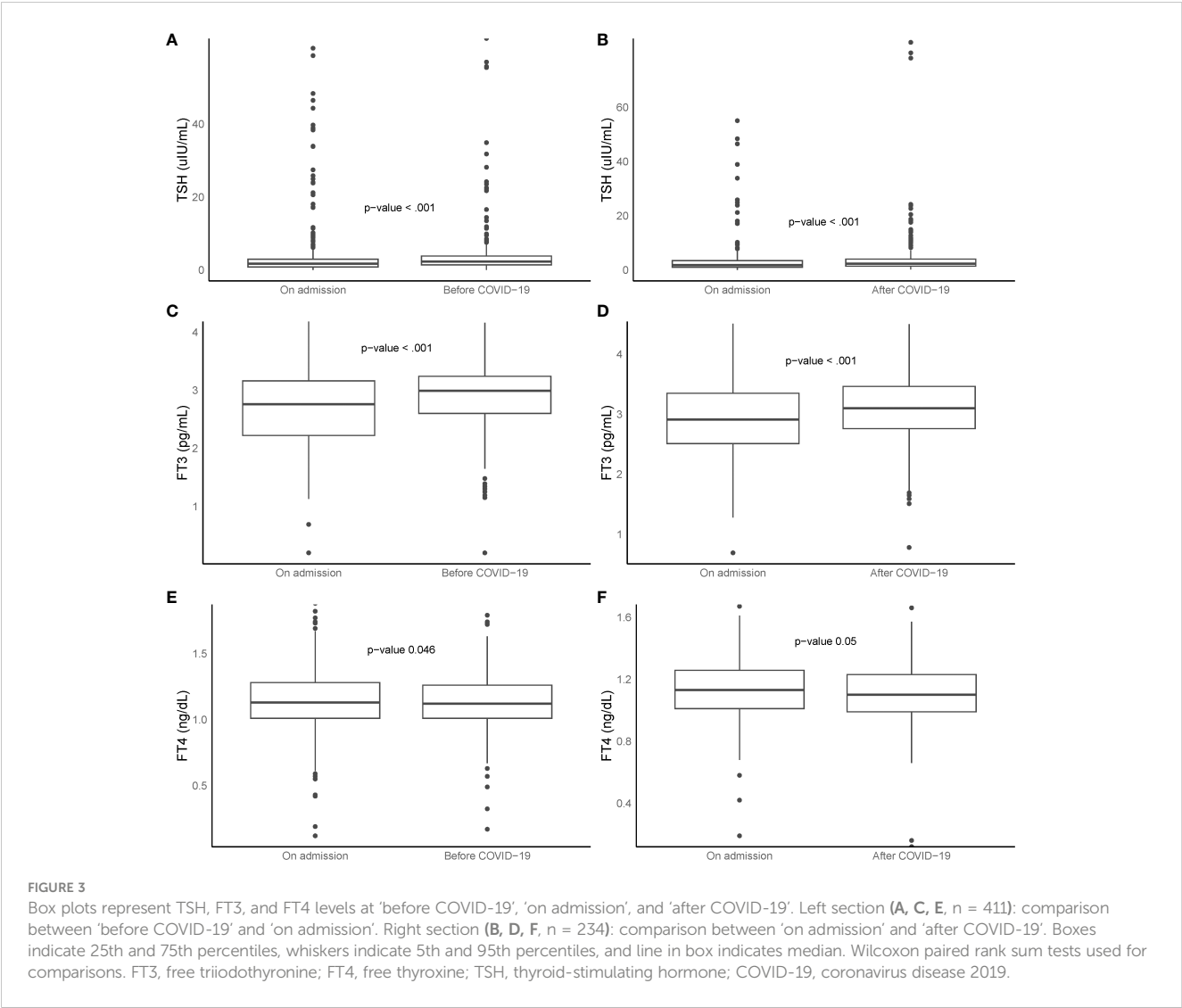


FIGURE 2

Gender-specific RCS curves for thyroid hormone levels and COVID-19 mortality. The figure is divided into six panels. (A, C, and E (left column) illustrate the association between TSH, FT3, and FT4 levels respectively, and COVID-19 mortality in females. (B, D, and F (right column) depict the corresponding associations in males. OR, odds ratio; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.



Although a history of thyroid disease was not found to be associated with COVID-19 outcomes, this study discovered a correlation between thyroid dysfunction resulting from COVID-19 and an increased risk of mortality. Our findings confirmed that ESS was a risk factor for death from COVID-19, and that the high mortality rate of severe COVID-19 could be partially attributed to ESS, with a mediation effect ratio of 14.4%. ESS was typically associated with the severity of the disease and a deteriorating prognosis in critical illnesses. Consistent with previous studies, ESS was associated with severe disease and death from COVID-19, and was considered an early and reliable indicator of poor prognosis for COVID-19 (8, 20). Our study further demonstrated through the RCS curve that across all populations, low TSH and low FT3 increased the risk of death from COVID-19, while high FT3 appeared to have a protective effect. Many previous studies have also observed that low FT3 was more common in patients who died from COVID-19. Low FT3 was associated with excessive inflammation, coagulation, and disorders of the fibrinolytic system, making low FT3 status a risk factor for death (20–23). FT3 was considered to prevent early tissue hypoxia during sepsis, potentially reducing secondary organ failure

(24). An ongoing randomized placebo-controlled clinical trial (NCT04348513) aims to investigate whether the administration of T3 (liothyronine, 0.8 g/kg i.v.) to ICU-admitted COVID-19 patients reduces their need for cardiorespiratory support (25). This suggests

TABLE 6 Thyroid function during COVID-19 convalescence*.

Variables	After COVID-19 (n = 234)
Follow-up time, days	47 (21, 98)
FT3, pg/mL	3.10 (2.75, 3.46)
FT4, ng/dL	1.10 (0.99, 1.23)
TSH, uIU/mL	2.360 (1.418, 4.083)
Euthyroid, n (%)	164 (70.1)
Hyperthyroid, n (%)	0 (0)

(Continued)

TABLE 6 Continued

Variables	After COVID-19 (n = 234)
Subclinical hyperthyroid, n (%)	4 (1.7)
Hypothyroid, n (%)	18 (7.7)
Subclinical hypothyroid, n (%)	29 (12.4)
ESS, n (%)	16 (6.8)
Euthyroid hyperthyroxinemia/TSH-mediated hyperthyroidism, n (%)	3 (1.3)

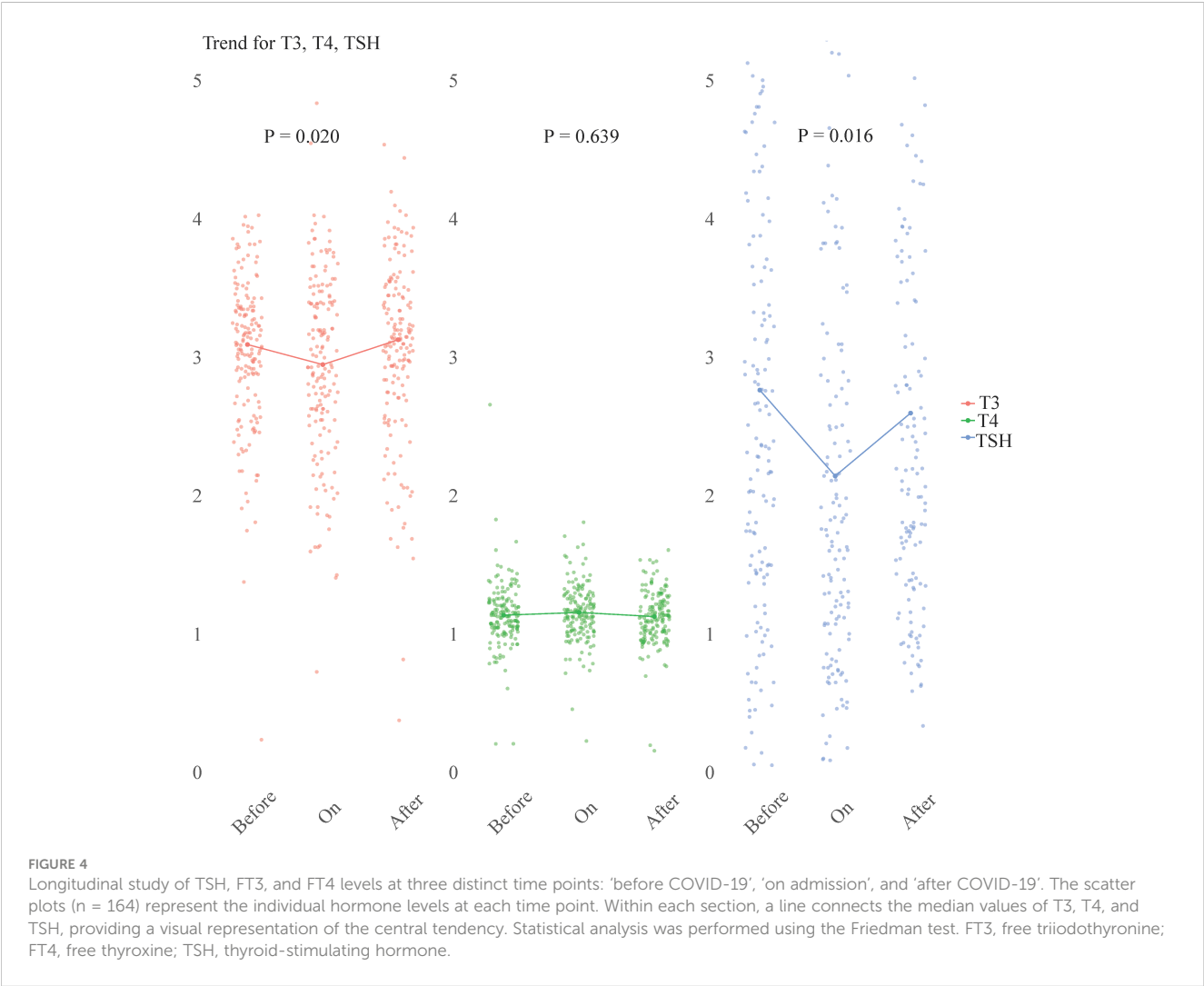
*Categorical data shown as number (percentage). Continuous variables displayed as median (interquartile range).
COVID-19, coronavirus disease 2019; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ESS, euthyroid sick syndrome.

that our nonlinear model provided a more comprehensive description of the relationship between thyroid hormones and COVID-19 mortality. It's important to note that the effects of FT3 and FT4 may differ between genders, and the protective effects of FT3 and FT4 may be more pronounced in women. This nuanced understanding of the role of thyroid hormones in COVID-19

outcomes underscores the complexity of this disease and the need for further research.

In paired analysis, we observed that the thyroid function in COVID-19 patients typically decreased upon admission and subsequently returned to baseline during the recovery phase. This observation aligned with previous research, which found that in follow-up studies of COVID-19 survivors, 82.4% (42 out of 51) of abnormal thyroid function tests observed during acute phase of COVID-19 resolved over a span of 6 months (26). Additionally, after a period of 3 or 4 months, COVID-19 patients who underwent pulmonary rehabilitation exhibited an increase in FT3 values (27). Moreover, the thyroid structure also demonstrated spontaneous recovery over time, with 85.7% (6 of 7) patients showing resolved features of thyroiditis after 4 months (28). However, it's crucial to remain cognizant of the fact that some individuals may continue to experience hypothyroidism.

Our study presents distinct advantages. The substantial sample size of the cohort we included was ample to unveil, for the first time, a comprehensive association between COVID-19 and thyroid function during the Omicron pandemic. However, our research also has its limitations. Firstly, our study lacks data on thyroid autoantibodies and thyroid ultrasound, and does not address the



development of autoimmune conditions post COVID-19. Secondly, this study did not collect information on the underlying disease status and treatment status of COVID-19 patients, with only age and gender employed as confounding factors for analysis and exclusion. It has been demonstrated that obesity is strongly associated with COVID-19 severity and poor outcome, yet our study lacks data on body mass index. Lastly, our study is not prospective and thus cannot establish a definitive causal relationship between COVID-19 and thyroid function.

Conclusion

Our study delineates a reciprocal relationship between COVID-19 and thyroid function during the Omicron variant pandemic. COVID-19 can detrimentally impact thyroid function, leading to a bimodal distribution of thyroid dysfunction. Inflammation mediates the effects of COVID-19 on ESS, and ESS partially mediates mortality from severe COVID-19. Decreased thyroid function increases the risk of death from COVID-19, while elevated FT3 and FT4 levels appear to confer a protective effect, especially in women. Additionally, there remains a risk of hypothyroidism during the recovery phase from COVID-19. These findings underscore the importance of monitoring thyroid function in COVID-19 patients and highlight the potential therapeutic implications of managing thyroid hormone levels during both treatment and recovery phases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Renmin Hospital of Wuhan University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because in accordance with standard research protocols, retrospective studies are typically exempt from the requirement of obtaining written informed consent. This is due to the fact that these studies utilize existing data and do not involve direct interaction with the participants or alterations to their behavior.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382(8):727–33. doi: 10.1056/NEJMoa2001017
2. Bakhshandeh B, Jahanafrooz Z, Abbasi A, Goli MB, Sadeghi M, Mottaqi MS, et al. Mutations in SARS-CoV-2; Consequences in structure, function, and pathogenicity of the virus. *Microb Pathog.* (2021) 154:104831. doi: 10.1016/j.micpath.2021.104831

Author contributions

QZ: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. ZZ: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. XL: Writing – review & editing, Resources, Formal analysis. YW: Writing – review & editing, Resources, Formal analysis. HC: Writing – original draft, Formal analysis, Data curation, Conceptualization. YYH: Writing – original draft, Formal analysis, Data curation, Conceptualization. SZ: Writing – original draft, Formal analysis, Data curation, Conceptualization. JZ: Writing – review & editing, Formal analysis. YH: Writing – review & editing, Formal analysis. BZ: Writing – review & editing, Formal analysis. KH: Writing – review & editing, Supervision, Methodology.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by grants from the National Natural Science Foundation of China (82270101), and the Science and technology key project on novel coronavirus pneumonia of Hubei province, China (2020FCA002).

Acknowledgments

The authors thank all participants included in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

3. Ashrafi S, Hatami H, Bidhendi-Yarandi R, Panahi MH. The prevalence of thyroid disorders in COVID-19 patients: a systematic review and meta-analysis. *BMC Endocr Disord.* (2024) 24(1):5. doi: 10.1186/s12902-023-01534-9
4. Macedo S, Pestana A, Santos L, Neves C, Guimarães S, Duarte-Neto A, et al. Detection of SARS-CoV-2 infection in thyroid follicular cells from a COVID-19 autopsy series. *Eur Thyroid J.* (2022) 11(4):e220074. doi: 10.1530/etj-22-0074
5. Poma AM, Basolo A, Bonuccelli D, Proietti A, Macerola E, Ugolini C, et al. Activation of type I and type II interferon signaling in SARS-CoV-2-positive thyroid tissue of patients dying from COVID-19. *Thyroid.* (2021) 31(12):1766–75. doi: 10.1089/thy.2021.0345
6. De Vito P, Incerpi S, Pedersen JZ, Luly P, Davis FB, Davis PJ. Thyroid hormones as modulators of immune activities at the cellular level. *Thyroid.* (2011) 21(8):879–90. doi: 10.1089/thy.2010.0429
7. Rossetti CL, Cazarin J, Hecht F, Beltrão FEL, Ferreira ACF, Fortunato RS, et al. COVID-19 and thyroid function: What do we know so far? *Front Endocrinol (Lausanne).* (2022) 13:1041676. doi: 10.3389/fendo.2022.1041676
8. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. *Front Endocrinol (Lausanne).* (2020) 11:566439. doi: 10.3389/fendo.2020.566439
9. Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. *J Endocrinol Invest.* (2021) 44(5):1031–40. doi: 10.1007/s40618-020-01460-w
10. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. *J Clin Endocrinol Metab.* (2021) 106(2):e926–35. doi: 10.1210/clinem/dgaa813
11. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* (2016) 26(10):1343–421. doi: 10.1089/thy.2016.0229
12. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet.* (2017) 390(10101):1550–62. doi: 10.1016/s0140-6736(17)30703-1
13. van Gerwen M, Alsen M, Little C, Barlow J, Naymagon L, Tremblay D, et al. Outcomes of patients with hypothyroidism and COVID-19: A retrospective cohort study. *Front Endocrinol (Lausanne).* (2020) 11:565. doi: 10.3389/fendo.2020.00565
14. Carvalho VP, Pontes JPP, Neto DRB, Borges CER, Campos GRL, Ribeiro HLS, et al. Mortality and associated factors in patients with COVID-19: cross-sectional study. *Vaccines (Basel).* (2022) 11(1):71. doi: 10.3390/vaccines11010071
15. Wei J, Zhang F. Effects of SARS-CoV-2 infection on hypothyroidism and subclinical hypothyroidism: a meta-analysis. *Front Endocrinol (Lausanne).* (2023) 14:1291774. doi: 10.3389/fendo.2023.1291774
16. Loyer C, Lapostolle A, Urbina T, Elabbadi A, Lavillegrand JR, Chaigneau T, et al. Impairment of neutrophil functions and homeostasis in COVID-19 patients: association with disease severity. *Crit Care.* (2022) 26(1):155. doi: 10.1186/s13054-022-04002-3
17. Li J, Zhang K, Zhang Y, Gu Z, Huang C. Neutrophils in COVID-19: recent insights and advances. *Virol J.* (2023) 20(1):169. doi: 10.1186/s12985-023-02116-w
18. Higaki A, Okayama H, Homma Y, Sano T, Kitai T, Yonetsu T, et al. Predictive value of neutrophil-to-lymphocyte ratio for the fatality of COVID-19 patients complicated with cardiovascular diseases and/or risk factors. *Sci Rep.* (2022) 12(1):13606. doi: 10.1038/s41598-022-17567-4
19. Mohammadi B, Dua K, Saghaei M, Singh SK, Heydarifard Z, Zandi M, et al. COVID-19-induced autoimmune thyroiditis: Exploring molecular mechanisms. *J Med Virol.* (2023) 95(8):e29001. doi: 10.1002/jmv.29001
20. Sparano C, Zago E, Moretti A, Nozzoli C, Yannas D, Adornato V, et al. Euthyroid sick syndrome as an early surrogate marker of poor outcome in mild SARS-CoV-2 disease. *J Endocrinol Invest.* (2022) 45(4):837–47. doi: 10.1007/s40618-021-01714-1
21. Lang S, Liu Y, Qu X, Lu R, Fu W, Zhang W, et al. Association between thyroid function and prognosis of COVID-19: A retrospective observational study. *Endocr Res.* (2021) 46(4):170–7. doi: 10.1080/07435800.2021.1924770
22. Colonnello E, Criniti A, Lorusso E, Curreli M, Santulli M, Angeloni A, et al. Thyroid hormones and platelet activation in COVID-19 patients. *J Endocrinol Invest.* (2023) 46(2):261–9. doi: 10.1007/s40618-022-01896-2
23. Deng J, Zhang S, Peng F, Zhang Q, Li Y, Zhong Y. The association between FT3 with the outcome and inflammation/coagulopathy/fibrinolysis of COVID-19. *Front Endocrinol (Lausanne).* (2022) 13:877010. doi: 10.3389/fendo.2022.877010
24. Loubopoulos AI, Mourouzis IS, Trikas AG, Tseti IK, Pantos CI. Effects of thyroid hormone on tissue hypoxia: relevance to sepsis therapy. *J Clin Med.* (2021) 10(24):5855. doi: 10.3390/jcm10245855
25. Pantos C, Kostopanagiotou G, Armaganidis A, Trikas A, Tseti I, Mourouzis I. Triiodothyronine for the treatment of critically ill patients with COVID-19 infection: A structured summary of a study protocol for a randomised controlled trial. *Trials.* (2020) 21(1):573. doi: 10.1186/s13063-020-04474-0
26. Lui DTW, Tsoi KH, Lee CH, Cheung CYY, Fong CHY, Lee ACH, et al. A prospective follow-up on thyroid function, thyroid autoimmunity and long COVID among 250 COVID-19 survivors. *Endocrine.* (2023) 80(2):380–91. doi: 10.1007/s12020-022-03281-8
27. Croce L, Zampogna E, Coperchini F, Costa P, Pignatti P, Visca D, et al. Thyroid hormones modifications among COVID-19 patients undergoing pulmonary rehabilitation. *Front Endocrinol (Lausanne).* (2023) 14:1192561. doi: 10.3389/fendo.2023.1192561
28. Fung MHM, Lui DTW, Chiu KWH, Lee SH, Lee CH, Chow WS, et al. A prospective follow-up of thyroid volume and thyroiditis features on ultrasonography among survivors of predominantly mild to moderate COVID-19. *PeerJ.* (2023) 11:e15034. doi: 10.7717/peerj.15034



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Clara Limback,
Oxford University Hospitals, United Kingdom
Eleonore Fröhlich,
Medical University of Graz, Austria

*CORRESPONDENCE

Qian Xing
✉ xingqian@dmu.edu.cn

†These authors have contributed equally to this work

RECEIVED 02 April 2024

ACCEPTED 31 July 2024

PUBLISHED 23 August 2024

CITATION

Dong S, Ding F, Wang Y, Liu S, Bai R, Liu Y, Zhao Y, Zhu Y, Liu M, Liu Y and Xing Q (2024) The relation between FT₃ and long-term fatigue in patients with COVID-19. *Front. Endocrinol.* 15:1411262. doi: 10.3389/fendo.2024.1411262

COPYRIGHT

© 2024 Dong, Ding, Wang, Liu, Bai, Liu, Zhao, Zhu, Liu, Liu and Xing. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](#). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The relation between FT₃ and long-term fatigue in patients with COVID-19

Shuo Dong[†], FanRui Ding[†], Yuan Wang, Shuo Liu, Ran Bai, YuanYuan Liu, Yin Zhao, YueRan Zhu, MengXue Liu, Yuenan Liu and Qian Xing*

Department of Endocrine and Metabolic Diseases, First Affiliated Hospital of Dalian Medical University, Dalian, China

Background: Under the current pandemic of Corona Virus Disease 2019 (COVID-19), The relationship between fatigue and COVID-19 has been found. Infection with COVID-19 is associated with fatigue long after the acute phase of COVID-19. Understanding the association of thyroid hormones levels with post-COVID condition, such as fatigue, is necessary to improve quality of life.

Methods: This population-based cohort study was conducted in Dalian, China, from December 2022, to March 2023, using a Yidu Core platform in the First Affiliated Hospital of Dalian Medical University, that integrates medical records, laboratory tests, and all diagnosis and treatment information based on patients in hospital. Eligible individuals were 40 patients with COVID-19, Divided them into fatigue group and non-fatigue group following up by telephone using the FS-14 scale after 6 months. The primary outcomes were the diagnoses of fatigue. The association between thyroid hormones levels and post-COVID condition, such as fatigue, was assessed using logistic regression analysis.

Results: Compared with the non-fatigue group, the FT₃ level in fatigue group was lower ($p < 0.05$). FT₃ was negatively correlated with fatigue after 6 months (OR 0.257, $p < 0.05$). After adjusting for confounding factors such as age and gender, low FT₃ was a risk factor for fatigue in patients with COVID-19, (OR 0.225, $p < 0.05$). And the FT₃ is less than 2.47 mol/L, it is the best critical value for predicting long-term fatigue, with a sensitivity of 92.3% and a specificity of 48.1%.

Conclusions: Most people still have fatigue 6 months after COVID-19 infection. FT₃ serves as the important index to predict fatigue in patients with COVID-19. it should be closely monitored during infection.

KEYWORDS

SARS-CoV-2, COVID-19, thyroid hormone, fatigue, risk factor

1 Introduction

The novel coronavirus, which is the cause of the Corona Virus Disease 2019 (COVID-19), has had a significant impact on human life and health. COVID-19 enters host cells to initiate immunity through the binding of angiotensin-converting enzyme 2 (ACE2) or transmembrane protease, serine 2 (TMPRSS2). The high expression of ACE2 and TMPRSS2 in the thyroid gland is even higher than that in lung tissue, so the thyroid gland may be directly affected by COVID-19 (1).

Non-thyroidal illness syndrome (NTIs) are patients without previous basic thyroid diseases. Due to severe systemic diseases, thyroid hormone levels in the blood circulation are abnormally changed. This change is mainly manifested in the decrease of total triiodothyronine (TT₃) and free triiodothyronine (FT₃) levels, normal or decreased levels of total thyroxine (TT₄) and free thyroxine (FT₄), increased levels of reverse T₃ (rT₃), and thyroid stimulating hormone (TSH) levels are in the normal range (2).

It has been observed that many patients diagnosed with COVID-19 often experience abnormal changes in their thyroid hormones, which is known as NTIs. Present, a number of studies have found that FT₃ levels in patients with COVID-19 are significantly reduced. Zhang et al. found that 28% of COVID-19 patients had thyroid diseases, mainly NTIs (48%) (3), and Łukasz and his colleagues found that COVID-19 patients had a significant decrease in FT₃ (4). COVID-19 caused changes in thyroid hormones, which may be related to the down-regulation of 5'-deiodinase activity caused by cytokine storm, *in vivo* consumption affecting serum thyroid hormone transporter levels, hypothalamic-pituitary-thyroid axis (HPT) dysfunction and other factors (2). Six months after COVID-19 infection, many people still feel muscle pain, muscle weakness (mild to severe), fatigue and exercise intolerance. Among them, fatigue plays a major role in long COVID syndrome (5).

Currently, there is limited research on the relationship between thyroid hormones and post-COVID syndrome both domestically and internationally. The objective of this study is to investigate the connection between thyroid hormones and long COVID syndrome-fatigue. Additionally, the study aims to identify risk factors that contribute to persistent fatigue following COVID-19 infection. The findings of this research can serve as a guide for the diagnosis, treatment, and comprehensive management of COVID-19 sequelae.

2 Methods

2.1 Study design and population

Patients with COVID-19 who had no previous or current treatment for hypo- or hyperthyroidism or thyroid surgery history from December in 2022 to March in 2023 in the Department of Endocrinology and Metabolic Diseases, the First Affiliated Hospital of Dalian Medical University were included in the present study. We excluded people with hypothalamic or

pituitary disorders, as well as people who were identified to primary neuromuscular or myopathy or who had malignant tumors history. We also excluded individuals who had received radiotherapy or chemotherapy in the past 6 months, and individuals with autoimmune diseases or incomplete data. Moreover, participants who were pregnant or possibly pregnant or ingested agents known to influence thyroid function were also excluded.

The Research Ethics Board at the Dalian Medical University First Affiliated Hospital reviewed and approved this study. All study participants gave their informed consent for participation.

2.2 Data source

Data were assembled from the Yidu Core, a large medical management intelligent platform. It contains information on clinical events recorded by health care professionals, including diagnosis, symptoms, and therapies.

2.3 Laboratory procedures

COVID-19 infection was defined as nucleic acid test or antigen test was positive. According to the scoring criteria of FS-14, the score ≥ 3 is fatigue, and < 3 is non-fatigue (6–8). The clinical and laboratory data of patients who met the inclusion and exclusion criteria were collected, including gender, age and laboratory examination indicators, such as thyroid stimulating hormone (TSH), serum free triiodothyronine (FT₃), serum free thyroxine (FT₄), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP), myoglobin (MYO), high-sensitivity troponin I (hs-TnI), creatine kinase isoenzyme (CK-MB), creatine phosphokinase (CK), procalcitonin (PCT), C-reactive protein (CRP), creatinine (Cr), the sum activity of deiodinases (SPINA-GD), the secretory capacity of the thyroid gland (SPINA-GD), TSH index (TSHI), etc. They were followed up by telephone using the FS-14 scale at 6 months after COVID-19 infection. According to their scale scores, they were divided into fatigue group and non-fatigue group.

2.4 Biochemical assays

A Mindray automated chemiluminescence immunoassay analyzer CL-6000i (Mindray, China) was used to detect serum TSH, FT₃ and FT₄ levels. All test reagents were provided by Shenzhen Mindray Biomedical Electronics Co., Ltd. (Mindray, China). In our laboratory, the reference ranges for TSH, FT₄, and FT₃ were 0.35–5.1 uIU/ml, 11.2–23.81 pmol/L, and 2.76–6.45 pmol/L, respectively.

2.5 Statistical analysis

Data were analyzed using SPSS 27.0 software. The normality test was performed on the measurement data. Continuous variables are expressed as either the mean – standard deviation or median and

interquartile range. T-test or Mann-Whitney U-test was used for comparison between the two groups. Spearman method was used for correlation analysis between index groups, and bilateral test was used. The statistical description of the count data was expressed as [n (%)], and the chi-square test was used for comparison. Binary Logistic regression analysis was used to analyze the risk factors of fatigue. The receiver operating characteristic curve (ROC) and the area under the curve (AUC) were used to compare the cut-off points and predictive values. $p < 0.05$ was deemed to show statistical significance.

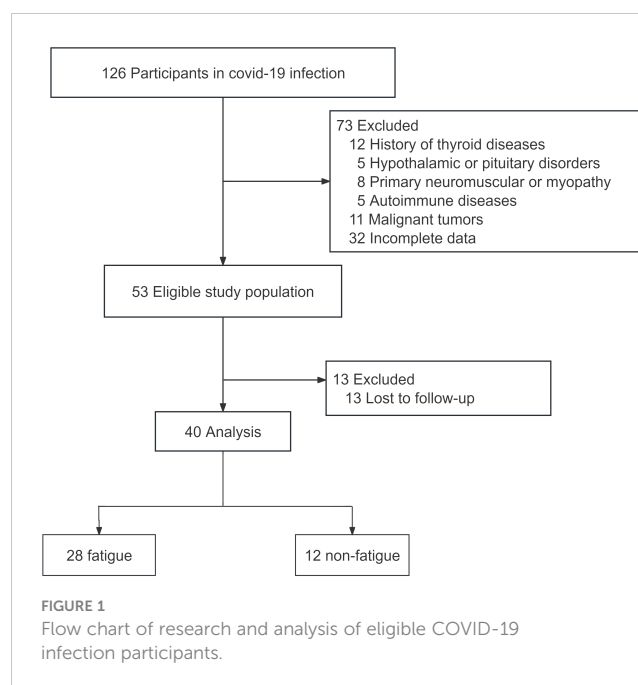
3 Results

3.1 Participant demographics

In this study, a total of 126 patients infected with COVID-19 were recruited. After applying the inclusion and exclusion criteria, 40 patients were selected for the study. These patients were followed up by telephone six months after being infected with COVID-19 (Figure 1). Based on their fatigue scores, they were divided into a fatigue group and a non-fatigue group. The results showed that there was no statistically difference in sex ratio and age between the two groups ($p > 0.05$). The FT_3 level in the fatigue group was significantly lower than that in the non-fatigue group ($p < 0.05$). The difference in CK, TSH, FT_4 , FT_3/FT_4 levels, SPINA-GD, SPINA-GT, TSHi was not statistically significant (Table 1).

3.2 Association between thyroid hormone and 6-month fatigue in COVID-19

Correlation analysis showed that fatigue scores were significantly negatively correlated with FT_3/FT_4 and SPINA-GD levels ($r = -0.329$, $p < 0.05$), and fatigue scores had no significantly correlation with Ca, P, CK, and CK-MB ($p < 0.05$) (Table 2). FT_3/FT_4 levels were significantly negatively correlated with hs-TnI ($r = -0.409$, $p < 0.05$). FT_3/FT_4 levels did not significantly correlate with Ca, P, CK, and CK-MB ($p > 0.05$) (Supplementary Table 1). Binary logistic regression analysis was performed with whether fatigue occurred in patients with COVID-19 as the dependent variable and thyroid hormone level as the independent variable, and the results showed that FT_3 level was negatively correlated with the occurrence of fatigue in patients with COVID-19, and that low T_3 was a risk factor for the occurrence of fatigue in patients with COVID-19 ($p < 0.05$). After correcting for confounding factors such as age, gender, Ca, and P, FT_3 was negatively correlated with the occurrence of fatigue in patients with COVID-19, suggesting that low FT_3 was a risk factor for the occurrence of fatigue in patients with COVID-19 ($p < 0.05$) (Table 3). There was no statistically difference between TSH, FT_4 , and FT_3/FT_4 and the occurrence of fatigue in patients with COVID-19 ($p > 0.05$) (Supplementary Table 2).



3.3 Predictive value of FT_3 levels in fatigue in COVID-19 patients

The ROC curve was plotted with FT_3 as the test variable and whether fatigue occurred in patients with COVID-19 as the state variable, and the results showed that the AUC of FT_3 level for predicting the occurrence of fatigue in patients with COVID-19 was 0.702 (95% CI 0.54–0.87, $p < 0.05$). Based on the maximum of the Jordon index as the critical value, when FT_3 took a value less than 2.47 pmol/L, it was the best critical value to predict the occurrence of fatigue in patients with COVID-19, with a sensitivity of 92.3% and a specificity of 51.9% (Figure 2).

4 Discussion

COVID-19 can affect multiple systems throughout the body. As an important organ of the endocrine system, the thyroid gland is directly or indirectly affected by COVID-19. The effect of COVID-19 on the thyroid gland may be caused by directly (caused by direct cytotoxicity of the virus) or indirectly (caused by abnormal immune inflammatory response to the virus, which may involve coagulation, cytokines and complement systems) (9). NTIs is common in COVID-19 patients. A retrospective cohort study of Zou et al. included 149 COVID-19 patients, of which 41 (27.52%) were diagnosed with NTIs (10). A prospective study included 196 patients diagnosed with COVID-19 and found that 60% of ICU patients and 36% of general ward patients showed NTIs (11). In our study, 57.5% of all follow-up patients showed NTIs.

The main manifestation of NTIs is the decrease in T_3 level. The mechanism includes the change of half-life of thyroid hormone in

TABLE 1 Demographic, clinical and biochemical characteristics of the study population.

	Fatigue(n=28)	non-fatigue(n=12)	<i>p</i>
Age year	72.00(50.00-80.00)	64.00(55.50-78.00)	0.654
Sex Female (n%)	13(33%)	7(59%)	0.739
TSH(μIU/ml)	1.37(0.60-2.43)	1.06(0.73-1.63)	0.444
FT ₃ (pmol/L)	2.52 ± 0.63	3.00 ± 0.56	0.023*
FT ₄ (pmol/L)	15.91 ± 3.53	16.36 ± 1.15	0.552
FT ₃ /FT ₄	0.16 ± 0.035	0.18 ± 0.041	0.160
CK(U/L)	64.00(37.50-145.50)	46.00(20.00-183.50)	0.569
ALT(U/L)	21.00(19.00-43.00)	21.00(13.50-46.00)	0.783
AST(U/L)	28.00(21.00-42.00)	29.00(17.50-42.00)	0.874
ALP(U/L)	81.00(68.00-124.00)	74.00(49.50-100.00)	0.260
MYO(ng/ml)	71.17(34.07-176.43)	47.06(27.09-319.02)	0.638
hs-TnI(μg/ml)	0.016(0.006-0.037)	0.006(0.0055-0.0185)	0.080
CK-MB(μg/ml)	0.92(0.48-1.97)	0.92(0.37-2.33)	0.931
BNP(ng/L)	82.04(47.48-191.18)	50.51(27.70-125.97)	0.128
P(mmol/L)	1.06 ± 0.47	1.10 ± 0.45	0.806
Ca(mmol/L)	2.06(1.96-2.23)	2.08(1.975-2.195)	0.897
PCT(ng/ml)	0.19(0.10-0.52)	0.20(0.02-0.37)	0.754
CRP(mg/L)	13.59(5.33-74.63)	25.10(8.34-33.00)	0.529
fatigue scores	7.00(5.00-9.00)	1.00(0.00-1.50)	<0.001*
SPINA-GD	14.67(12.85-19.81)	17.19(13.87-19.82)	0.069
TSHI	-1.97(-3.11-0.40)	-2.43(-2.91-1.59)	0.453
SPINA-GT	5.06 ± 3.77	5.49 ± 3.38	0.733

TSH, thyroid stimulating hormone; FT₃, serum free triiodothyronine; FT₄, serum free thyroxine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; MYO, myoglobin; hs-TnI, high-sensitivity troponin; CK-MB, creatine kinase isoenzyme; Ca, Calcium; CK, creatine phosphokinase; P, phosphorus; PCT, procaltitonin; CRP, c-reactive protein; SPINA-GD, the sum activity of deiodinases; SPINA-GT, the secretory capacity of the thyroid gland; TSHI, thyroid stimulating hormone index.
*Level of significance $p<0.05$.

circulation, the change of cell sensitivity to thyroid hormone, the change of tissue uptake of thyroid hormone and the change of deiodinase activity which converts thyroid hormone into active and inactive forms respectively (12). After T₄ deiodination, plasma T₃ is mainly derived from the role of DIO1 in the liver. During NTIs, the activity of DIO1 in the liver and DIO2 in skeletal muscle decreased, and the activity of DIO3 in the liver and skeletal muscle increased (13). This may be a physiological adaptation to reduce energy needs during acute diseases. Under high energy demand conditions such as diseases, skeletal muscle is the main organ responsible for glucose uptake in response to insulin. In this case, muscle protein catabolism can be stimulated to maintain energy in other organs, and a decrease in T₃ levels reduces metabolic activity and reduces energy loss in these patients (14–17).

After the recovery of COVID-19, some people still suffer from persistent and periodic symptoms. A Chinese study that included 1733 patients who had been hospitalized for COVID-19 found that

TABLE 2 Results of correlation analysis of features associated with fatigue scores.

	<i>r</i>	<i>p</i>
TSH	0.022	0.893
FT ₃	-0.251	0.119
FT ₄	0.076	0.642
FT ₃ /FT ₄	-0.329	0.038*
Ca	0.173	0.286
P	-0.045	0.782
CK	-0.077	0.647
ALT	0.055	0.737
AST	0.018	0.91
SPINA-GD	-0.369	0.019*
TSHI	-0.146	0.370
FT ₄ /TSH	-0.014	0.932

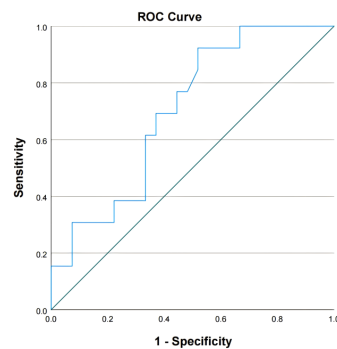
TSH, thyroid stimulating hormone; FT₃, serum free triiodothyronine; FT₄, serum free thyroxine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Ca, Calcium; CK, creatine phosphokinase; P, phosphorus; PCT, procaltitonin; CRP, c-reactive protein; SPINA-GD, the sum activity of deiodinases; SPINA-GT, the secretory capacity of the thyroid gland; TSHI, thyroid stimulating hormone index.
*Level of significance $p<0.05$.

at least one skeletal muscle-related symptom was still present in 76% of patients at 6 months, with fatigue or muscle weakness accounting for 63% of these (18). An Italian study reported fatigue as the predominant symptom (53.1%) of persistent symptoms 60 days after a COVID-19 infection (19). A meta-analysis showed that fatigue was the most common symptom of long covid syndrome (28.4%). Even in the non-hospitalized population, the most common long covid syndrome symptom is still fatigue, which is present in 34.8% (20). Therefore, chronic fatigue syndrome (CFS) is the most common complaint of patients. CFS, also known as myalgia encephalomyelitis, is a complex heterogeneous disorder characterized by disabling fatigue, cognitive impairment, sleep disruption, and accompanying bone and muscle pain that persists for more than 6 months and does not improve with rest (21, 22). The global pooled prevalence of CFS among long covid syndrome patients is 45.2% (23). A meta-analysis showed that the total prevalence reported by Western and Asian populations was

TABLE 3 Associated FT₃ related to fatigue by multivariate binary logistic analysis in COVID- 19 patients.

	B	S.E	Wald	<i>p</i>	OR	95%CI
FT ₃	-1.358	0.639	4.510	0.034*	0.257	0.074 0.901
Age	0.003	0.021	0.023	0.880	1.003	0.962 1.046
sex	0.583	0.777	0.563	0.453	1.791	0.391 8.211
Ca	0.190	2.284	0.007	0.934	1.209	0.014 106.375
P	-0.608	0.972	0.391	0.532	0.544	0.081 3.661
FT ₃ *	-1.491	0.712	4.387	0.036**	0.225	0.056 0.909

*adjusted for age, sex, calcium and phosphorus.
**Level of significance $p<0.05$.



	n	AUC	sensitivity	specificity	Jordon index	optimal threshold	p
FT ₃	40	0.702	0.923	0.481	0.404	2.465	0.04*

FIGURE 2

Receiver operating characteristic curve analysis determining the optimal threshold of FT₃ for predicting fatigue after 6 months of COVID-19 infection.

comparable ($1.32 \pm 1.45\%$ vs 1.51 ± 1.74) (24). A prospective study showed that 75.9% of patients reported fatigue 3–6 months after infection with COVID-19, which was consistent with our study (5). In our study, 70% of patients were still fatigued 6 months after infection with COVID-19. The prevalence of CFS has been reported to be 2–3 times higher in females than in males, but there was no significant gender difference in this study (25). A retrospective study showed that 48.9% of CFS patients diagnosed after COVID-19 infection were male and 51.1% were female (26). We speculate that this may be due to the fact that infections are a significant trigger for the development of CFS, and that infections make the gender difference negligible.

CFS may be associated with changes in hormone levels in the hypothalamus-pituitary-thyroid axis (27). Studies have shown that thyroid hormone function in CFS is similar to NTIs. A Serbian study found that compared with the healthy group, although the basal serum T₃ of all subjects was normal, the T₃ concentration in the CFS group was significantly reduced (28). In this study, the level of FT₃ in the fatigue group was significantly lower than that in the non-fatigue group (2.52 ± 0.63 vs 3.00 ± 0.56 $p < 0.05$), and 64.3% of the fatigue group showed NTIs. FT₃/FT₄ is commonly used to evaluate the sensitivity of peripheral thyroid, which reflects 5'-deiodinase activity. SPINA-GD represents the total activity of peripheral deiodinase. This study shows that although there is no statistical difference in SPINA-GD between the two groups, SPINA-GD in the fatigue group is lower than that in the non-fatigue group. Correlation analysis shows that FT₃/FT₄ and SPINA-GD are related to fatigue ($p < 0.05$), which indicates that fatigue in patients with COVID-19 may be related to subtle changes in deiodinase. Although NTIs may be beneficial in the acute phase of critical illness, it may hinder the recovery of patients in the case of long-term critical illness (29). Low T₃ may affect brain tissue perfusion and energy metabolism, leading to fatigue (30). This study shows that low T₃ is a risk factor for fatigue. When FT₃ value is less than 2.47 pmol/L, it is the best critical value to predict fatigue in COVID-19 patient.

Even though the study has provided interesting findings, it had some few limitations. Certain limitations of the study are as follows: Firstly, the sample size is relatively small, resulting in a higher number of patients lost to follow-up, which may introduce a bias of loss of follow-up. Secondly, The patients included were all Chinese, potentially limiting the generalizability of the findings to other regions or ethnic groups. Thirdly, the thyroid hormone levels of COVID-19 patients after 6 months were not measured again, potentially limiting the understanding of the long-term effects of thyroid hormones on CFS. Fourthly, the average age of both groups is over 60 years old, and there is a lack of data on the young population. Finally, a meta study showed that the prevalence of CFS was 0.10% based on the physician diagnosis, and the prevalence of CFS was 2.03% in the questionnaire interview without medical testing (24). Therefore, the prevalence of CFS based on the questionnaire survey in our study may be overestimated. In the future, large-scale prospective studies are needed to further explore the mechanism of thyroid hormones affecting CFS after COVID-19.

Furthermore, in addition to thyroid hormones, symptoms of chronic fatigue may also be caused by damage to multiple organ systems during COVID-19. The occurrence of CFS in COVID-19 may be related to excessive anti-inflammatory response, and the dominant disease pattern of alternatively polarized macrophage cells directly induces the occurrence of CFS (31). Hypothalamic-pituitary-adrenal (HPA) axis disturbances have also been found in CFS, which are manifested by mild cortisol decrease, enhanced negative feedback, and a blunted response to excitation (32). COVID-19 can also cause skeletal muscle damage resulting from changes in the structure and function of the neuromuscular system through mechanisms such as direct infiltration, inflammatory response, hypoxia and other mechanisms to cause skeletal muscle damage, resulting in fatigue (33). A study reported that the immune system of ME/CFS patients produces an imbalanced ratio of pro-inflammatory and anti-inflammatory cytokines in the early stages of the disease (34). But CRP and PCT are not statistically significant in our study. In conclusion, the occurrence of CFS in COVID-19

patients is not a role of a single hormonal axis, but a combination of factors.

5 Conclusions

In summary, this study demonstrates that the majority of patients still experience fatigue six months after contracting the COVID-19 infection. The level of FT₃ in the fatigue group was lower, suggesting a potential correlation between FT₃ and the persistence of fatigue following COVID-19 infection. The mechanism of fatigue may be related to subtle changes in the hypothalamus-pituitary-thyroid axis and deiodinase. In addition, this study found that low T₃ is a risk factor for fatigue. When the value of FT₃ is less than 2.47 pmol/L, it serves as the optimal critical threshold to predict fatigue in patients with COVID-19. In the future, prospective studies are needed to confirm whether monitoring serum FT₃ level can predict the occurrence of CFS in patients with COVID-19, and then help to improve the symptoms of patients.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Affiliated Hospital of Dalian Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SD: Writing – original draft, Writing – review & editing. FD: Writing – original draft, Writing – review & editing. YW: Writing –

review & editing. SL: Writing – review & editing. RB: Writing – review & editing. YYL: Writing – review & editing. YiZ: Writing – review & editing. YuZ: Writing – review & editing. ML: Writing – review & editing. YNL: Writing – review & editing. QX: Writing – review & editing, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank the members of information department and medical ethics committee of The First Affiliated Hospital of Dalian Medical University for their helpful data and critical reading and review of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1411262/full#supplementary-material>

References

- Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. *Rev Endocr Metab Disord*. (2021) 22:803–15. doi: 10.1007/s11154-020-09615-z
- Feng W, Zongxun Y. Study on the relationship between thyroid hormone level and post-stroke fatigue. *Chin J Med Guide*. (2020) 22:544–8. doi: 10.12083/SYSJ.2020.14.277
- Zhang Y, Lin F, Tu W, Zhang J, Choudhry AA, Ahmed O, et al. Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19. *Mol Cell Endocrinol*. (2021) 521:111097. doi: 10.1016/j.mce.2020.111097
- Szczerbiński Ł, Okruszko MA, Szablowski M, Solomacha S, Sowa P, Kiszkiel Ł, et al. Long-term effects of COVID-19 on the endocrine system – a pilot case-control study. *Front Endocrinol (Lausanne)*. (2023) 14:1192174. doi: 10.3389/fendo.2023.1192174
- Cornelissen MEB, Bloemasma LD, Vaes AW, Baalbaki N, Deng Q, Beijers RJHCG, et al. Fatigue and symptom-based clusters in post COVID-19 patients: a multicenter, prospective, observational cohort study. *J Transl Med*. (2024) 22:191. doi: 10.1186/s12967-024-04979-1
- Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. *J Psychosom Res*. (1993) 37:147–53. doi: 10.1016/0022-3999(93)90081-P

7. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAFM-DQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAFNRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken)*. (2011) 63 Suppl 11:S263–S86. doi: 10.1002/acr.20579
8. Xuelin T, Ji G, Yan Z, Yingchun Z. Research progress on the application of fatigue scale (FS-14). *Chin Gen Pract Nurs*. (2022) 20:2193–7. doi: 10.12104/j.issn.1674-4748.2022.16.008
9. Ruiz-Núñez B, Tarasce R, Vogelaar EF, Janneke Dijk-Brouwer DA, Muskiet FAJ. Higher prevalence of “Low T3 syndrome” in patients with chronic fatigue syndrome: A case-control study. *Front Endocrinol*. (2018) 9:97. doi: 10.3389/fendo.2018.00097
10. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. *Front Endocrinol*. (2020) 11:566439. doi: 10.3389/fendo.2020.566439
11. Vassiliadi DA, Ilias I, Pratikaki M, Jahaj E, Vassiliou AG, Detsika M, et al. Thyroid hormone alterations in critically and non-critically ill patients with SARS-CoV-2 infection. *Endocrine Connections*. (2021) 10:646–55. doi: 10.1530/EC-21-0029
12. Stanculescu D, Bergquist J. Perspective: drawing on findings from critical illness to explain myalgic encephalomyelitis/chronic fatigue syndrome. *Front Med*. (2022) 9:818728. doi: 10.3389/fmed.2022.818728
13. Lado-Abeal J, Romero A, Castro-Piedras I, Rodriguez-Perez A, Alvarez-Escudero J. Thyroid hormone receptors are down-regulated in skeletal muscle of patients with non-thyroidal illness syndrome secondary to non-septic shock. *Eur J Endocrinol*. (2010) 163:765–73. doi: 10.1530/EJE-10-0376
14. Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J Am Med Directors Assoc*. (2016) 17:789–96. doi: 10.1016/j.jamda.2016.04.019
15. Van den Berghe G. On the neuroendocrinopathy of critical illness. Perspectives for feeding and novel treatments. *Am J Respir Crit Care Med*. (2016) 194:1337–48. doi: 10.1164/rccm.201607-1516CI
16. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol*. (2015) 3:816–25. doi: 10.1016/S2213-8587(15)00225-9
17. Bloise FF, Cordeiro A, Ortega-Carvalho TM. Role of thyroid hormone in skeletal muscle physiology. *J Endocrinol*. (2018) 236:R57–68. doi: 10.1530/JOE-16-0611
18. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. RETRACTED: 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. (2021) 397:220–32. doi: 10.1016/S0140-6736(20)32656-8
19. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *Jama*. (2020) 324(6):603–605. doi: 10.1001/jama.2020.12603
20. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalized and non-hospitalized populations: a systematic review and meta-analysis. *eClinicalMedicine*. (2023) 55:101762. doi: 10.1016/j.eclim.2022.101762
21. Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med*. (1988) 108:387–9. doi: 10.7326/0003-4819-108-3-387
22. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. (1994) 121:953–9. doi: 10.7326/0003-4819-121-12-199412150-00009
23. Salari N, Khodayari Y, Hosseini-Far A, Zarei H, Rasoulpoor S, Akbari H, et al. Global prevalence of chronic fatigue syndrome among long COVID-19 patients: A systematic review and meta-analysis. *BioPsychoSocial Med*. (2022) 16(1):21. doi: 10.1186/s13030-022-00250-5
24. Lim EJ, Ahn YC, Jang ES, Lee SW, Lee SH, Son CG. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *J Transl Med*. (2020) 18:100. doi: 10.1186/s12967-020-02269-0
25. Arron HE, Marsh BD, Kell DB, Khan MA, Jaeger BR, Pretorius E. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: the biology of a neglected disease. *Front Immunol*. (2024) 15:1386607. doi: 10.3389/fimmu.2024.1386607
26. Tokumasu K, Honda H, Sunada N, Sakurada Y, Matsuda Y, Yamamoto K, et al. Clinical characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) diagnosed in patients with long COVID. *Medicina (Kaunas)*. (2022) 58:850. doi: 10.3390/medicina58070850
27. Fuite J, Vernon SD, Broderick G. Neuroendocrine and immune network remodeling in chronic fatigue syndrome: An exploratory analysis. *Genomics*. (2008) 92:393–9. doi: 10.1016/j.ygeno.2008.08.008
28. Tomic S, Brkic S, Lendak D, Maric D, Medic Stojanoska M, Novakov Mikic A. Neuroendocrine disorder in chronic fatigue syndrome. *Turkish J Med Sci*. (2017) 47:1097–103. doi: 10.3906/sag-1601-110
29. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. *Endocrine Rev*. (2011) 32:670–93. doi: 10.1210/er.2011-0007
30. Min L, Hao L, Youming W, Mengge Z. Study on the relationship between thyroid hormone level and post-stroke fatigue. *Chin J Pract Nervous Dis*. (2020) 23:1221–4. doi: 10.12083/SYSJ.2020.14.277
31. Kovarik JJ, Bileck A, Hagn G, Meier-Menches SM, Frey T, Kaempf A, et al. A multi-omics based anti-inflammatory immune signature characterizes long COVID-19 syndrome. *iScience*. (2023) 26(1):105717. doi: 10.1016/j.isci.2022.105717
32. Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. *Trends Endocrinol Metab*. (2004) 15:55–9. doi: 10.1016/j.tem.2003.12.002
33. Soares MN, Eggelbusch M, Naddaf E, Gerrits KHL, van der Schaaf M, van den Borst B, et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle*. (2022) 13:11–22. doi: 10.1002/jcsm.12896
34. Hornig M, Montoya JG, Klimas NG, Levine S, Felsenstein D, Bateman L, et al. Distinct plasma immune signatures in ME/CFS are present early in the course of illness. *Sci Adv*. (2015) 1(1):e1400121. doi: 10.1126/sciadv.1400121



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Mohammed Amir Rais,
University of Algiers, Algeria
Eva Szabo,
University of Pécs, Hungary

*CORRESPONDENCE

Jingye Zhou
✉ jingyehou116@gmail.com

RECEIVED 08 May 2024

ACCEPTED 08 August 2024

PUBLISHED 26 August 2024

CITATION

Zhou J, Wang Y and Xu R (2024) Association of COVID-19 infection and the risk of new incident diabetes: a systematic review and meta-analysis.
Front. Endocrinol. 15:1429848.
doi: 10.3389/fendo.2024.1429848

COPYRIGHT

© 2024 Zhou, Wang and Xu. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](#). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Association of COVID-19 infection and the risk of new incident diabetes: a systematic review and meta-analysis

Jingye Zhou^{1,2*}, Yuzhu Wang^{1,2} and Ruolan Xu^{1,2}

¹International Medical College, Chongqing Medical University, Chongqing, China, ²College of Life Sciences, University of Leicester, Leicester, United Kingdom

Background: As the world population recovers from the COVID-19 infection, a series of acute sequelae emerge including new incident diabetes. However, the association between COVID-19 infection and new incident diabetes is not fully understood. We purpose to determine the risk of new incident diabetes after COVID-19 infection.

Methods: PubMed, Embase, and Cochrane Library were used as databases to search for cohort studies published from database inception to February 4, 2024. Two reviewers independently conducted the study screening, data extraction, and risk of bias assessment. A random-effects model was adopted to pool the hazard ratio (HR) with corresponding 95% confidence intervals (CI). Subgroup analysis was conducted to explore the potential influencing factors.

Results: A total of 20 cohort studies with over 60 million individuals were included. The pooling analysis illustrates the association between COVID-19 infection and an increased risk of new incident diabetes (HR = 1.46; 95% CI: 1.38–1.55). In subgroup analysis, the risk of type 1 diabetes was HR=1.44 (95% CI: 1.13–1.82), and type 2 diabetes was HR=1.47 (95% CI: 1.36–1.59). A slightly higher risk of diabetes was found in males (HR=1.37; 95% CI: 1.30–1.45) than in females (HR=1.29; 95% CI: 1.22–1.365). The risk of incident diabetes is associated with hospitalization: non-hospitalized patients have an HR of 1.16 (95% CI: 1.07–1.26), normal hospitalized patients have an HR of 2.15 (95% CI: 1.33–3.49), and patients receiving intensive care have the highest HR of 2.88 (95% CI: 1.73–4.79).

Conclusions: COVID-19 infection is associated with an elevated risk of new incident diabetes. Patients ever infected with COVID-19 should be recognized as a high-risk population with diabetes.

Systematic review registration: <https://www.crd.york.ac.uk/prospero>, identifier CRD42024522050.

KEYWORDS

COVID-19, long COVID, SARS-CoV-2, diabetes mellitus, public health

1 Introduction

Diabetes is a chronic non-communicable disease characterized by impaired glucose metabolism that results in persistently raised blood glucose in the context of insufficient insulin caused by autoimmune-mediated destruction of pancreatic β -cells or insulin resistance combined with pancreatic β -cell insufficiency (1). Despite significant process has been made in the exploration of risk factors for diabetes and the implementation of prevention programs, there is a globally increasing incidence and prevalence of the disease (2). Early detection and intensive patient-centered management are expected to optimize the prognosis, reducing morbidity and mortality by preventing or delaying complications (2). A previous study has explored the primary risk factors of diabetes, including BMI, genetics, atmosphere, diet habit, drug use, sedentary way of life, lack of physical exercise, smoking, alcoholic beverages, dyslipidemia, hyperinsulinemia, and improved glucagon activity (3). Recently, the bidirectional interaction between coronavirus disease 2019 (COVID-19) and diabetes has been revealed (4–7). COVID-19 presumably increases the risk of new incident diabetes (8, 9).

The pandemic of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is recognized as the greatest worldwide public health threat of this century (10). Although the World Health Organization (11) has declared that COVID-19 is no longer a public health emergency of international concern in May 2023, it continues to circulate and evolve, and remains a potentially serious risk to public health. Simultaneously, sequelae after the acute phase of COVID-19 (called long COVID) have aroused wild attention in the medical field (12). Patients with long COVID experience lingering symptoms across multiple organ systems, with common new incident conditions such as diabetes (13). Current reviews revealed an association between COVID and increased incidence of diabetes (14–16), but Zareini et al. (17) indicated an opposite perspective. Therefore, we systematically reviewed the existing cohort studies to clarify the association between COVID-19 and the risk of new incident diabetes.

2 Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (18). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) platform on March 12, 2024 (CRD42024522050).

2.1 Search strategy

We systematically searched PubMed, Embase, and Cochrane Library for studies published up to February 4, 2024. No language restrictions were applied, and the search strategy combined the use of medical subject headings (MeSH) and free text. The search terms

were related to COVID-19, Post-Acute COVID-19 Syndrome, Diabetes Mellitus, and risk. The full search strategies are included in [Supplementary Tables 1–3](#). The reference lists of other published meta-analyses were also considered to identify relevant cohort studies.

2.2 Eligibility criteria

Original research studies must meet all the following criteria to be included: (1) the study design was a prospective or retrospective cohort study investigating the association between COVID-19 and the risk of new incident all-type diabetes (no prior history of diabetes); (2) COVID-19 and diabetes were defined based on medical records or International Classification of Diseases (ICD) codes; (3) the hazard ratio (HR) or odds ratio (OR) and its corresponding 95% confidence interval (CI) were reported.

The following were excluded: reviews, study protocols, and commentaries.

2.3 Study selection

Study selection was performed by two reviewers (JYZ and YZW), independently. Titles and abstracts were first screened to exclude duplicate and irrelevant articles. Thereafter, the full texts were examined to identify all eligible studies. If multiple studies conducted assessments from the same database, we include the one with more adequate data based on its sample size and follow-up duration. Any disagreements were resolved by discussing them with the third reviewer (RLX).

2.4 Data extraction

Two reviewers mentioned above (JYZ and YZW) extracted data independently consulting the guidelines on data extraction for systematic reviews and meta-analysis (19). Predesigned forms were used for data extraction, including the first author, year of publication, country, study type, data source, sample size, follow-up duration, mean age, diagnosis criteria of COVID/diabetes, type of diabetes, interval (interval between the first diagnosis of COVID and the onset of diabetes). Disagreements were resolved by consensus with all researchers (JYZ, YZW, and RLX).

2.5 Risk of bias

The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS) (20). A “star system” was used to judge the studies from three broad perspectives: the selection of participants a measurement of exposure, the comparability of the study groups, and the assessment of outcomes and adequacy of follow-up. Each assessment was carried out by two reviewers (JYZ and YZW) separately and repeatedly. Disagreements were solved by discussion with the third reviewer (RLX).

2.6 Statistical analysis

For this meta-analysis, we sought to identify HRs and 95% CI to assess the association between COVID-19 and the risk of new incident diabetes. Heterogeneity among the studies was evaluated by the χ^2 -test and the I^2 -values. If $I^2 > 50\%$, a random-effects model of analysis was used. We applied a sensitivity analysis by excluding one study each time and rerunning it to verify the robustness of the overall effects. The funnel plot was constructed to inspect and visualize publication bias, and Egger's regression test was conducted to statically assess it. Subgroup analyses were performed if two or more cohorts were identified. p-values < 0.05 were considered to be statistically significant. All analyses were performed using Stata software (Stata Corp V.14, Texas, USA).

3 Results

3.1 Literature search

21386 results were obtained after the systematic search. After removing duplicate content and screening the title and abstract, 42 articles were potentially eligible. Full-text articles were all accessible in the remaining 42 studies. Twenty-two studies were excluded after full-text review: 2 were not cohort studies, 1 was commentary, 5 were

conference proceedings, 12 did not provide our interested effect sizes and 3 used duplicated data sources. Bowe et al. (21) used the same dataset as Xie and Al-Aly (22) but focused on different outcomes, so we included both. 20 cohort studies (17, 21–39) were included in the meta-analysis. The PRISMA flow diagram illustrating the search and selection process is provided in Figure 1.

3.2 Study characteristics

This meta-analysis included 20 cohort studies covering 60,221,176 individuals, which were published between 2021 and 2023. Out of the 20 studies, one was a prospective cohort study, while the other 19 were retrospective studies. Among all the studies included, one reported gestational diabetes mellitus (GDM), five reported type 1 diabetes (T1D), seven reported type 2 diabetes (T2D), and eight reported both T1D and T2D. The follow-up duration of participants ranges from 3 to 84 months. Additional characteristics of the included studies are shown in Table 1.

3.3 Quality assessment

According to the NOS criteria, the average score of all included cohort studies was 8, and the score for five trials (21, 22, 29, 34, 39)

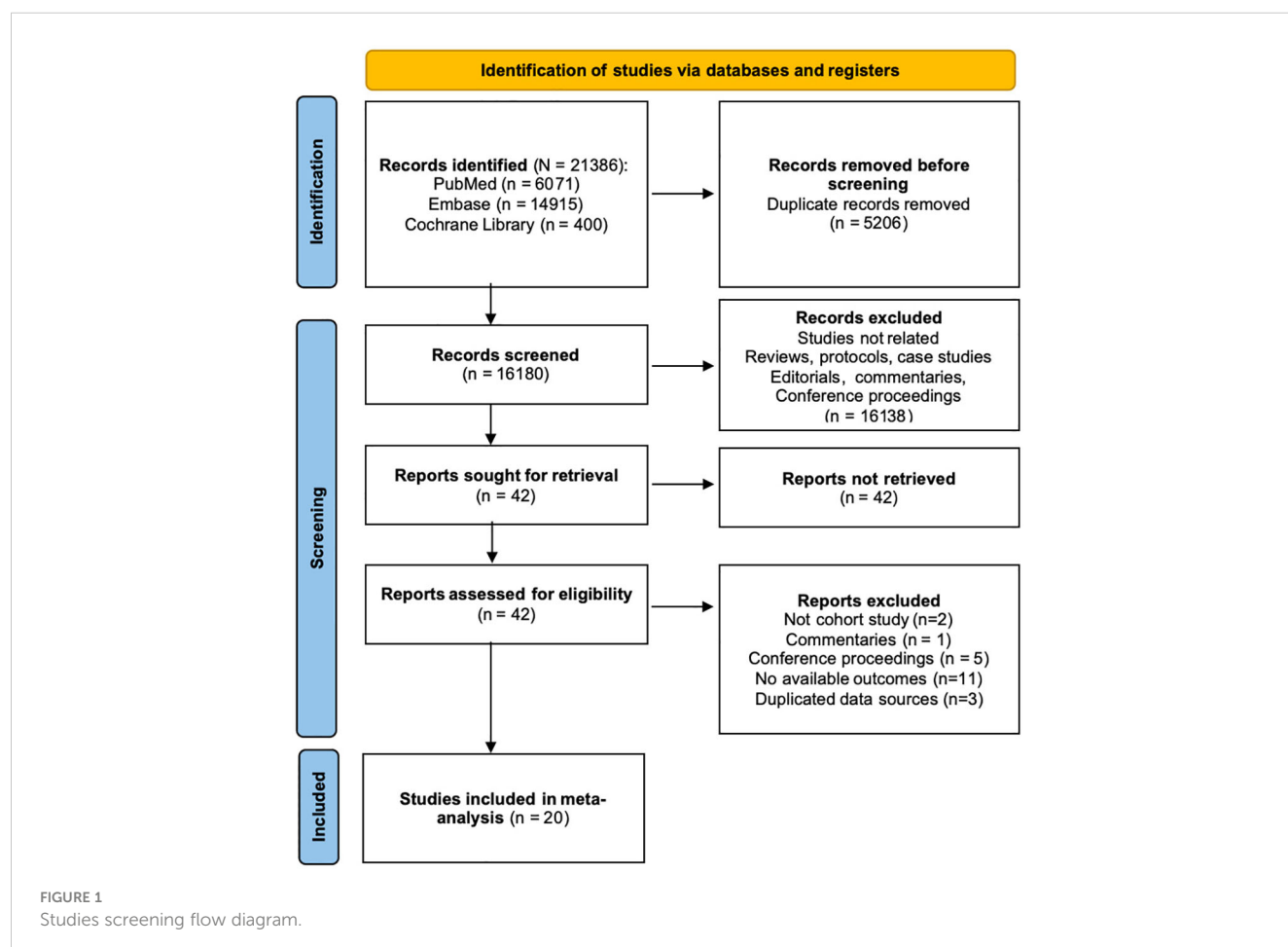


TABLE 1 Basic characteristics of the included studies.

Author	Year	Country	Study type	Data source	Sample size, n	Follow-up duration, months	Mean age, years	Diagnosis of COVID-19/ diabetes	Diabetes type	Interval, days	NOS scores	Adjusted factors
Aslam et al. (23)	2023	Pakistan	Retrospective cohort	Department of respiratory physiology and medicine of independent University Hospital	COVID: 55 Control: 50	5	COVID: 39.5 Control: 25.65	COVID: medical records, RT-PCR Diabetes: medical records, HbA1c	T2D	>1	7	NR
Barrett et al. (24)[1]	2022	USA	Retrospective cohort	IQVIA	COVID: 80,893 Control: 404,465	12	COVID: 12.3 Control: 12.3	COVID: medical records, ICD-10 Diabetes: medical records, ICD-10	T1D/T2D	>30	8	Age, sex
Barrett et al. (24)[2]	2022	USA	Retrospective cohort	Health Verity	COVID: 439,439 Control: 439,439	16	COVID: 12.7 Control: 12.7	COVID: medical records, PCR, ICD-10 Diabetes: medical records, ICD-10	T1D/T2D	>30	8	Age, sex
Bowe et al. (21)	2022	USA	Retrospective cohort	VHSUS Veterans Health Administration	COVID: 234,990 Control: 5,334,729	27.8	COVID: 60.12 Control: 60.12	COVID: medical records, RT-PCR, ICD-10 Diabetes: medical records, HbA1c, ICD-10	T2D	>1	6	Age, sex, race, BMI, vaccination status, area deprivation index, smoking
Choi et al. (25)	2023	South Korea	Retrospective cohort	Health Insurance Review and Assessment Service	COVID: 348,180 Control: 1,044,540	12.5	COVID: 43.3 Control: 43.3	COVID: medical records, ICD-10 Diabetes: medical records, ICD-10	T2D	>30	9	Age, sex, hypertension, dyslipidemia
Daugherty et al. (26)	2021	USA	Retrospective cohort	United Health Group Clinical Discovery Database	COVID: 266,586 Control: 8,980,919	10	COVID: 41.7 Control: 42.4	COVID: medical records, PCR, ICD-10 Diabetes: medical records, ICD-10	T2D	>21	7	Age, sex, race
Jun Zhang et al. (27)	2022	China	Prospective cohort	Wuhan Hospital of Traditional Chinese Medicine	COVID: 171 Control: 77	3.3	Total: 61.0	COVID: medical records, RT-PCR Diabetes: fasting blood glucose	T1D/T2D	After discharge	7	Age, sex, BMI, smoking, drinking, hypertension, comorbidities
Kendall et al. (28)	2022	USA	Retrospective cohort	TriNetX	COVID: 314,917 Control: 776,577	6	COVID: 10.3 Control: 10.3	COVID: medical records, ICD-10 Diabetes: NR	T1D	>1	7	NR

(Continued)

TABLE 1 Continued

Author	Year	Country	Study type	Data source	Sample size, n	Follow-up duration, months	Mean age, years	Diagnosis of COVID-19/ diabetes	Diabetes type	Interval, days	NOS scores	Adjusted factors
Kwan et al. (29)	2023	USA	Retrospective cohort	Cedars-Sinai Health System	Total: 23,709	6	Total: 47.4	COVID: medical records, ICD-9, ICD-10 Diabetes: medical records, ICD-9, ICD-10	T1D/T2D	0-90	6	Age, sex, hypertension, hyperlipidaemia
Lu et al. (30)	2023	USA	Retrospective cohort	Montefiore Health System in Bron	COVID: 19,427 Control: 5,730	3	NR	COVID: medical records, RT-PCR Diabetes: medical records, ICD-10	T2D	>1	9	Age, sex, race, ethnicity, BMI, hypertension, HF, CKD, COPD
McKeigue et al. (31)	2022	UK	Retrospective cohort	REACT-SCOT	COVID: 365,080 Control: 1,484,331	20.6	Range: <35	COVID: medical records, PCR Diabetes: medical records	T1D	>1	9	Sex, vaccination status
Naveed et al. (32)	2023	Canada	Retrospective cohort	British Columbia COVID-19 Cohort	COVID: 125,987 Control: 503,948	24	COVID: 45 Control: 41.5	COVID: medical records, RT-PCR Diabetes: medical records, ICD-9, ICD-10	T1D/T2D	>30	7	Age, sex, vaccination status
Noorzae et al. (33)	2023	Denmark	Retrospective cohort	The Danish Civil Registration System	COVID: 419,260 Control: 1,174,677	30	Range: 0-17	COVID: medical records Diabetes: medical records, ICD-10	T1D	>30	7	Age, sex, comorbidities, vaccination status
Qeadan et al. (34)	2022	USA	Retrospective cohort	Cerner Real-World Data	COVID: 2,489,266 Control: 24,803,613	22	COVID: 44.5 Control: 41.1	COVID: medical records, laboratory test Diabetes: medical records, ICD-10	T1D	>1	6	Age, sex, race, ethnicity, marital status, region
Rathmann et al. (35)	2022	Germany	Retrospective cohort	Disease Analyzer	COVID: 35,865 Control: 35,865	16.7	COVID: 42.6 Control: 42.6	COVID: medical records, ICD-10 Diabetes: medical records, ICD-10	T2D	>1	9	Age, sex, obesity, hypertension, hyperlipidemia
Rege et al. (36)	2023	Israel	Retrospective cohort	Clalit	COVID: 157,936 Control: 157,936	10.9	COVID: 43 Control: 43	COVID: medical records, PCR Diabetes: medical records, ICD-9	T1D/T2D	>1	9	Age, BMI, socioeconomic status, hypertension, dyslipidemia, smoking status

(Continued)

TABLE 1 Continued

Author	Year	Country	Study type	Data source	Sample size, n	Follow-up duration, months	Mean age, years	Diagnosis of COVID-19/ diabetes	Diabetes type	Interval, days	NOS scores	Adjusted factors
Rezel-Potts et al. (37)	2022	UK	Retrospective cohort	CPRD Aurum	COVID: 428,650 Control: 428,650	12	COVID: 35 Control: 35	COVID: medical records, PCR Diabetes: medical records, HbA1c	T1D/T2D	0-120	9	Age, sex, ethnicity, BMI, smoking status
Soysal and Yilmaz (38)	2022	Turkey	Retrospective cohort	Obstetrics outpatient clinic of the Obstetrics and Gynecology Department of Ankara	COVID: 150 Control: 150	27	COVID: 28.73 Control: 28.29	COVID: medical records Diabetes: medical records, OGTT	GDM	>1	9	NR
Xie and Al-Aly (22)	2022	USA	Retrospective cohort	VHA	COVID: 181,280 Control: 4,278,701	11.6	COVID: 60.9 Control: 61.5	COVID: medical records, laboratory test Diabetes: medical records, ICD-10	T2D	>30	6	Age, sex, race, area deprivation index, BMI, smoking status, comorbidities
Yongkang Zhang et al. (39)	2022	USA	Retrospective cohort	PCORnet	COVID: 316,249 Control: 2,775,331	3	Non-hospitalized COVID: 48.9 Hospitalized COVID: 59.9 Non-hospitalized control: 52.8 Hospitalized control: 55.9	COVID: medical records, PCR, ICD-10 Diabetes: medical records, ICD-10	T1D/T2D	31-150	6	Age, sex, race, BMI, ethnicity, smoking status, comorbidities
Zareini et al. (17)	2023	Denmark	Retrospective cohort	Danish National Patient Registry; Danish National Prescription Registry; The Danish Cause of Death Registry; Danish Population Registry Danish Microbiology Database	COVID: 338,670 Control: 1,004,688	84	Total: 12.8	COVID: medical records, PCR Diabetes: medical records	T1D	>1	9	Age, sex, vaccination status

T1D, type 1 diabetes; T2D, type 2 diabetes; GDM, gestational diabetes mellitus; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; ICD-10, International Classification of Diseases 10th Revision; ICD-9, International Classification of Diseases 9th Revision; BMI, body mass index; OGTT, oral glucose tolerance test; HF, heart failure; CKD, chronic kidney diseases; COPD, chronic obstructive pulmonary disease; NR, not reported.

was 6 while other 14 trials (17, 23–28, 30–33, 35–38) was 7 or above, indicating that all cohort studies were of relatively high quality in this meta-analysis. The score of each study is shown in Table 1.

3.4 COVID-19 infection and the risk of overall diabetes

We used data from twenty cohort studies (17, 21–39) to explore the association between a history of COVID-19 and the risk of overall diabetes. The pooling analysis reveals that a history of COVID-19 infection is associated with an increased risk of overall diabetes (HR = 1.46; 95% CI: 1.38-1.55; I² = 92.4%, p < 0.001; Figure 2). The significant heterogeneity in the included studies was interpreted by using a random effect model meta-analysis. Sensitivity analysis shows that none of the individual studies reversed the pool-effect size, indicating that the results are robust (Supplementary Figure 1).

3.5 Subgroup analysis

The results of the subgroup analysis are summarized in Table 2. Increased risks of new incident T1D and T2D are associated with COVID-19 infection but there are no significant differences between the two, T1D (HR=1.44; 95% CI: 1.13-1.82; I² = 89.1%, p = 0.003), and T2D (HR=1.47; 95% CI: 1.36-1.59; I² = 94.6%, p < 0.001). With stratification by sex, males (HR=1.37; 95% CI: 1.30-1.45; I² = 86.2%, p < 0.001) are observed with higher risks compared to those for females (HR=1.29; 95% CI: 1.22-1.365; I² = 75.6%, p < 0.001). In hospitalization-

stratified analysis, the pooled risks of new incident diabetes are significantly higher for patients in intensive care (HR=2.88; 95% CI: 1.73-4.79; I² = 95.4%, p < 0.001) than those for non-hospitalized patients (HR=1.16; 95% CI: 1.07-1.26; I² = 98.8%, p = 0.002) and normal hospitalized patients (HR=2.15; 95% CI: 1.33-3.49; I² = 94.6%, p < 0.001). No significant associations are found in the stratification of vaccination status. For populations from different regions, pooled risks were evaluated as America (HR=1.52; 95% CI: 1.40-1.64; I² = 93.0%, p < 0.001), Asian (HR=1.39; 95% CI: 1.25-1.54; I² = 92.3%, p < 0.001), and Europe (HR=1.60; 95% CI: 1.03-2.49; I² = 90.8%, p = 0.036).

3.6 Publication bias

There is no evidence of a significant publication bias in the COVID-19 infection and risk of new incident diabetes revealed from the visual inspection of the funnel plot (Figure 3). Egger’s test (P = 0.166) shows no publication bias in our meta-analysis either.

4 Discussion

4.1 Main findings

We conducted a meta-analysis of 20 cohort studies covering 60,221,176 individuals, which provided a comprehensive evaluation of the association between COVID-19 and new incident diabetes. We find a significant increase in the risk of all-type diabetes among individuals after COVID-19 infection, with an overall 1.46-fold increase in risk. This indicated that COVID-19 infection might be

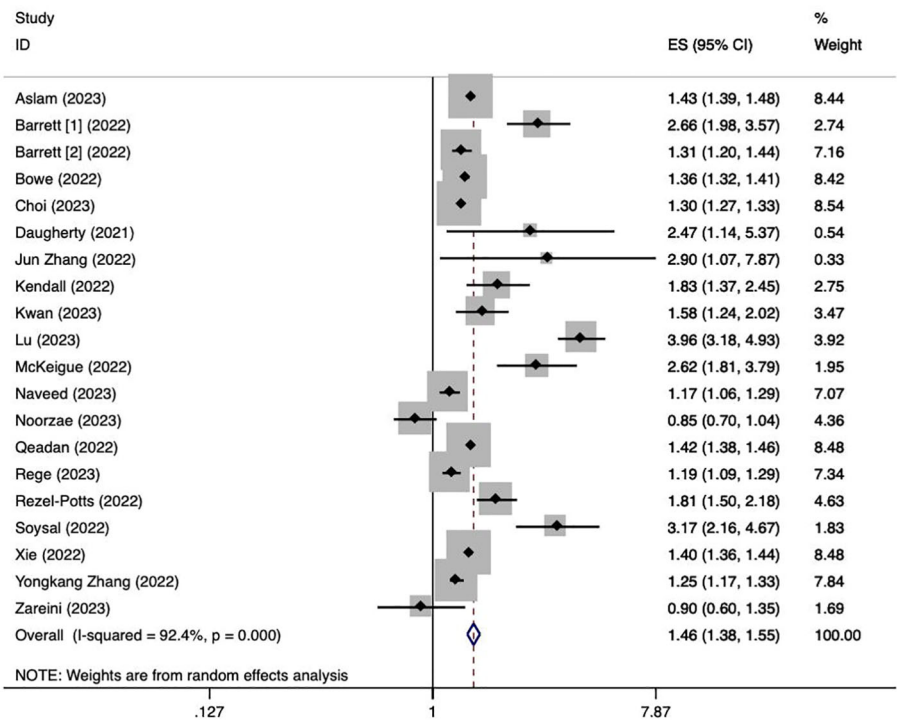


FIGURE 2
Meta-analysis of the risk of overall diabetes after a history of COVID-19. Barrett [1]: data from IQVIA; Barrett [2]: data from Health Verity.

TABLE 2 Subgroup analysis for the risk of diabetes in patients with COVID-19.

Subgroups	Included studies, n	HR (95% CI)	Heterogeneity	
			<i>I</i> ² (%)	<i>p</i> -values
Type of diabetes				
Type 1 diabetes	6	1.44 (1.13,1.82)	89.1%	0.003
Type 2 diabetes	8	1.47 (1.36,1.59)	94.6%	0.000
Sex				
Male	7	1.37 (1.30,1.45)	86.2%	0.000
Female	7	1.29 (1.22,1.36)	75.6%	0.000
Hospitalization				
Non-hospitalized	3	1.16 (1.07,1.26)	87.5%	0.000
Hospitalized	4	2.15 (1.33,3.49)	98.8%	0.002
Intensive care	4	2.88 (1.73,4.79)	95.4%	0.000
Vaccination status				
0 vaccine received	4	1.27 (0.99,1.63)	86.3%	0.064
1 vaccine received	4	1.09 (0.73,1.63)	67.9%	0.676
≥2 vaccine received	3	1.21 (0.92,1.60)	55.7%	0.178
Region				
America	11	1.52 (1.40,1.64)	93.0%	0.000
Asian	5	1.39 (1.25,1.54)	92.3%	0.000
Europe	5	1.60 (1.03,2.49)	90.8%	0.036

an independent risk factor for new incident diabetes. The importance of screening, prevention, and management of diabetes for patients ever infected with COVID-19 should be emphasized.

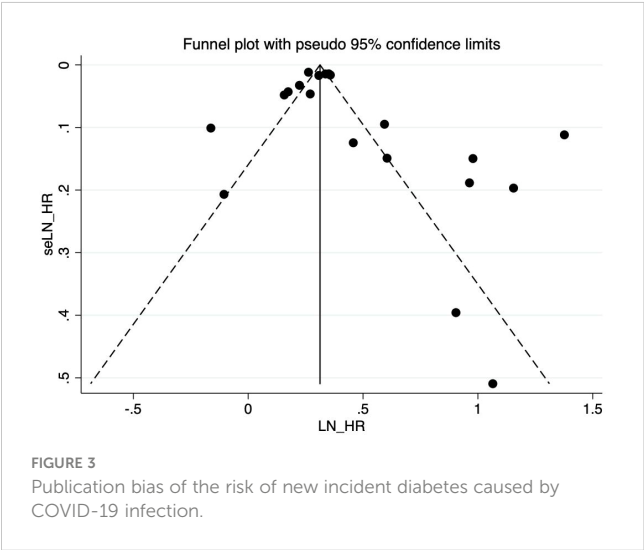
4.2 Comparison with previous studies

Our analysis demonstrated a consistent result with previous reviews (14–16), showing that COVID-19 infection increased the

risk of all-type diabetes. In addition, Li et al. (40) explored the relationship between new-onset diabetes, hyperglycemia, and COVID-19 infection, showing an elevated incidence and risk. In a review that specifically targeted T2D (41), a higher prevalence of diabetes in people with previous COVID-19 was illustrated, which further corroborated our findings. Compared to prior studies, we added more recent studies and analyzed the data in subgroups, to provide stronger evidence for the association between COVID-19 and diabetes. Simultaneously, we only included data from cases with a confirmed diagnosis of diabetes, contributing to reduced clinical heterogeneity and greater reliability. Although the risk variance between T1D and T2D is not significant in this analysis, a previous study found a higher risk for new incident T2D than T1D for all included cohorts (16). They also indicated that males with COVID-19 were associated with a higher risk of diabetes compared to females, which echoed our conclusions. We assessed the risks between subgroups of hospitalization, vaccination status, and incident diabetes for the first time, and found that an increased risk of diabetes was associated with the exacerbation of hospitalization. However, the risk of new incident diabetes in patients who received vaccination was not statistically significant.

4.3 Interpretation of findings

So far, the pathophysiological mechanism of the association between COVID-19 and diabetes is not entirely clear. It has been



suggested that SARS-CoV-2 specifically induces the damage of β -cells, thereby impairing insulin production (42, 43). Angiotensin-converting enzyme 2 (ACE2) is the main receptor of SARS-CoV-2 to gain entry into human cells (44). Several studies have found the ACE2 expression in pancreatic β -cells (42, 45–47), leading to speculation that SARS-CoV-2 may triggers β -cell damage by penetrating the cells using ACE2 (48). In addition to ACE2, other SARS-CoV-2 related entry factors such as TMPRSS2, NRP1, and TRFC are also expressed in pancreatic β -cells, which might play roles in β -cell damage through similar mechanisms (42, 49). However, the expressions of ACE2 and TMPRSS2 in pancreatic β -cells were doubted in other studies (50–52). Therefore, further research is necessary.

ACE2 is a key enzyme in the renin-angiotensin system (RAS). Membrane-bound ACE2 is responsible for catalyzing the conversion from Ang II into Ang-(1-7) (53). Down-regulation of ACE2 is found in patients with COVID-19 that enhances activation of the RAS axis, resulting in decreased insulin and glucose delivery to tissues and impairment of insulin signaling pathways, all of which lead to insulin resistance (54, 55). Additionally, uncontrolled inflammatory response caused by RAS imbalance might account for the potential role in pancreatic dysfunction (53, 54).

Autopsy tissue from deceased COVID-19 patients showed that local inflammation and infiltration of immune cells were associated with impairment of β -cells, causing various degrees of metabolic dysregulation (50). SARS-CoV-2 triggers a macrophage-mediated cytokine storm in which the overactivation of immune cells and persistently increasing cytokines promote excessive inflammation and further induced β -cell damage (56). SARS-CoV-2 induce a decreased chromatin-modifying enzyme SETDB2, causing increased transcription of inflammatory cytokines which impair the pancreas (56).

Steroids are used to treat COVID-19, but their pharmacological effects pose extra burden on blood glucose control (57). Steroid-induced hyperglycemia in patients with COVID-19 may be associated with an increased risk of new incident diabetes (9). A cohort study revealed a higher risk of diabetes in COVID-19 patients using glucocorticoids compared to those without steroid treatments (58), which corroborates this perspective.

Lockdowns during the COVID-19 pandemic slowed the rate of infection but caused negative mental health consequences and adverse health-related behaviors, including reduced physical activities, unhealthy eating, smoking, and binge drinking, which are risk factors for diabetes (59). Symptoms of long COVID such as fatigue, muscle pain, and dyspnea, limit exercise capacity (60), therefore sedentary lifestyles have become common. These changes of lifestyle have a series of pathophysiological effects, including metabolic consequences represented by insulin resistance, which might increase the risks of new incident diabetes (61).

In the subgroup analysis, males with a history of COVID-19 have a higher risk of new incident diabetes than females. A previous study has shown that males infected with COVID-19 are more susceptible to worse outcomes and death, independent of age (62). From another perspective, a study on rats indicated a gender-related difference of ACE2 expression, that ACE2 content was slightly lower in males compared to females (63). This might be attributed to diabetes-related pathophysiological changes. Considering

vaccination has shown a potential effectiveness on improvement in long-COVID symptoms (64), it might be also helpful to prevent new incident diabetes in patients ever infected with COVID-19, which accounted for the insignificant association between COVID-19 and incident diabetes.

4.4 Implications and limitations

The pandemic of COVID-19 has placed a tremendous burden on humanity and might co-exist with us for many years. Our meta-analysis summarizes the existing evidence of the association between COVID-19 infection and the risk of new incident diabetes and shows that a history of COVID-19 is a risk factor for all-type diabetes. It suggests that the identification of high-risk groups of diabetes should cover patients with COVID-19, which is conducive to the early detection and management of diabetes. Vaccination is of critical importance for individuals to reduce the risks of adverse outcomes. More studies should be fostered to clarify the potential mechanisms underlying the COVID-related diabetes, given there might be a complex combination of pathophysiological processes behind the COVID-19 infection and new incident diabetes.

Meanwhile, this study has certain limitations. We only included cohort studies of which retrospective cohort studies are the majority. Though there is a broad and deep use of electronic databases based on validated definitions, it still cannot exclude the bias caused by misclassification, particularly for diabetes types. Moreover, the intervals between COVID-19 infection and diabetes diagnosis differ in studies, which might lead to high heterogeneity, and make it hard to discuss the risks of incident diabetes in different phases of COVID-19. Age stratification is diverse among included studies, so we did not pool related data.

5 Conclusions

Patients ever infected with COVID-19 had an elevated incidence and risk of new incident diabetes. However, more studies are necessary to specify the pathophysiological mechanisms underlying this association.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

Author contributions

JZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. YW: Data curation, Formal analysis,

Investigation, Methodology, Writing – review & editing. RX: Data curation, Investigation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Harcourt BE, Penfold SA, Forbes JM. Coming full circle in diabetes mellitus: from complications to initiation. *Nat Rev Endocrinol.* (2013) 9:113–23. doi: 10.1038/nrendo.2012.236
- Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet (London England).* (2017) 389:2239–51. doi: 10.1016/S0140-6736(17)30058-2
- Alam S, Hasan MK, Neaz S, Hussain N, Hossain MF, Rahman T. Diabetes mellitus: insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. *Diabetology.* (2021) 2:36–50. doi: 10.3390/diabetology2020004
- Rey-Reñones C, Martínez-Torres S, Martín-Luján FM, Pericas C, Redondo A, Vilaplana-Carnerero C, et al. Type 2 diabetes mellitus and COVID-19: A narrative review. *Biomedicine.* (2022) 10:2089. doi: 10.3390/biomedicine10092089
- Lima-Martínez MM, Carrera Boada C, Madera-Silva MD, Marín W, Contreras M. COVID-19 and diabetes: A bidirectional relationship. *Clinica e investigación en arteriosclerosis: publicación oficial la Sociedad Española Arterioscler.* (2021) 33:151–7. doi: 10.1016/j.arteri.2020.10.001
- Raveendran AV, Misra A. Post COVID-19 syndrome (“Long COVID”) and diabetes: challenges in diagnosis and management. *Diabetes Metab syndrome.* (2021) 15:102235. doi: 10.1016/j.dsx.2021.102235
- Cao H, Baranova A, Wei X, Wang C, Zhang F. Bidirectional causal associations between type 2 diabetes and COVID-19. *J Med Virol.* (2023) 95:e28100. doi: 10.1002/jmv.28100
- Sathish T, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. *Diabetes Metab.* (2021) 47:101204. doi: 10.1016/j.diabet.2020.10.002
- Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. *Diabetes Care.* (2021) 44:2645–55. doi: 10.2337/dc21-1318
- Yuan Y, Jiao B, Qu L, Yang D, Liu R. The development of COVID-19 treatment. *Front Immunol.* (2023) 14:1125246. doi: 10.3389/fimmu.2023.1125246
- World Health Organization. *Statement on the fifteenth meeting of the IHR, (2005) Emergency Committee on the COVID-19 pandemic* (2023). Available online at: <https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-%282005%29-emergency-committee-regarding-the-coronavirus-disease-%28covid-19%29-pandemic> (Accessed 11 April 2024).
- Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* (2023) 21:133–46. doi: 10.1038/s41579-022-00846-2
- Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature.* (2021) 594:259–64. doi: 10.1038/s41586-021-03553-9
- Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes Obes Metab.* (2021) 23:870–4. doi: 10.1111/dom.14269
- Zhang T, Mei Q, Zhang Z, Walline JH, Liu Y, Zhu H, et al. Risk for newly diagnosed diabetes after COVID-19: a systematic review and meta-analysis. *BMC Med.* (2022) 20:444. doi: 10.1186/s12916-022-02656-y
- Lai H, Yang M, Sun M, Pan B, Wang Q, Wang J, et al. Risk of incident diabetes after COVID-19 infection: A systematic review and meta-analysis. *Metabolism: Clin Exp.* (2022) 137:155330. doi: 10.1016/j.metabol.2022.155330
- Zareini B, Sørensen KK, Eiken PA, Fischer TK, Kristensen PL, Lendorf ME, et al. Association of COVID-19 and development of type 1 diabetes: A Danish nationwide register study. *Diabetes Care.* (2023) 46:1477–82. doi: 10.2337/dc23-0428
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Rev.* (2021) 10:89. doi: 10.1186/s13643-021-01626-4
- Taylor KS, Mahtani KR, Aronson JK. Summarising good practice guidelines for data extraction for systematic reviews and meta-analysis. *BMJ Evidence-Based Med.* (2021) 26:88–90. doi: 10.1136/bmjebm-2020-111651
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses* (2014). Oxford. Available online at: http://www.evidencebasedpublichealth.de/download/Newcastle_Ottawa_Scale_Pope_Bruce.pdf (Accessed March 12, 2023).
- Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med.* (2022) 28:2398–405. doi: 10.1038/s41591-022-02051-3
- Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* (2022) 10:311–21. doi: 10.1016/S2213-8587(22)00044-4
- Aslam B, Naeem B, Aman S, Majeed M. Association between covid-19 and diabetes mellitus. *Pakistan J Med Health Sci.* (2023) 17:117–9. doi: 10.53350/pjmhs2023174117
- Barrett CE, Koyama AK, Alvarez P, Chow W, Lundeen EA, Perrine CG, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years - United States, March 1, 2020-June 28, 2021. *MMWR. Morbidity Mortality Weekly Rep.* (2022) 71:59–65. doi: 10.15585/mmwr.mm7102e2
- Choi JH, Kim KM, Song K, Seo GH. Risk for Newly Diagnosed Type 2 Diabetes Mellitus after COVID-19 among Korean Adults: A Nationwide Matched Cohort Study. *Endocrinol Metab (Seoul Korea).* (2023) 38:245–52. doi: 10.3803/EnM.2023.1662
- Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ (Clinical Res ed.).* (2021) 373:n1098. doi: 10.1136/bmj.n1098
- Zhang J, Shu T, Zhu R, Yang F, Zhang B, Lai X. The long-term effect of COVID-19 disease severity on risk of diabetes incidence and the near 1-year follow-up outcomes among postdischarge patients in Wuhan. *J Clin Med.* (2022) 11:3094. doi: 10.3390/jcm11113094
- Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Association of SARS-coV-2 infection with new-onset type 1 diabetes among pediatric patients from 2020 to 2021. *JAMA Network Open.* (2022) 5:e2233014. doi: 10.1001/jamanetworkopen.2022.33014
- Kwan AC, Ebinger JE, Botting P, Navarette J, Claggett B, Cheng S. Association of COVID-19 vaccination with risk for incident diabetes after COVID-19 infection. *JAMA Network Open.* (2023) 6:e2255965. doi: 10.1001/jamanetworkopen.2022.55965
- Lu JY, Wilson J, Hou W, Fleysler R, Herold BC, Herold KC, et al. Incidence of new-onset in-hospital and persistent diabetes in COVID-19 patients: comparison with influenza. *EBioMedicine.* (2023) 90:104487. doi: 10.1016/j.ebiom.2023.104487
- McKeigue PM, McGurnaghan S, Blackburn L, Bath LE, McAllister DA, Caparrotta TM, et al. Relation of incident type 1 diabetes to recent COVID-19 infection: cohort study using e-health record linkage in Scotland. *Diabetes Care.* (2023) 46:921–8. doi: 10.2337/dc22-0385

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1429848/full#supplementary-material>

32. Naveed Z, Velásquez García HA, Wong S, Wilton J, McKee G, Mahmood B, et al. Association of COVID-19 infection with incident diabetes. *JAMA Network Open*. (2023) 6:e238866. doi: 10.1001/jamanetworkopen.2023.8866
33. Noorzae R, Junker TG, Hviid AP, Wohlfahrt J, Olsen SF. Risk of type 1 diabetes in children is not increased after SARS-CoV-2 infection: A nationwide prospective study in Denmark. *Diabetes Care*. (2023) 46:1261–4. doi: 10.2337/dc22-2351
34. Qeadan F, Tingey B, Egbert J, Pezzolesi MG, Burge MR, Peterson KA, et al. The associations between COVID-19 diagnosis, type 1 diabetes, and the risk of diabetic ketoacidosis: A nationwide cohort from the US using the Cerner Real-World Data. *PLoS One*. (2022) 17:e0266809. doi: 10.1371/journal.pone.0266809
35. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia*. (2022) 65:949–54. doi: 10.1007/s00125-022-05670-0
36. Reges O, Test T, Hoshen M, Cicurel A, Saliba W, Greenland P, et al. Time-varying association of acute and post-acute COVID-19 with new-onset diabetes mellitus among hospitalized and non-hospitalized patients. *BMJ Open Diabetes Res Care*. (2023) 11:e003052. doi: 10.1136/bmjdc-2022-003052
37. Rezel-Potts E, Douiri A, Sun X, Chowieniczky PJ, Shah AM, Gulliford MC. Cardiometabolic outcomes up to 12 months after COVID-19 infection: A matched cohort study in the UK. *PLoS Med*. (2022) 19:e1004052. doi: 10.1371/journal.pmed.1004052
38. Soysal Ç, Yilmaz E. The effect of previous covid-19 infection on gestational diabetes mellitus. *Gazi Med J*. (2022) 33:397–400. <https://medicaljournal.gazi.edu.tr/index.php/GMJ/article/view/3594>.
39. Zhang Y, Romieu-Hernandez A, Boehmer TK, Azziz-Baumgartner E, Carton TW, Gundlapalli AV, et al. Association between SARS-CoV-2 infection and select symptoms and conditions 31 to 150 days after testing among children and adults. *BMC Infect Dis*. (2024) 24:181. doi: 10.1186/s12879-024-09076-8
40. Li J, Li Y, Wang Z, Liu N, He L, Zhang H. Increased risk of new-onset diabetes in patients with COVID-19: a systematic review and meta-analysis. *Front Public Health*. (2023) 11:1170156. doi: 10.3389/fpubh.2023.1170156
41. Bellia C, Andreoli A, D'Ippolito I, Scola L, Barraco S, Meloni M, et al. Prevalence and risk of new-onset diabetes mellitus after COVID-19: a systematic review and meta-analysis. *Front Endocrinol*. (2023) 14:1215879. doi: 10.3389/fendo.2023.1215879
42. Wu CT, Lidsky PV, Xiao Y, Lee IT, Cheng R, Nakayama T, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab*. (2021) 33:1565–1576.e5. doi: 10.1016/j.cmet.2021.05.013
43. Accili D. Can COVID-19 cause diabetes? *Nat Metab*. (2021) 3:123–5. doi: 10.1038/s42255-020-00339-7
44. Gusev E, Sarapultsev A, Solomatina L, Chershevnev V. SARS-CoV-2-specific immune response and the pathogenesis of COVID-19. *Int J Mol Sci*. (2022) 23:1716. doi: 10.3390/ijms23031716
45. Fignani D, Licata G, Brusco N, Nigi L, Grieco GE, Marselli L, et al. SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β -cells and in the human pancreas microvasculature. *Front Endocrinol*. (2020) 11:596898. doi: 10.3389/fendo.2020.596898
46. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol*. (2020) 18:2128–2130.e2. doi: 10.1016/j.cgh.2020.04.040
47. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta diabetologica*. (2010) 47:193–9. doi: 10.1007/s00592-009-0109-4
48. Wang Y, Guo H, Wang G, Zhai J, Du B. COVID-19 as a trigger for type 1 diabetes. *J Clin Endocrinol Metab*. (2023) 108:2176–83. doi: 10.1210/clinem/dgad165
49. Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. (2021) 3:149–65. doi: 10.1038/s42255-021-00347-1
50. Steenblock C, Richter S, Berger I, Barovic M, Schmid J, Schubert U, et al. Viral infiltration of pancreatic islets in patients with COVID-19. *Nat Commun*. (2021) 12:3534. doi: 10.1038/s41467-021-23886-3
51. Coate KC, Cha J, Shrestha S, Wang W, Gonçalves LM, Almaça J, et al. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β Cells. *Cell Metab*. (2020) 32:1028–1040.e4. doi: 10.1016/j.cmet.2020.11.006
52. Kusmartseva I, Wu W, Syed F, van der Heide V, Jorgensen M, Joseph P, et al. Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. *Cell Metab*. (2020) 32:1041–1051.e6. doi: 10.1016/j.cmet.2020.11.005
53. Lanza K, Perez LG, Costa LB, Cordeiro TM, Palmeira VA, Ribeiro VT, et al. Covid-19: the renin-angiotensin system imbalance hypothesis. *Clin Sci (London England: 1979)*. (2020) 134:1259–64. doi: 10.1042/CS20200492
54. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J hypertension*. (2005) 23:463–73. doi: 10.1097/01.hjh.0000160198.05416.72
55. Mehrabadi ME, Hemmati R, Tashakor A, Homaei A, Yousefzadeh M, Hemati K, et al. Induced dysregulation of ACE2 by SARS-CoV-2 plays a key role in COVID-19 severity. *Biomedicine pharmacotherapy = Biomedicine pharmacotherapie*. (2021) 137:111363. doi: 10.1016/j.biopha.2021.111363
56. Melvin WJ, Audu CO, Davis FM, Sharma SB, Joshi A, DenDekker A, et al. Coronavirus induces diabetic macrophage-mediated inflammation via SETDB2. *Proc Natl Acad Sci United States America*. (2021) 118:e2101071118. doi: 10.1073/pnas.2101071118
57. Sosale A, Sosale B, Kesavadev J, Chawla M, Reddy S, Saboo B, et al. Steroid use during COVID-19 infection and hyperglycemia - What a physician should know. *Diabetes Metab syndrome*. (2021) 15:102167. doi: 10.1016/j.dsx.2021.06.004
58. Jabbour RM, Hallit S, Saliby R, Baydoun AEK, Nakhoul N. Is COVID-19 incriminated in new onset type 2 diabetes mellitus in Lebanese adults? *BMC Res Notes*. (2023) 16:176. doi: 10.1186/s13104-023-06454-4
59. Keng SL, Stanton MV, Haskins LB, Almenara CA, Ickovics J, Jones A, et al. COVID-19 stressors and health behaviors: A multilevel longitudinal study across 86 countries. *Prev Med Rep*. (2022) 27:101764. doi: 10.1016/j.pmedr.2022.101764
60. Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its management. *Int J Biol Sci*. (2022) 18:4768–80. doi: 10.7150/ijbs.75056
61. Martinez-Ferran M, de la Guía-Galipienso F, Sanchis-Gomar F, Pareja-Galeano H. Metabolic impacts of confinement during the COVID-19 pandemic due to modified diet and physical activity habits. *Nutrients*. (2020) 12:1549. doi: 10.3390/nu12061549
62. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health*. (2020) 8:152. doi: 10.3389/fpubh.2020.00152
63. Xie X, Chen J, Wang X, Zhang F, Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci*. (2006) 78:2166–71. doi: 10.1016/j.lfs.2005.09.038
64. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. *EclinicalMedicine*. (2022) 53:101624. doi: 10.1016/j.eclinm.2022.101624



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Marcos Edgar Herkenhoff,
University of São Paulo, Brazil
Xia Jiang,
Karolinska Institutet (KI), Sweden

*CORRESPONDENCE

Jie He
✉ cqmuhejie@stu.cqmu.edu.cn

RECEIVED 17 April 2024

ACCEPTED 19 August 2024

PUBLISHED 10 September 2024

CITATION

Li S, Du Z, Ma H, Cai L, Liu X and He J (2024)
Mendelian randomization provides causal
association between COVID-19 and thyroid
cancer: insights from a multi-cancer analysis.
Front. Oncol. 14:1419020.
doi: 10.3389/fonc.2024.1419020

COPYRIGHT

© 2024 Li, Du, Ma, Cai, Liu and He. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/)
(CC BY). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Mendelian randomization provides causal association between COVID-19 and thyroid cancer: insights from a multi-cancer analysis

Shuhong Li¹, Zedong Du¹, Hui Ma¹, Liang Cai¹, Xiao Liu¹
and Jie He^{2*}

¹Department of Oncology, Chengdu Second People's Hospital, Chengdu, China, ²Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Since the onset of the COVID-19 pandemic, the SARS-CoV-2 virus has caused over 600 million confirmed infections and more than 6.8 million deaths worldwide, with ongoing implications for human health. COVID-19 has been extensively documented to have extrapulmonary manifestations due to the widespread expression of necessary ACE2 receptors in the human body. Nevertheless, the association between COVID-19 and cancer risk remains inadequately explored. This study employs Mendelian randomization (MR) methods to examine the causal relationship between genetic variations associated with COVID-19 and the risk of developing cancer. The findings indicate that COVID-19 has negligible impact on most cancer risks. Interestingly, a higher COVID-19 impact is associated with a decreased risk of thyroid cancer. In summary, our findings demonstrate a genetic correlation between COVID-19 and thyroid cancer, contributing to our understanding of the interplay between COVID-19 and cancer risk.

KEYWORDS

Mendelian randomization, COVID-19, SARS-CoV-2, cancer risk, thyroid

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease primarily characterized by respiratory symptoms caused by the SARS-CoV-2 virus. It rapidly spread worldwide after its initial reporting in 2019. As of now, there have been over 600 million confirmed cases and over 6.8 million reported deaths (1–3). Despite the highly contagious and harmful nature of

Abbreviations: MR, Mendelian randomization; COVID-19, Coronavirus Disease 2019; ARDS, Acute respiratory distress syndrome; GWAS, Genome-Wide Association Study; IV, Instrumental Variable; SNP, Single Nucleotide Polymorphism; IVW, inverse-variance weighted; OR, odds ratios; CI, confidence interval; FDR, False Discovery Rate; HT, Hashimoto's Thyroiditis; GD, Graves' Disease.

the SARS-CoV-2 virus, not all individuals progress to severe illness. Studies indicate that approximately 81% of patients infected with the SARS-CoV-2 virus exhibit mild symptoms, 14% develop severe symptoms requiring hospitalization, and 5% progress to critical conditions requiring intensive care and respiratory support (4). Furthermore, the SARS-CoV-2 virus infects human cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in the human body (5). This infection leads to extensive extrapulmonary effects, including hematologic, cardiovascular, neurologic, and dermatologic systems, among others (6). Observations suggest that COVID-19 causes acute damage and functional abnormalities in these organs and tissue during the infection period, with long-term effects that require further observation (7).

Despite more than three years having passed since the beginning of the pandemic, research on the long-term effects of COVID-19 on humans is only just beginning. Follow-up studies on COVID-19 survivors have reported a series of long-term complications, including pulmonary abnormalities, endothelial damage, immune system dysregulation, and hypercoagulability, among others (7). However, the impact of cancer occurrence appears to have been overlooked in the assessment of numerous long-term effects, possibly due to the relatively short duration of the pandemic compared to the process of cancer development. The SARS-CoV-2 virus widely disseminates in the human body and persists for an extended period, which increases the risk of tumor occurrence in susceptible individuals (8–11). Limited studies have suggested that the SARS-CoV-2 virus might play a role similar to oncogenic viruses in the lungs and have emphasized the need for further research on the impact of COVID-19 on cancer (12, 13). In fact, virus-induced cancer occurrence is a common phenomenon in humans, including well-known viruses like the Epstein-Barr virus, hepatitis viruses, and human papillomavirus, which can cause carcinogenesis in multiple organs such as the blood, liver, reproductive system, skin, and more (14–16). Therefore, investigating the impact of COVID-19 on human cancer risk is a crucial research gap that needs to be addressed.

The development of cancer is a lengthy process, which poses challenges for existing observational data gathered from COVID-19 patients in generating robust conclusions regarding long-term cancer risk. Mendelian randomization (MR) can assist in overcoming this issue by examining genetic variation perspectives (17). MR uses randomly allocated genetic variants, known as Instrumental Variables (IV), to simulate the control of exposure factors in randomized controlled trials. Its goal is to obtain unconfounded estimates of the association between risk factors and outcomes, thereby avoiding potential residual confounding and reverse causation that observational studies might suffer from (18). Additionally, with the advancement of sequencing technologies, researchers have decoded extensive genomic sequences and mutations from various biological samples. Several large-scale Genome-Wide Association Study (GWAS) datasets have been shared, and analysis tools have been developed to facilitate the evaluation of the impact of SARS-CoV-2 virus on human cancer occurrence (18, 19). In our study, we employed MR analysis to assess the impact of three COVID-19 traits on the risk of 16 types of

cancer and thyroid-related disorders in humans. We believe that this research enhances our understanding of COVID-19, particularly by providing new insights into the relationship between COVID-19 and human cancer risk.

Methods

Data source

This study utilized a total of 23 open-access Genome-Wide Association Study (GWAS) summary datasets, which included 3 datasets related to COVID-19, 16 datasets related to cancer. The summary data for all these datasets were obtained from the IEU OPEN GWAS PROJECT database (19). The selection criteria were based on incorporating the most recent, largest sample size, and openly accessible research data. The study numbers, along with detailed phenotype definitions, sample sizes, and other relevant information, have been provided in [Supplementary Table S1](#).

Filtration of IV

IV are tools used in mendelian randomization analysis to address endogeneity issues (20). They utilize genetic variations as instrumental variables to help infer causal relationships between observed variables (exposure factors) and outcomes. For each observed variable or exposure factor, genetic variations that are associated with the phenotype ($p < 5 \times 10^{-8}$) and are unrelated in terms of clustering and physical distance ($r^2 < 0.001$, distance $> 10,000$ kb) across the entire genome are selected (18). In the end, 17 Single Nucleotide Polymorphisms (SNPs) related to the three COVID-19 phenotypes were identified and used as IVs for further analysis in Mendelian randomization, as outlined in [Supplementary Table S2](#).

MR and sensitivity analysis

Two-sample MR analysis was employed to infer the causal associations between the exposure factors represented by IVs and various cancer outcomes. In this analysis, the three COVID-19 traits serve as exposure factors, and their associations with multiple cancer outcomes are the primary focus of the study design. The main evaluation method utilized in this study is the inverse-variance weighted (IVW) method, which is one of the most important methods in MR analysis (18). Finally, the risk contribution of the exposure factors to the outcomes is described using odds ratios (OR) and 95% confidence intervals (CI). Additionally, the effects of individual exposure SNPs on outcomes are evaluated using the Wald ratio method (18).

Due to the potential influence of pleiotropy in MR analysis, supplementary evidence is provided using the weighted median method (21) and MR-Egger regression (22). The MR-Egger method is employed to fit a linear regression to estimate intercepts and conduct statistical tests to assess the presence of pleiotropy. To

evaluate the presence of heterogeneity in each design, Cochran’s Q test, funnel plots and MRPRESSO methods are utilized (23).

Statistical analysis and visualization

The statistical analysis for this study was conducted using R software (Version 4.2.1) (24). The software package employed in the analysis process was “TwoSampleMR” (18). Forest plots were generated using the “forestploter” package (25). Visualizations such as scatter plots and funnel plots were created using the “TwoSampleMR” package. In this study, a significance level of 0.05 was utilized, meaning that we rejected the null hypothesis when the p-value was less than 0.05. To address non-independent multiple hypothesis testing, the False Discovery Rate (FDR) method was applied for multiple hypothesis correction, ensuring accurate control over the p-values.

Results

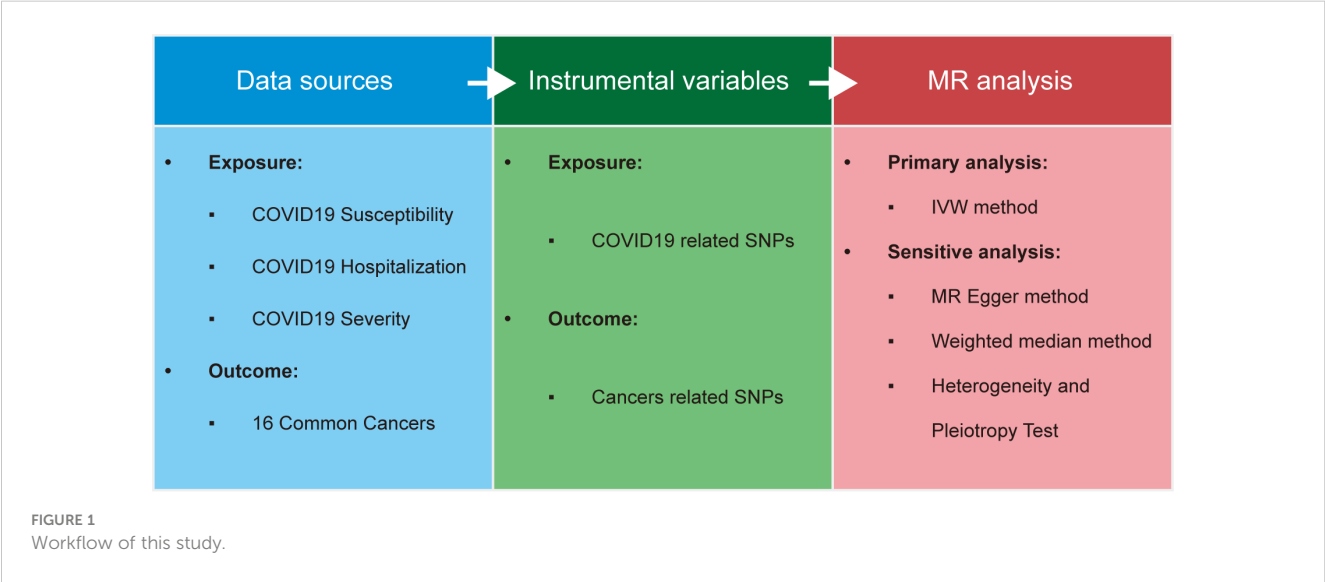
Identification of genetic IV

Complete Analytical Approach of the Study as Illustrated in Figure 1. Firstly, we extracted a total of 17 SNP loci (Supplementary Table S2) closely associated with COVID-19 exposure from summary data of Genome-Wide Association Studies (GWAS) conducted in three distinct cohorts investigating COVID-19 patient susceptibility, hospitalization, and severity. Most of these loci were unique to each phenotype, with the exception of rs2109069 (Supplementary Table S2), which was common across all three phenotypes. Simultaneously, we collected summary data from GWAS studies conducted on 16 common human multi-site cancers. In these datasets, we identified 277 SNP loci most relevant

to various types of cancer (Supplementary Table S3). The included study samples ranged from 182,625 to 1,887,658, with the number of cases ranging from 357 to 32,494. Detailed information about these cohorts is provided in the Supplementary Materials (Supplementary Table S1).

Association between COVID-19 risk and cancer risk

We utilized SNPs associated with COVID-19 susceptibility, hospitalization, and severity traits as exposure factors for mendelian randomization allocation. We assessed their impact on the risk of various cancers using the IVW, MR Egger, and Weighted Median methods (Supplementary Table S4). We found that COVID-19 susceptibility did not significantly influence the risk of various cancers, except for thyroid cancer (OR 0.52, 95% CI 0.33 to 0.84, p-value 0.007) (Figure 2). Additionally, intriguingly, the increase in the effects of COVID-19 hospitalization (OR 0.75, 95% CI 0.60 to 0.93, p-value 0.009) and severity (OR 0.86, 95% CI 0.75 to 0.98, p-value 0.029) was also associated with a reduced risk of thyroid cancer, while having no significant impact on other cancers (Figures 3, 4). MR Egger and Weighted Median methods displayed results similar to IVW, although some of the results were not significant (Figures 5A–C). Estimating the effects of individual SNPs on thyroid cancer outcomes using the Wald ratio method, we found it was the collective effect of multiple SNPs, rather than individual SNPs, that influenced the outcome (Figures 5D–F). In summary, these findings suggest a clear genetic-level causal link between the increased risks of COVID-19 susceptibility, hospitalization, and severity and the reduced risk of thyroid cancer, as indicated by various methods. However, reverse MR analysis suggests that there is no reverse causal relationship between exposure and outcome (Supplementary Table S5).



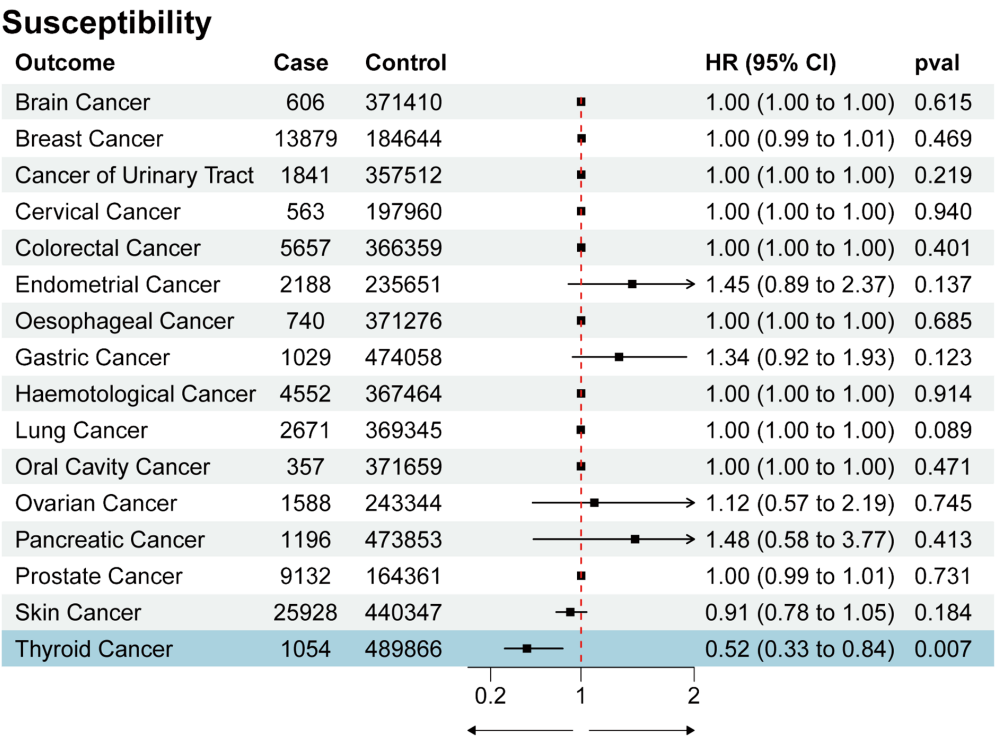


FIGURE 2
Forest plot of COVID-19 susceptibility effects on multi-cancer risk.

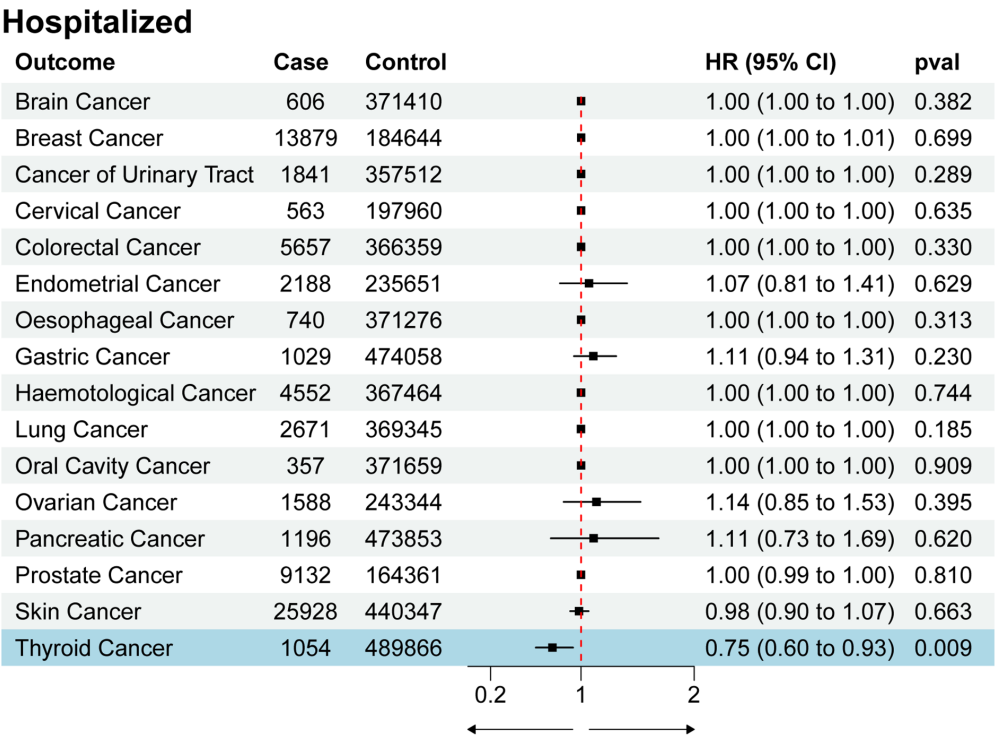


FIGURE 3
Forest plot of COVID-19 hospitalization effects on multi-cancer risk.

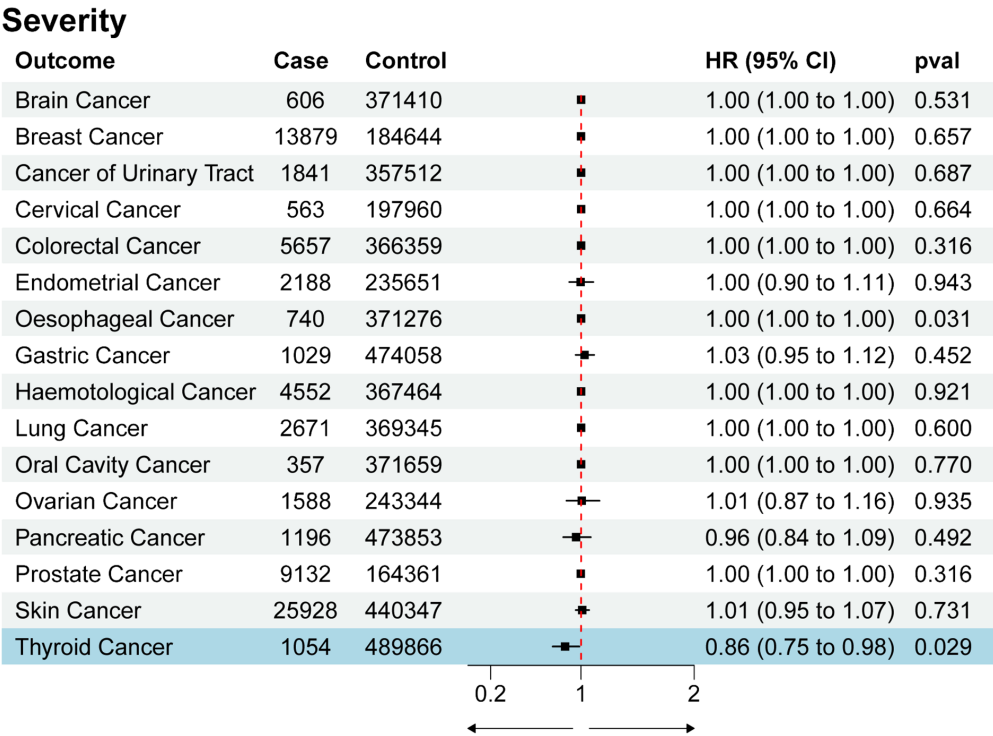


FIGURE 4
Forest plot of COVID-19 severity effects on multi-cancer risk.

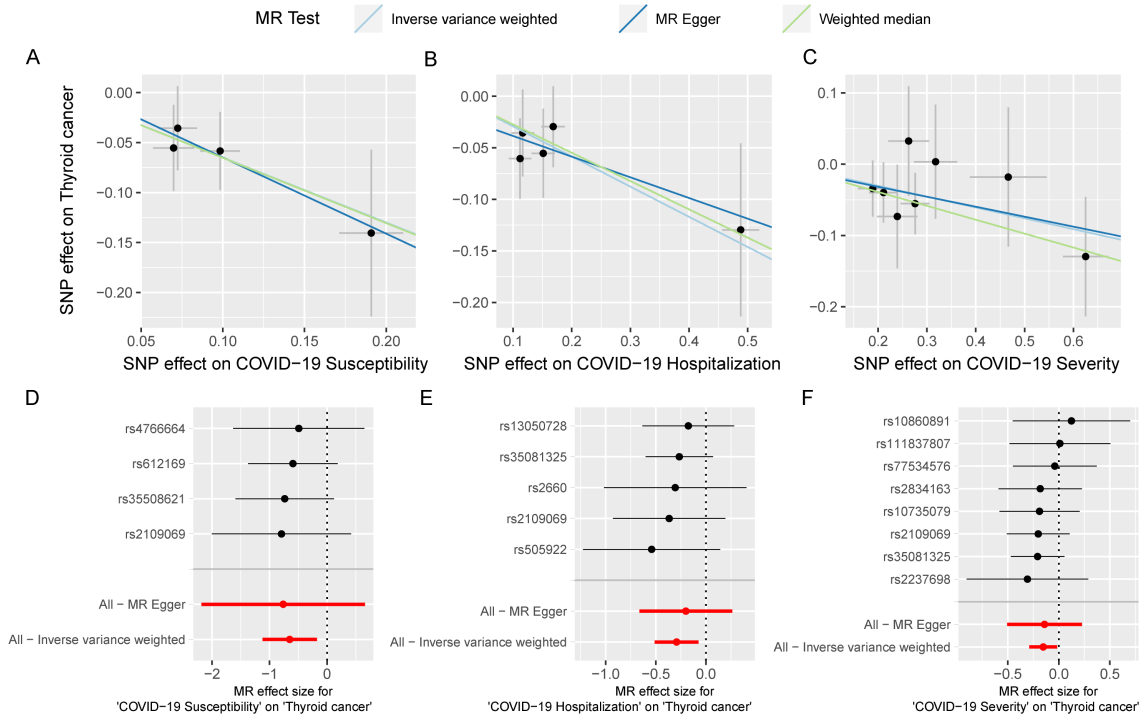


FIGURE 5
The MR analysis results between COVID-19 and multi-cancer risk are robust. scatter plot of casual estimate for MR test between COVID-19 susceptibility, hospitalization and severity on thyroid cancer (A-C); forest plot of single SNP effect of COVID-19 susceptibility, hospitalization and severity on thyroid cancer (D-F).

Sensitivity analysis

To validate the reliability of the analysis results, conducting sensitivity analysis is essential. We first used Cochran's Q statistic to test the heterogeneity of the studies to avoid the impact of errors from non-experimental designs on the results. However, no heterogeneity was found to exist (Supplementary Table S4). Funnel plots showed symmetrical effect sizes around the point estimates of the exposure factors, suggesting no apparent pleiotropy (Figures 6A–C). Employing MR-PRESSO, we further scrutinized horizontal pleiotropy in our MR analysis. The non-significant p values (0.995, 0.998, 1) confirm the robustness of our findings in thyroid cancer research (Supplementary Table S6). Furthermore, the results of the leave-one-out analysis indicated that no individual SNP significantly influenced the outcomes, demonstrating the stability of the results (Figures 6D–F). In summary, the sensitivity analysis results indicate that the findings of this study are robust, free from interference caused by heterogeneity and pleiotropy.

Discussion

Despite a wealth of evidence indicating that cancer patients face heightened risks of severe COVID-19 symptoms and increased mortality rates due to their compromised immune systems (26), limited research has been conducted on the potential cancer risk among individuals infected with COVID-19. The absence of

standardized long-term care and health guidelines for COVID-19 patients, particularly concerning its impact on the occurrence of malignancies, contributes to our limited understanding in this area. We propose that this represents a matter of significant public health concern with universal implications.

To address this question, we employed two-sample Mendelian randomization (MR) to evaluate the association between COVID-19 susceptibility, hospitalization, and severity and the risk of human cancers. Our findings suggest that, among these three types of exposure to COVID-19, there is no significant effect on the incidence risk of most cancers. Despite SARS-CoV-2 being primarily a respiratory virus, exposure to it does not increase the odds ratio (OR) for lung cancer. However, an interesting exception is observed in the case of thyroid cancer in which both COVID-19 susceptibility, hospitalization, and severity are associated with a reduced risk (OR 0.52 for susceptibility, OR 0.75 for hospitalization, and OR 0.86 for severity). This suggests that genetic susceptibility to COVID-19 may have a potential protective effect on thyroid function and the risk of thyroid cancer, although the precise underlying mechanisms remain unclear.

The first question is why COVID-19 does not impact the incidence of most human cancers. However, our findings suggest that COVID-19 does not appear to raise the risk of cancer. One potential explanation is that the duration of SARS-CoV-2 infection and the symptoms of post-infection syndrome, although longer than typical acute viral infections, still constitute an acute process. This duration is still too brief when considering the extended period

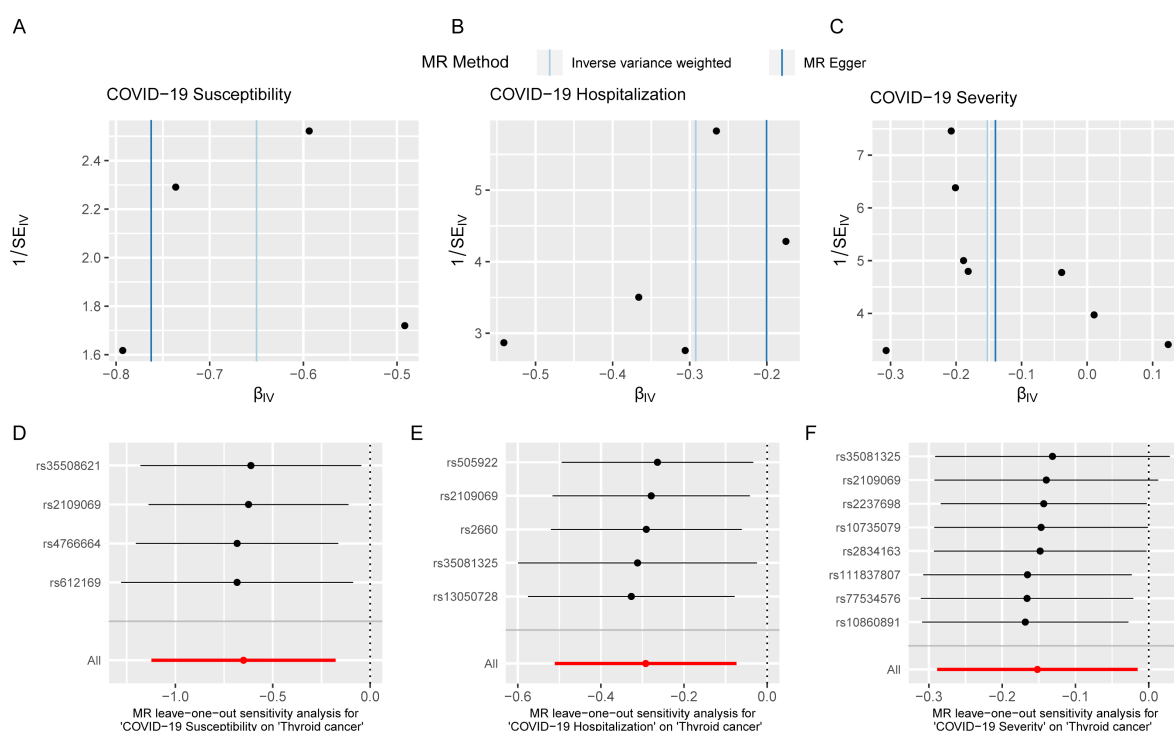


FIGURE 6

Sensitivity analysis indicates that the MR analysis was not affected by heterogeneity and pleiotropy. Funnel plot of single SNP effect (A–C); forest plot of leave-one-out analysis (D–F).

necessary for the accumulation of mutations required to initiate malignancy. Consequently, it is justifiable to conclude that COVID-19 may not have a significant influence on the risk of developing various cancers in the human body. Although studies have found that symptoms caused by SARS-CoV-2 infection can persist long-term, there is no substantial evidence reporting that the SARS-CoV-2 virus can persist in the human body long after infection, unlike carcinogenic viruses such as HPV that can persist in the body long-term. The transient nature of SARS-CoV-2 infection in the human body may physiologically reduce the risk of carcinogenesis.

Another key issue is why there is a negative causal relationship between the occurrence of thyroid cancer and exposure to COVID-19. A recent study has reported similar findings, although the results were not significant, possibly due to the significantly smaller sample size in the dataset used by the authors (174,995 vs. 490,920) (27). Experimental reports also support this conclusion; the SARS-CoV-2 virus does not seem to strongly attack the human thyroid (28, 29), despite the thyroid being one of the organs with abundant expression of ACE2 in the human body (30, 31). Moreover, pathological reports show that it is challenging to detect the presence of the SARS-CoV-2 virus in thyroid tissue after COVID-19 infection (32–34). This suggests that mechanistically, SARS-CoV-2 is unlikely to have an impact on thyroid carcinogenesis. One possible explanation for these phenomena is that they are related to genetic variations and immune surveillance mechanisms. Studies have indicated that COVID-19 infection can activate the immune system, including attacking immune cells, which may make the body more vigilant in monitoring and clearing potential cancer cells (35). We believe that individuals susceptible to COVID-19 have more pronounced symptoms, indicating an easily activated immune system. In this scenario, the activated immune system increases the detection of cancer cells, which can reduce the occurrence of thyroid cancer.

An interesting result is that as the severity of COVID-19 increases, the risk of various cancers decreases (the highest OR for COVID susceptibility and cancer risk is 1.48, while for COVID hospitalized it is 1.14, and for COVID severity it drops to 1.03), despite the results not being significant. And not only the overall trend of cancer decreases with increasing COVID-19 degree, but also the OR values for thyroid cancer follow this pattern. Another study also found similar patterns, which suggests that as the severity of COVID-19 increases, the relative risk of cancer in patients decreases (27). Based on this, we believe that this is unlikely to be a coincidence in the data, but rather a general trend. This is consistent with our speculation that carriers of genetic variations associated with more severe COVID-19 symptoms may have higher levels of immune surveillance, thereby possessing stronger abilities to eliminate malignant cells, leading to a lower likelihood of thyroid cancer occurrence. The severity of COVID-19 symptoms and the immune levels of patients after infection are related, which is also one of the reasons why younger patients typically have more severe symptoms. Research conclusions support this viewpoint; levels of cytokines and neutrophils increase in the bodies of severe COVID-19 patients (36). Therefore, we speculate that individuals susceptible

to COVID-19 may have higher levels of innate immune activity, and the increased threshold of innate immunity not only leads to more pronounced symptoms during COVID-19 infection but also increases the probability of clearing cancerous cells in the body.

Despite providing evidence and revealing the connection between COVID-19 infection and various cancers, our study has some limitations. Firstly, the samples studied were predominantly from individuals of European descent, limiting the generalizability of the conclusions as the incidence rates of thyroid cancer vary across different countries (37). Secondly, The study included 16 types of cancer datasets available in public databases. However, these datasets do not encompass all known human cancers, and reliance on a single database source may introduce selection bias. Additionally, MR studies explain the impact of genetic variations on outcomes. However, in the real world, interference from environmental factors, lifestyle habits, and other acquired factors might not yield the same results.

Conclusion

In conclusion, this study utilizes the Mendelian randomization (MR) method and incorporates comprehensive genome-wide association studies (GWAS) data to clarify that the susceptibility to COVID-19 does not have a significant impact on the risk of most cancers. However, our research emphasized a specific protective effect of COVID-19 against thyroid cancer. These findings are of great importance as they provide essential evidence for the development of effective screening strategies for patients with various types of cancer and enhance our comprehension of the association between COVID-19 and the risk of cancer in humans.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#). Further inquiries can be directed to the corresponding author.

Author contributions

SL: Conceptualization, Writing – original draft, Writing – review & editing. ZD: Resources, Supervision, Writing – review & editing. HM: Data curation, Formal Analysis, Resources, Writing – review & editing. LC: Formal Analysis, Investigation, Methodology, Resources, Software, Writing – review & editing. XL: Writing – review & editing. JH: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2024.1419020/full#supplementary-material>

References

1. Coronavirus disease (COVID-19) situation reports (2023). Available online at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. (Accessed October 07, 2023)
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* (2020) 20:533–4. doi: 10.1016/S1473-3099(20)30120-1
3. CSSEGISandData. COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (2023). Available online at: <https://github.com/CSSEGISandData/COVID-19> (Accessed October 6, 2023).
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA.* (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
5. Ashraf UM, Abokor AA, Edwards JM, Waigi EW, Royfman RS, Hasan SA-M, et al. SARS-CoV-2, ACE2 expression, and systemic organ invasion. *Physiol Genomics.* (2021) 53:7. doi: 10.1152/physiolgenomics.00087.2020
6. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* (2020) 26:1–11. doi: 10.1038/s41591-020-0968-3
7. Desai AD, Lavelle M, Boursiquot BC, Wan EY. Long-term complications of COVID-19. *Am J Physiol-cell Ph.* (2022) 322:C1–C11. doi: 10.1152/ajpcell.00375.2021
8. Simmonds P, Williams S, Harvala H. Understanding the outcomes of COVID-19 – does the current model of an acute respiratory infection really fit? *J Gen Virol.* (2020) 102:1545. doi: 10.1099/jgv.0.001545
9. Vivaldi G, Pfeffer PE, Talaei M, Basera TJ, Shaheen SO, Martineau AR. Long-term symptom profiles after COVID-19 vs other acute respiratory infections: an analysis of data from the COVidence UK study. *eClinicalMedicine.* (2023) 65. doi: 10.1016/j.eclinm.2023.102251
10. Baskett WI, Qureshi AI, Shyu D, Armer JM, Shyu CR. COVID-specific long-term sequelae in comparison to common viral respiratory infections: an analysis of 17 487 infected adult patients. *Open Forum Infect Dis.* (2022) 10:ofac683. doi: 10.1093/ofid/ofac683
11. Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, et al. Post-acute COVID-19 syndrome. *Nat Med.* (2021) 27:601–15. doi: 10.1038/s41591-021-01283-z
12. Khiali S, Rezagholizadeh A, Entezari-Maleki T. SARS-CoV-2 and probable lung cancer risk. *Bioimpacts.* (2022) 12:291–2. doi: 10.34172/bi.2022.23266
13. Jyotsana N, King MR. The impact of COVID-19 on cancer risk and treatment. *Cell Mol Bioeng.* (2020) 13:285–91. doi: 10.1007/s12195-020-00630-3
14. Farrell PJ. Epstein-barr virus and cancer. *Annu Rev Pathol.* (2019) 14:29–53. doi: 10.1146/annurev-pathmechdis-012418-013023
15. Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B virus: advances in prevention, diagnosis, and therapy. *Clin Microbiol Rev.* (2020) 33:e00046–19. doi: 10.1128/CMR.00046-19
16. Burd EM. Human papillomavirus and cervical cancer. *Clin Microbiol Rev.* (2003) 16:1–17. doi: 10.1128/CMR.16.1.1-17.2003
17. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med.* (2008) 27:1133–63. doi: 10.1002/sim.3034
18. Hemani G, Tilling K, Smith GD. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* (2017) 13: e1007081. doi: 10.1371/journal.pgen.1007081
19. IEU OpenGWAS project. Available online at: <https://gwas.mrcieu.ac.uk/> (Accessed September 27, 2023).
20. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. *Am J Epidemiol.* (2013) 178:1177–84. doi: 10.1093/aje/kwt084
21. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol.* (2016) 40:304–14. doi: 10.1002/gepi.21965
22. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. *Epidemiology.* (2017) 28:30–42. doi: 10.1097/EDE.0000000000000559
23. Bowden J, Spiller W, Del Greco MF, Sheehan N, Thompson J, Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. *Int J Epidemiol.* (2018) 47:1264–78. doi: 10.1093/ije/dyy101
24. R Core Team. *R: A language and environment for statistical computing.* (2022). Available at: <https://www.r-project.org/>.
25. Dayimu A. *forestploter: create flexible forest plot* (2023). Available online at: <https://github.com/adayim/forestploter>. (Accessed October 07, 2023)
26. Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S. Severity of COVID-19 in patients with lung cancer: evidence and challenges. *J Immunother Cancer.* (2021) 9:e002266. doi: 10.1136/jitc-2020-002266
27. Li J, Bai H, Qiao H, Du C, Yao P, Zhang Y, et al. Causal effects of COVID-19 on cancer risk: A Mendelian randomization study. *J Med Virol.* (2023) 95:e28722. doi: 10.1002/jmv.28722
28. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Zhonghua Bing Li Xue Za Zhi.* (2020) 49:411–7. doi: 10.3760/cma.j.cn112151-20200312-00193
29. Caron P. Thyroid disorders and SARS-CoV-2 infection: From pathophysiological mechanism to patient management. *Ann Endocrinol (Paris).* (2020) 81:507–10. doi: 10.1016/j.ando.2020.09.001
30. Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine significance of SARS-CoV-2's reliance on ACE2. *Endocrinology.* (2020) 161:bqaa108. doi: 10.1210/endo/bqaa108
31. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissue. *Infect Dis Poverty.* (2020) 9:45. doi: 10.1186/s40249-020-00662-x
32. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intens Care Med.* (2020) 46:846–8. doi: 10.1007/s00134-020-05991-x
33. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal infections in Washington State: case series COVID-19, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet.* (2020) 396:320–32. doi: 10.1016/S0140-6736(20)31305-2
34. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. *Am J Clin Pathol.* (2020) 153:725–33. doi: 10.1093/ajcp/aqaa062
35. Boechat JL, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology – Current perspectives. *Pulmonology.* (2021) 27:423–37. doi: 10.1016/j.pulmoe.2021.03.008
36. Nasrollahi H, Talepoor AG, Saleh Z, Eshkevar Vakili M, Heydarinezhad P, et al. Immune responses in mildly versus critically ill COVID-19 patients. *Front Immunol.* (2023) 14:1077236. doi: 10.3389/fimmu.2023.1077236
37. Chen DW, Lang BHH, McLeod DSA, Newbold K, Haymart MR. Thyroid cancer. *Lancet.* (2023) 401:1531–44. doi: 10.1016/S0140-6736(23)00020-X



OPEN ACCESS

EDITED BY

Kamyar Asadipooya,
University of Kentucky, United States

REVIEWED BY

Giuseppe Lisco,
University of Bari Aldo Moro, Italy
Clodoveo Ferri,
University of Modena and Reggio Emilia, Italy

*CORRESPONDENCE

Xiaolong Zhao
✉ zhaoxiaolong@fudan.edu.cn

RECEIVED 26 December 2023

ACCEPTED 09 September 2024

PUBLISHED 24 September 2024

CITATION

Yang Y, Qian L, Wu C, Xu X, Qu D, Zhou L,
Liu J, Zhu Q, Wang C and Zhao X (2024)
Association between thyroid function and
prognosis of severe COVID-19 among
patients with SARS-CoV-2 infection:
a retrospective cohort study in China.
Front. Endocrinol. 15:1361479.
doi: 10.3389/fendo.2024.1361479

COPYRIGHT

© 2024 Yang, Qian, Wu, Xu, Qu, Zhou, Liu,
Zhu, Wang and Zhao. This is an open-access
article distributed under the terms of the
[Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).
The use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Association between thyroid function and prognosis of severe COVID-19 among patients with SARS-CoV-2 infection: a retrospective cohort study in China

Yaling Yang¹, Lifang Qian², Chenwei Wu¹, Xinyue Xu¹,
Duoduo Qu¹, Lihua Zhou¹, Jia Liu¹, Qin Zhu¹,
Chunhong Wang¹ and Xiaolong Zhao^{1*}

¹Department of Endocrinology, Shanghai Public Health Clinical Center, Shanghai, China, ²Department of Medicine, Shanghai Qingpu District Zhujiajiao People's Hospital, Shanghai, China

Objective: This study aims to examine the thyroid hormone profile and its association with severe coronavirus disease 2019 (COVID-19) in patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: This retrospective cohort study enrolled patients admitted to a tertiary hospital due to SARS-CoV-2 infection between February 18 and May 18, 2022. Clinical data were collected retrospectively from the electronic medical record system. Based on the thyroid function, patients were divided into five groups: normal, non-thyroid illness syndrome (NTIS), hypothyroidism, thyrotoxicosis, and unclassified. The association between thyroid function and severe COVID-19 was detected using multivariable logistic regression and restricted cubic splines analysis.

Results: This study included 3,161 patients, with 7.7% of them developing severe COVID-19. 44.9% of the patients had normal thyroid function, 36.5% had NTIS, 6.7% had hypothyroidism, and 1.0% had thyrotoxicosis on admission. After adjusting for age, sex, and relevant clinical characteristics, NTIS and hypothyroidism were associated with increased risks of severe COVID-19 (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.59-3.56 and OR 2.29, 95% CI 1.23-4.26, respectively), compared to normal thyroid function group. Among patients with NTIS or hypothyroidism, higher levels of total triiodothyronine (TT3) are associated with lower risks of severe COVID-19 (OR 0.73, 95% CI 0.64-0.82, for every 0.1nmol/L increase in TT3 level).

Conclusion: Thyroid hormone profiles of NTIS or hypothyroidism are associated with increased risks of severe COVID-19. The decreased level of TT3 correlated with the increased risk of severe COVID-19 in patients with NTIS or hypothyroidism.

KEYWORDS

SARS-CoV-2, severe COVID-19, non-thyroid illness syndrome, thyroid function, total triiodothyronine

Introduction

Since it first emerged in 2019, the Coronavirus disease-2019 (COVID-19) pandemic has had a profound and far-reaching impact on global health. It continues to pose a significant and ongoing threat to public well-being. This disease presents a wide array of symptoms, ranging from mild to severe and even fatal, affecting multiple organs and systems of the human body, including the endocrine glands and the thyroid gland (1).

Following the publication of a case report on subacute thyroiditis after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by Brancatella et al. (2), considerable attention has been given to the research on the relationship between COVID-19 and the thyroid gland (3). However, as more clinical evidence accumulated, a wide range of thyroid function abnormalities have been noticed, including thyroiditis, non-thyroidal illness syndrome (NTIS), clinical and subclinical hypothyroidism, central hypothyroidism, and clinical and subclinical hyperthyroidism (4). It is now well recognized that NTIS, characterized by low levels of triiodothyronine (T3) and normal or low levels of thyroid-stimulating hormone (TSH) (5, 6), is quite common among patients with SARS-CoV-2 infection (5, 7–10).

NTIS has been reported to be a complex condition associated with severe diseases, such as poor nutrition, heart failure, chronic obstructive pulmonary (COPD), and community-acquired pneumonia (6, 11). Some scholars have concluded that NTIS could predict clinical deterioration in COVID-19 patients (9, 12). And some studies have found that low triiodothyronine levels hold significant predictive value for COVID-19 patients (13, 14). These results have motivated us to conduct further research. In this study, we conducted a retrospective analysis to investigate the thyroid hormone profiles, especially NTIS, in SARS-CoV-2 infected patients. We also explored the relationship between triiodothyronine and the risk of developing severe COVID-19 during hospital stays and examined the predictive value of thyroid function tested on admission.

Methods

Study population

This retrospective cohort study analyzed data from inpatients in a tertiary hospital during the 2022 COVID-19 outbreak in Shanghai. The study subjects were adults (≥ 18 years) admitted due to SARS-CoV-2 infection from February 18 to May 18, 2022. Clinical Data were collected retrospectively from the electronic medical record system. The subjects were all Chinese residents with routine clinical data and laboratory tests, including complete blood count, renal and liver function, thyroid function, and coagulation function, which were conducted on admission.

Thyroid function

Thyroid function was tested within 24 hours after admission, including total triiodothyronine (TT3), total thyroxine (TT4), free

triiodothyronine (FT3), free thyroxine (FT4), and TSH. Based on the thyroid hormone levels, the thyroid hormone patterns were categorized into five groups: NTIS, hypothyroidism, thyrotoxicosis, normal, and unclassified.

1. NTIS was defined as low TT3 with either normal TSH or low TSH (15).
2. Hypothyroidism was defined as overt hypothyroidism (high TSH and low FT4) or subclinical hypothyroidism (high TSH and normal FT4) (16).
3. Thyrotoxicosis was defined as overt thyrotoxicosis (low TSH, high TT3, and high FT4), mild (low TSH, high TT3, and normal FT4), or subclinical thyrotoxicosis (low TSH, normal TT3, and normal FT4) (17).
4. The normal group was defined as normal TSH, TT3, and FT4 levels.
5. The unclassified group includes individuals with thyroid hormone profiles that do not fit the criteria mentioned above. This includes:

- Normal TSH, TT3, and high or low FT4.
- Normal TSH, FT4, and high TT3.
- High TSH, FT4, and low or normal TT3.
- Low TSH, normal TT3, and high FT4.

Covariates

Covariates included age, gender, diabetes, vaccination status, and laboratory tests examined within 24 hours of admission, which included complete blood count, renal and liver function, thyroid function, and coagulation function. The combination of diabetes was established based on a prior diabetes diagnosis or an HbA1C level of $\geq 6.5\%$ on admission. The vaccinated status of individuals was determined based on having received at least one dose of any COVID-19 vaccine.

Clinical outcomes

The primary outcome is the occurrence of severe COVID-19, which was determined by a particular expert group after discussion, according to Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (Trial Version 9) (18), when patients met any of the following criteria: respiratory rate $\geq 30/\text{min}$, $\text{SpO}_2 \leq 93\%$ at rest, and $>50\%$ progression in 48 h on imaging, critical disease state which was defined as respiratory failure requiring mechanical ventilation, shock, and intensive care unit (ICU) admission.

Secondary outcomes encompassed several variables: 1. Oxygen therapy status, categorized as no oxygen treatment, oxygen inhalation, non-invasive mechanical ventilation, or invasive mechanical ventilation. 2. Hemodialysis treatment, administered during the hospital stay. 3. Time to SARS-CoV-2 RNA turning negative, defined as the number of days from confirming SARS-CoV-2 infection to when SARS-CoV-2 RNA tests showed cycle

threshold (Ct) <35 for at least two consecutive days. 4. Length of hospitalization, defined as the number of days between the date of discharge and the initial date of hospitalization. All the clinical outcome data were retrospectively extracted from the hospital information system's electronic medical record.

Laboratory measurement

SARS-CoV-2 infection was defined as SARS-CoV-2 RNA with the Ct value <35 in either target gene at least twice. Samples were extracted from nasal/throat swabs and detected with SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) by the dual-target (ORF1ab and N genes), using detection kits from DAAN Inc.

Thyroid function was measured using automated competitive immunoassays: Alinity I (Abbott) according to the manufacturer's protocol. The normal range is 0.98–2.33 nmol/L for TT3, 62.68–150.84 nmol/L for TT4, 2.43–6.01 pmol/L for FT3, 9.01–19.05 pmol/L for FT4, and 0.35–4.94 uIU/mL for TSH.

Serum amyloid A (SAA) was performed using a specific protein analyzer and accompanying reagents manufactured by Upper Bio-teach Pharma Co. in Shanghai, China. The methods were Particle-Enhanced immunoturbidimetric. All items were operated strictly with the operating procedures, reagent instructions, and indoor quality control.

High-sensitivity C-reactive protein (hs-CRP) was measured using the hs-CRP Assay Kit produced by Shenzhen Lifotronic Technology Co. through scatter turbidimetry, according to the manufacturer's protocol.

Interleukin-6 (IL-6) was measured using the cytokine detection kits produced by Qingdao Rasecare Biological Technology Co. using the multiple microsphere flow immunofluorescence luminescence method.

Statistical analysis

Continuous variables were reported as the median and interquartile range (IQR) since most of the variables were not distributed normally. Category variables were reported as frequency and percentage. Demographic and clinical characteristics of the patients were compared between the normal thyroid function group and other thyroid function groups using the Wilcoxon rank-sum or Kruskal–Wallis H test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

Initially, we conducted univariate logistic regression to assess the association between thyroid hormone patterns and severe COVID-19. We adjusted for age, sex, diabetes, and vaccination in Model 1. In Model 2, we additionally adjusted aspartate transaminase (AST) levels exceeding three times the upper normal limit (ULN), estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m², serum calcium (Ca), white blood cell count (WBC), neutrophil-lymphocyte ratio (N/Ly), and D-Dimer. Odds ratios (OR) with corresponding 95% confidence intervals (CI)

were reported. Missing data were filled using the K-nearest neighbors (KNN) method with a value of K=10.

To evaluate the association between TT3 levels and severe COVID-19, we used a logistic regression model with restricted cubic splines (RCS) to examine nonlinear relationships among all patients affected with SARS-CoV-2. The logistic regression was adjusted for the same baseline clinical characteristics as in Model 2. The median value of the predictor variable was chosen as the reference value. If the curve exhibited a U-shape, Inverted U-shape, or L-shape, the inflection point (i.e., the point where the curve changed its direction) was set as the cut-off value. The correlations between TT3 and inflammatory factors and lymphocyte subsets, stratified by thyroid function pattern, were determined by the Spearman correlation coefficient.

Statistical analyses were performed using SPSS 26 (SPSS/IBM, Armonk, NY, USA). RCS analyses were performed using R software, version 4.2.2, with the rms package. P value <0.05 was considered statistically significant, and a two-tailed P value was reported.

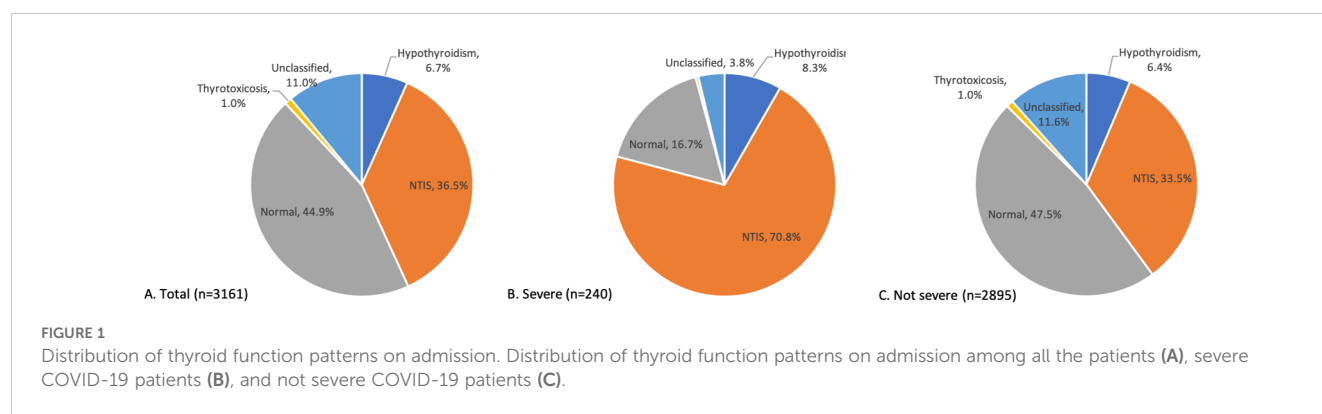
Results

Study participants

This study was conducted from February 18 to May 18, 2022, during the prevalence of the BA.2.2 variant of SARS-CoV-2. A total of 3636 hospitalized patients admitted due to SARS-CoV-2 infection were initially screened. Among this group, sixty-eight patients were excluded due to reinfection with SARS-CoV-2, and an additional four hundred and seven patients were excluded because their thyroid function was not tested. Ultimately, 3161 patients were included in this study.

Thyroid hormone profile of patients on admission

Normal thyroid dysfunction was present in 44.9% of the 3161 patients included in this study, as shown in [Figure 1A](#). NTIS is the most common form of abnormal thyroid dysfunction, affecting 36.5% of the entire study population. Hypothyroidism was found in 6.7% of the patients, with overt hypothyroidism accounted for only 0.16% of the study cohort. Thyrotoxicosis was observed in 1.0% of the study population, while overt thyrotoxicosis was rare, with only two patients (0.06%) exhibiting this condition. The unclassified group comprised 11.0% of the study population. Within the unclassified group, 89% of the patients presented with only high FT4 levels (309 out of 347). 4.6% presented with normal TT3, low TSH, and high FT4, and 3.5% presented with normal TT3, high TSH, and high FT4. For more detailed information, please refer to [Supplementary Table 1](#). Among the patients who developed severe COVID-19 during hospitalization, the proportion of nonthyroidal illness syndrome (NTIS) was significantly higher compared to non-severe patients (70.8% vs. 33.5%) on admission ([Figures 1B, C](#)).



Clinical characteristics of patients according to thyroid hormone patterns

The clinical characteristics are presented in [Table 1](#). The median age of the patients was 60 years (IQR 42, 75); 1657 (52.4%) were male, 28.3% had diabetes, and 54.2% had received at least one dose of the COVID-19 vaccine. Compared to normal thyroid function patients, NTIS patients were much older: median 67 vs 54 years and had more patients with diabetes (36.1% vs 26.3%). In general, NTIS patients had worse conditions in liver and kidney function tests, such as higher lactate dehydrogenase (LDH) levels, lower albumin (ALB), and lower eGFR (median 91 vs. 102, ml/min/1.73m²). NTIS patients had lower serum Ca levels (median 1.99 vs. 2.06 mmol/L) and higher D-Dimer levels (median 0.53 vs. 0.26 ug/ml). Hypothyroid patients, when compared to normal thyroid function patients, were older (median 63 vs. 54 years) and less male (40.8% vs. 54.4%). Additionally, hypothyroid patients had higher LDH (median 215 vs. 200, U/L), lower eGFR and Ca levels, and higher D-Dimer levels than the normal thyroid function patients.

The incidence of severe COVID-19 was as high as 14.9% among the NTIS group, followed by hypothyroidism, thyrotoxicosis, and the unclassified group, which was 10.0%, 3.2%, and 2.9%, respectively, compared with 2.8% in normal thyroid function group, see [Table 1](#). Regarding oxygen therapy, 30.6% of the NTIS group were prescribed oxygen therapy during hospital stay, which was as low as 12.2% in the normal thyroid function group. The oxygen therapy comprised oxygen inhalation, non-invasive mechanical ventilation, and invasive mechanical ventilation, which were 18.0%, 7.5%, and 5.1% in the NTIS group. Compared with the normal group, NTIS patients had more extended hospital stays (median 11 vs. 9 days).

Association of thyroid function patterns and severe COVID-19

The odds of severe COVID-19 were significantly higher in NTIS and hypothyroid patients, as indicated by unadjusted ORs of 6.03 (95% CI, 4.24, 8.59, $P < 0.001$) and 3.81 (95% CI, 2.20, 6.60, $P < 0.001$) respectively, compared to normal thyroid function patients, [Figure 2](#). In model 1, after adjusting for age, sex, vaccination

status, and diabetes, the ORs remained high at 3.57 (95% CI, 2.46, 5.18; $P < 0.001$) for NTIS, and at 2.85 (95% CI, 1.58, 5.12; $P < 0.001$) for hypothyroidism. In model 2, additional adjustment for clinical characteristics at admission resulted in ORs of 2.38 (95% CI, 1.59, 3.56; $P < 0.001$) for NTIS and 2.29 (95% CI, 1.23, 4.26; $P < 0.001$) for hypothyroidism.

Association of TT3 levels and severe COVID-19 clinical outcomes

The RCS analysis showed that the curve in [Figure 3](#) was an L-shape and suggested a non-linear association. The inflection point of the RCS curve was identified at TT3 = 1.06 mmol/L, representing a turning point in the relationship between the TT3 level and severe COVID-19. Both NTIS and hypothyroid patients had TT3 levels below the turning point of 1.06 nmol/L. In the NTIS and hypothyroidism subgroups, after adjustment for clinical characteristics as in Model 2, the odds of severe COVID-19 decreased significantly with each increment of 0.1 nmol/L of TT3 level, 0.73 (95% CI, 0.64, 0.82; $P < 0.001$).

Association of TT3 levels and inflammatory factors and lymphocyte subset

Significant negative correlations were found between the TT3 levels and T lymphocyte subsets in SARS-CoV-2 infected patients, as shown in [Supplementary Figure 1A-C](#). Furthermore, TT3 levels were negatively correlated with inflammatory cytokines, including hs-CRP, SAA, and IL-6, especially among the NTIS and hypothyroidism subgroups, as shown in [Supplementary Figure 1D-F](#) and [Supplementary Table 2](#).

Discussion

The prevalence of NTIS was observed in 36.5% of patients upon admission in this study. NTIS has been commonly reported among individuals with SARS-CoV-2 infection ([7, 9, 10](#)), with rates ranging from 1.7–66.3%, mainly depending on study cohorts and disease severity ([19](#)). This study confirmed that NTIS was associated with

TABLE 1 Baseline characteristics and COVID-19 clinical outcome in different thyroid function patterns.

Characteristics	Total	Normal	NTIS	Hypothyroidism	Thyrotoxicosis	Unclassified	Missing, n (%)
Patient, n (%)	3161	1418 (44.9%)	1154 (36.5%)	211 (6.7%)	31 (1.0%)	347 (11.0%)	
Baseline Characteristics							
Age, years	60 (42, 75)	54 (38, 69)	67 (48, 83) *	63 (48, 81) *	40 (32, 69)	62 (43, 74) *	0
Age ≥60 years, n (%)	1595 (50.5%)	585 (41.3%)	699 (60.6%) *	117 (55.5%) *	11 (35.5%)	183 (52.7%) *	0
Male, n (%)	1657 (52.4%)	771 (54.4%)	596 (51.6%)	86 (40.8%) *	15 (48.4%)	189 (54.5%)	0
Diabetes, n (%)	896 (28.3%)	341 (26.3%)	389 (36.1%) *	55 (28.9%)	10 (35.7%)	101 (31.3%)	245 (7.8%)
Vaccinated, n (%)	1714 (54.2%)	884 (66.9%)	496 (46.6%) *	114 (58.8%)	17 (60.7%)	203 (61.3%)	221 (7.0%)
Waiting time ¹ , days	1 (1, 6)	2 (1, 8)	1 (1, 4) *	2 (1, 8)	1 (1, 1) *	1 (1, 5) *	30 (0.9%)
Laboratory tests							
HbA1c, %	5.9 (5.6, 6.4)	5.9 (5.5, 6.3)	6.0 (5.6, 6.5) *	5.9 (5.6, 6.4)	5.9 (5.6, 6.6)	6.0 (5.6, 6.5) *	83 (2.6%)
ALT, U/L	18 (12, 28)	19 (13, 31)	17 (11, 26) *	18 (12, 29)	17 (12, 28)	19 (12, 29)	43 (1.4%)
AST, U/L	20 (16.27)	20 (16, 26)	21 (16, 29) *	22 (17, 30)	18 (15, 26)	20 (16, 26)	7 (0.2%)
LDH, U/L	204 (177, 242)	200 (174, 230)	211 (180, 257) *	215 (183, 254) *	195 (161, 227)	202 (178, 242)	9 (0.3%)
ALB, g/L	40 (37, 43)	41 (39, 44)	39 (34, 42) *	40 (36, 43) *	40 (37, 42)	41 (38, 43)	3 (0.1%)
eGFR, ml/min/1.73m ²	97.4 (79.1, 115.2)	101.5 (85.6, 116.6)	90.8 (67.7, 112.6) *	90.4 (73.0, 112.3) *	106.2 (70.1, 128.6)	98.8 (83.2, 116.0)	6 (0.2%)
AST≥3ULN	55 (1.7%)	9 (0.6%)	42 (3.6%) *	1 (0.5%)	0 (0.0%)	3 (0.9%)	7 (0.2%)
eGFR<30 ml/min/1.73m ² , n (%)	126 (4.0%)	13 (0.9%)	99 (8.6%) *	12 (5.7%) *	1 (3.3%)	1 (0.3%)	6 (0.2%)
K, mmol/L	3.8 (3.5, 4.1)	3.8 (3.5, 4.0)	3.8 (3.5, 4.1)	3.8 (3.6, 4.1)	3.7 (3.4, 4.0)	3.8 (3.5, 4.1)	8 (0.3%)
Na, mmol/L	39 (138, 141)	140 (138, 141)	139 (137, 141) *	140 (138, 141)	138 (136, 139) *	140 (138, 141)	7 (0.2%)
Ca, mmol/L	2.04 (1.92, 2.18)	2.06 (1.95, 2.19)	1.99 (1.88, 2.15) *	2.02 (1.90, 2.18) *	2.07 (1.94, 2.15)	2.08 (1.95, 2.21)	78 (2.5%)
TT3, nmol/L	1.04 (0.88, 1.22)	1.18 (1.07, 1.35)	0.84 (0.75, 0.91) *	1.06 (0.89, 1.26) *	1.23 (1.08, 1.33)	1.14 (1.05, 1.24) *	3 (0.1%)
TT4, nmol/L	8.2 (7.1, 13.0)	8.7 (7.5, 95.7)	7.4 (6.5, 8.7) *	7.7 (6.6, 55.0) *	10.4 (8.2, 100.9)	9.2 (8.4, 10.1) *	1 (0.03%)
FT3, pmol/L	4.6 (4.0, 5.3)	4.9 (4.3, 5.4)	4.1 (3.5, 4.7) *	4.7 (4.0, 5.2) *	4.7 (3.9, 5.3)	5.4 (4.9, 5.8)	1 (0.03%)
FT4, pmol/L	16.1 (14.1, 18.3)	15.4 (13.9, 17.0)	16.3 (14.3, 18.6) *	14.3 (12.9, 16.5) *	15.9 (14.8, 16.8)	20.4 (19.6, 21.6) *	0
TSH, uIU/mL	1.7 (1.1, 2.8)	1.8 (1.3, 2.7)	1.4 (0.8, 2.2) *	6.6 (5.5, 8.7) *	0.2 (0.1, 0.3) *	1.6 (1.0, 2.5) *	0
WBC, 10 ⁹ /L	5.5 (4.3, 7.1)	5.5 (4.3, 6.9)	5.4 (4.3, 7.4)	5.7 (4.4, 7.3)	4.9 (4.0, 6.2)	5.3 (4.3, 6.9)	14 (0.4%)
Neutrophils, 10 ⁹ /L	3.3 (2.3, 4.6)	3.2 (2.2, 4.3)	3.4 (2.5, 5.3) *	3.2 (2.3, 4.7)	3.4 (2.5, 4.4)	3.1 (2.2, 4.3)	14 (0.4%)
Lymphocyte, 10 ⁹ /L	1.4 (1.0, 1.9)	1.6 (1.2, 2.0)	1.2 (0.8, 1.6) *	1.4 (1.1, 2.0)	0.9 (0.6, 1.3) *	1.5 (1.1, 1.9)	15 (0.5%)
N/ly	2.2 (1.5, 3.7)	2.0 (1.4, 3.0)	2.9 (1.8, 5.3) *	2.0 (1.5, 3.1)	3.1 (2.2, 6.1) *	2.0 (1.4, 3.2)	14 (0.4%)
Hemoglobin, g/L	131 (118, 146)	134.5 (123, 148)	126 (111, 142) *	128 (114, 142) *	126 (114, 136) *	135 (123, 149)	14 (0.4%)
Platelet, 10 ⁹ /L	200 (160, 249)	203 (164, 250)	193 (150, 245) *	199 (167, 253)	195 (170, 249.5)	211 (174, 256) *	14 (0.4%)
D-Dimer, ug/ml	0.33 (0.21, 0.78)	0.26 (0.19, 0.55)	0.53 (0.25, 1.27) *	0.45 (0.23, 1.02) *	0.34 (0.22, 0.61) *	0.33 (0.20, 0.72) *	45 (1.4%)

(Continued)

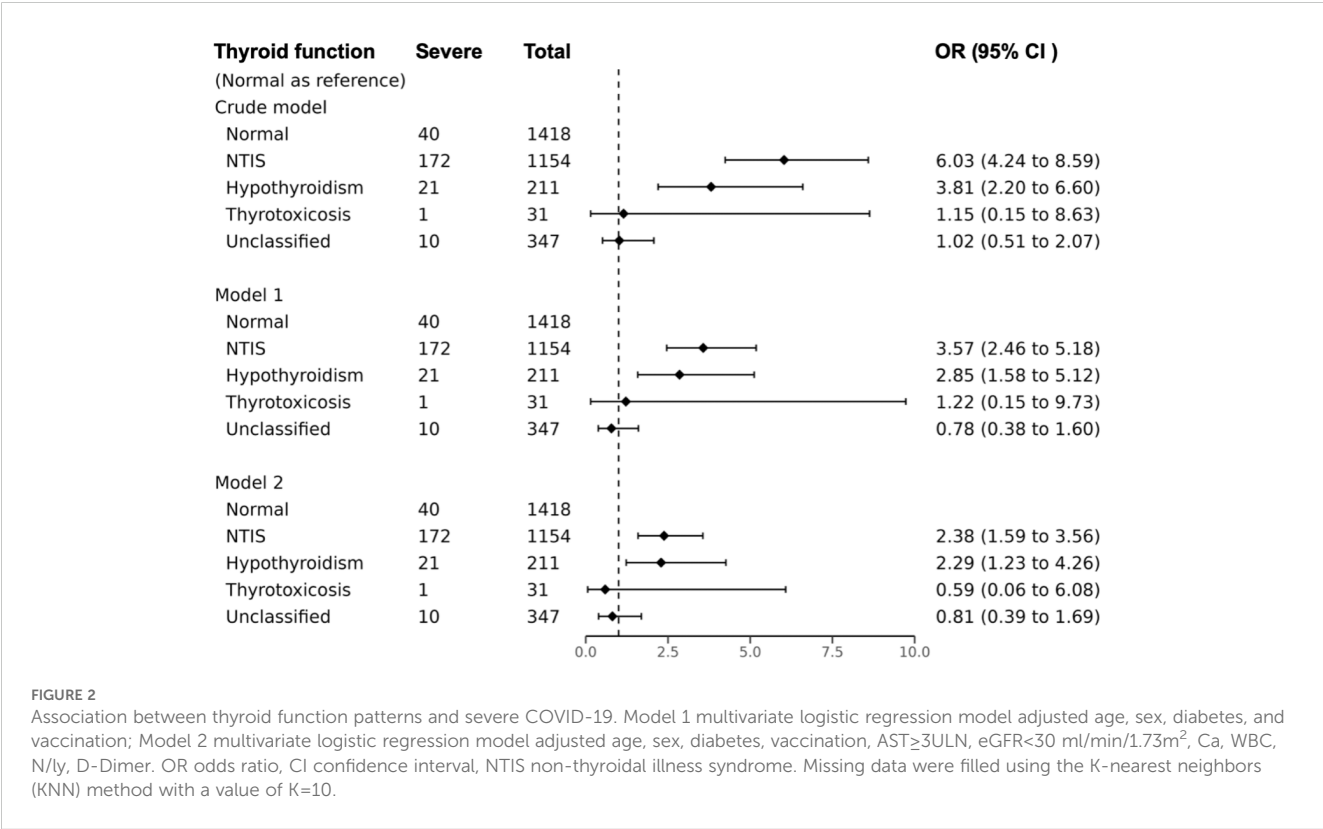
TABLE 1 Continued

Characteristics	Total	Normal	NTIS	Hypothyroidism	Thyrotoxicosis	Unclassified	Missing, n (%)
COVID-19 Clinical outcomes							
Severe, n (%)	244 (7.7%)	40 (2.8%)	172 (14.9%) *	21 (10.0%) *	1 (3.2%)	10 (2.9%)	0
Oxygen therapy, n (%)							0
No	2534 (80.2%)	1245 (87.8%)	801 (69.4%) *	164 (77.7%) *	28 (90.3%)	296 (85.3%)	
Oxygen inhalation	443 (14.0%)	154 (10.9%)	208 (18.0%) *	34 (16.1%)	2 (6.5%)	45 (13.0%)	
Non-invasive assisted breathing	113 (3.6%)	11 (0.8%)	86 (7.5%) *	10 (4.7%) *	1 (3.2%)	5 (1.4%)	
Invasive mechanical ventilation	71 (2.2%)	8 (0.6%)	59 (5.1%) *	3 (1.4%)	0	1 (0.3%)	
Hemodialysis treatment, n (%)	68 (2.2%)	10 (0.3%)	52 (1.6%) *	4 (0.1%)	0	2 (0.1%)	0
Time to negative ² , days	12 (9, 16)	12 (9, 15)	12 (9, 16)	12 (8,17)	11 (4, 15)	12 (9,16)	19 (0.6%)
Hospital stays, days	10 (5, 13)	9 (5, 12)	11 (7, 15) *	9 (5, 13)	11 (4, 15)	10 (6,14) *	6 (0.2%)

¹ Waiting time defined as days from SARS-CoV-2 infection confirmed to admission, ² Time to negative defined as days from SARS-CoV-2 infection to SARS-CoV-2 RNA CT<35 at least twice in consecutive days; * Compared with the normal group, P<0.05. NTIS non-thyroidal illness syndrome, HbA1C glycated hemoglobin, ALT alanine transaminase, AST aspartate transaminase, LDH lactate dehydrogenase, ALB albumin, eGFR estimated glomerular filtration rate, ULN upper normal limit, K serum potassium, Na serum sodium, Ca serum calcium, TT3 total triiodothyronine, TT4 total thyroxine, FT3 free triiodothyronine, FT4 free thyroxine, TSH thyrotropin, WBC white blood cell, N/ly, neutrophil-to-lymphocyte ratio.

severe clinical outcomes, with NTIS patients having 2.4 times the odds of developing severe COVID-19 compared to the normal thyroid group after adjusting for multiple relevant clinical characteristics. Additionally, NTIS patients had more extended hospital stays and a higher need for oxygen therapy compared to the normal thyroid function group. NTIS can be recognized as an

early indicator of severe COVID-19, supporting the conclusions of previous research (5, 7, 9). Previous research has demonstrated that NTIS was linked to a 3.2-3.5 times greater risk of severe COVID-19 (7, 9). However, there are discrepancies in the literature regarding the study populations, the definition of NTIS, and the reference group used. In this study, we included 3161 SARS-CoV-2 infected



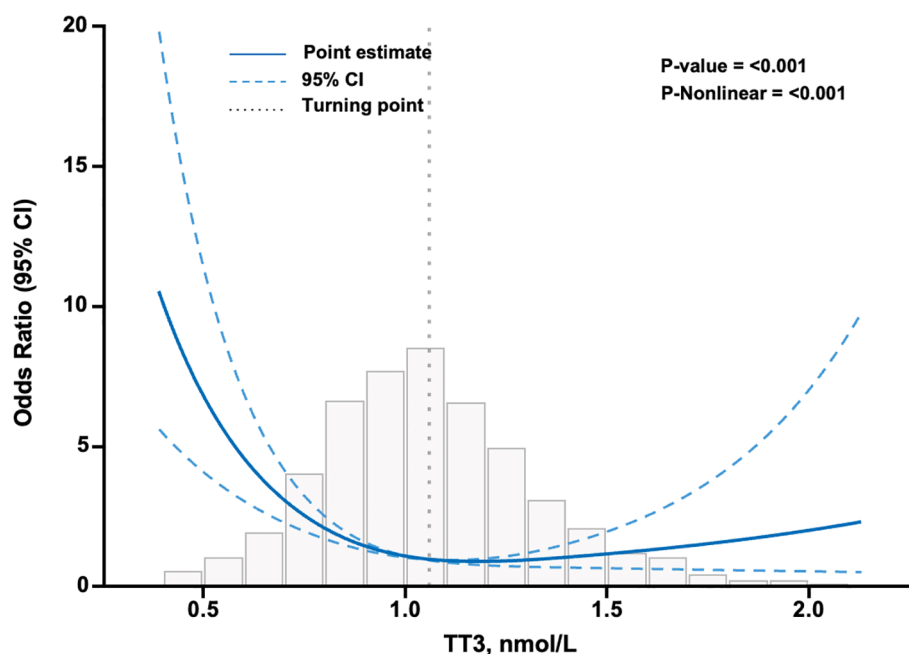


FIGURE 3

Association between TT3 level and severe COVID-19 in patients infected with SARS-CoV-2 using restricted cubic splines. The model has 3 knots at 10th, 50th, and 90th percentiles. The Y-axis represents the OR of severe COVID-19 for any value of TT3 compared to individuals with a TT3 level of 1.06 nmol/L. The logistic regression was adjusted for age, sex, diabetes, vaccination, $AST \geq 3ULN$, $eGFR < 30$ ml/min/1.73m², Ca, WBC, N/ly, and D-Dimer. Missing data were filled using the K-nearest neighbors (KNN) method with a value of K=10. N=3161. CI confidence interval, TT3 total triiodothyronine.

patients with varying severity of COVID-19. The definition of NTIS used in this study was based on low TT3 levels, while some studies used a low FT3 level and non-NTIS patient as a reference group.

In this study, hypothyroidism only accounts for 6.7% of the study population, we still observed an elevated risk of severe COVID-19 in hypothyroid patients, that hypothyroid patients were associated with 2.3-fold higher odds of developing severe COVID-19 compared to the normal thyroid group. Similar results were also noticed in a retrospective study, in which 7.23% of patients had subclinical hypothyroidism, and the hazard ratio (HR) of severe COVID-19 was 4.04 compared to those with normal thyroid function (20). In certain circumstances, distinguishing between hypothyroid patients and those with NTIS can be challenging. Since NTIS is a complex condition, it demonstrates heterogeneity in the progressive stages of the disease. Notably, during the recovery phase of chronic illnesses, it may present as elevated TSH levels (21). We speculate there exists an overlap between NTIS and hypothyroidism in this study. At present, the research on the association between hypothyroidism and severe COVID-19 is limited. Additional studies are required to understand and verify this association comprehensively.

Interestingly, this elevated risk of severe COVID-19 in hypothyroid patients was found to be comparable to that of NTIS patients in model 2. Since low plasma TT3 levels were the most consistent and significant alteration in NTIS and hypothyroid patients, further investigation was conducted to explore the correlation between TT3 levels and severe COVID-19. Among NTIS and hypothyroid patients, higher levels of TT3 were

associated with lower risks of severe COVID-19 (OR 0.73, 95% CI 0.64–0.82, every 0.1nmol/L increment in TT3 level). TT3 levels have been observed to decrease shortly after surgery (22) and persist throughout the disease in both acute and chronically ill patients (23). This decrease in TT3 level becomes more pronounced as the disease worsens (6, 24, 25). Other studies have also reported the correlation between TT3 levels and the severity of COVID-19. At the early start of the COVID-19 epidemic, one retrospective cohort study including 50 patients concluded that the degree of TT3 decrease correlated with the severity of COVID-19 (26). Another study carried out among 119 SARS-CoV-2 infected patients presented that the patients in the lowest TT3 tertile (HR, 5.07) and the middle tertiles (HR, 2.05) had higher risks of death compared with those in the highest TT3 tertile (8). In addition to TT3, decreased FT3 levels have been reported to be an independent factor for poor clinical outcomes and death in mild and critical COVID-19 patients (7, 9, 10, 27). According to our knowledge, this is currently the only study that quantitatively describes the correlation between the extent of TT3 reduction and the increased risk of severe COVID-19.

This study observed a significant negative correlation between TT3 levels and proinflammatory biomarkers such as hs-CRP, SAA, and IL-6, especially in the NTIS and hypothyroidism subgroups, see [Supplementary Figure 1](#) and [Supplementary Table 2](#). This finding aligns with previous studies that have also reported a negative correlation between T3 levels and hs-CRP (8), SAA (28), and IL-6 (7) levels. We speculate that pro-inflammatory factors may catalyze changes in thyroid function. Although the exact pathophysiological

mechanisms linking thyroid function and SARS-CoV-2 infection are not fully understood, it is plausible that COVID-19 infection can induce inflammation and trigger immune responses (29), impacting various organs, including the thyroid-pituitary-hypothalamic axis. Previous research has shown that proinflammatory cytokines play a significant role in developing NTIS in severe patients (30). There is decreased pulsatile secretion of TSH and impaired TSH response to low levels of circulating T3 and T4 at the pituitary level (31, 32). Additionally, in peripheral tissues, pro-inflammatory cytokines have been found to suppress deiodinase 1 and increase deiodinase 3, leading to a sudden decrease in T3 levels and an increase in reverse T3 (rT3) in circulation (33). Considering the potential impact of SARS-CoV-2 infection, it is reasonable to suggest that proinflammatory factors may also be the driving force behind changes in thyroid function.

This study also revealed a positive correlation between TT3 levels and lymphocyte subset counts, particularly with the CD3+ subset (Spearman's rho 0.331, $P < 0.001$). Other studies have reported similar findings, showing that TT3 levels, rather than TSH or other thyroid hormones, are associated with lymphocyte counts in patients with bacterial sepsis (34) and that FT3 levels correlate with lymphocyte counts in COVID-19 patients (35, 36). Previous research has suggested that thyroid function plays a role in regulating cell-mediated immunity and lymphocyte proliferation. In healthy individuals, TT3 and TT4 levels were positively linked to various lymphocyte subgroups, particularly memory T cells, natural killer T cells, and CD3+/CD4+/CD45RO+ memory T helper cells (37). People with hypothyroidism presented a decrease in lymphocyte function, which could be restored after exogenous hormone administration (38). Therefore, TT3 levels may serve as a reliable indicator for assessing disease severity and predicting clinical outcomes in COVID-19. Our subgroup analysis observed weaker correlations among patients with normal thyroid function. However, the correlations were more significant in the hypothyroidism and NTIS subgroups, as shown in [Supplementary Table 2](#).

This study focused on the TT3 level instead of the FT3 level. Since it is widely accepted that a decrease in TT3 level is positively correlated with the severity of the disease. Additionally, the reduction in TT3 amplitude is generally more significant than that of FT3 (23). Furthermore, our study cohort found that decreased TT3 levels were more common than decreased FT3 levels (39.1% vs. 1.5%). All 46 patients with low FT3 levels in our study also had low TT3 levels. When exploring the association between T3 and severe COVID-19, we identified a turning point for TT3 at 1.06 nmol/L, which is close to the lower limit of the reference range for TT3 based on immunoassays. Considering the convenience in clinical practice, we ultimately decided to use low TT3 levels in defining NTIS.

This study has several limitations that should be considered. Firstly, it was conducted at a single center, which may limit the generalizability of the findings. However, the study population included over three thousand individuals with varying degrees of SARS-CoV-2 infection, which partially enhances the generalizability of the results. Secondly, there was a lack of medical history regarding preexisting thyroid disease and

potential drug confounders that could interfere with the accurate detection of thyroid function. Thirdly, it is essential to note that thyroid function was tested within 24 hours of admission before any subsequent treatment was administered during hospital stays. Fourth, we relied solely on medical history, medication use, or HbA1c levels to confirm the presence of diabetes, which may have excluded certain individuals. Lastly, the absence of follow-up to track changes in thyroid function is another limitation of this study. Future research should incorporate follow-up assessments to provide a more comprehensive understanding of the long-term effects on thyroid function in patients with SARS-CoV-2 infection.

Conclusion

Patients with thyroid hormone profiles of NTIS or hypothyroidism on admission were associated with increased risks of developing severe COVID-19 during hospital stays. The decreased level of TT3 correlated with the increased risk of severe COVID-19 in patients with NTIS or hypothyroidism.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by The ethics committee of Shanghai Public Health Clinical Center (No. 2023-S069-01). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because This research is an observational study, involving analyzing anonymized records or existing data.

Author contributions

YY: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Methodology. LQ: Resources, Writing – review & editing, Methodology. CWu: Data curation, Writing – review & editing, Resources. XX: Data curation, Resources, Software, Writing – review & editing. DQ: Data curation, Writing – review & editing, Resources. LZ: Resources, Writing – review & editing, Data curation. JL: Data curation, Resources, Writing – review & editing. QZ: Data curation, Resources, Writing – review & editing. CWa: Data curation, Writing – review & editing, Software. XZ: Investigation, Project administration, Supervision, Writing – review & editing, Funding acquisition, Resources.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Programs of Science and Technology Commission of Shanghai Municipality (21Y11904700), Shanghai Municipality Health Commission (202140085), Jinshan District Science and Technology Committee (2023-WS-04), and Shanghai Public Health Clinical Center (KY-GW-2022-06).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Puig-Domingo M, Marazuela M, Yildiz BO, Giustina A. COVID-19 and endocrine and metabolic diseases. An updated statement from the European Society of Endocrinology. *Endocrine*. (2021) 72:301–16. doi: 10.1007/s12020-021-02734-w
- Brancatella A, Ricci D, Viola N, Sgrò D, Santini F, Latrofa F. Subacute thyroiditis after sars-COV-2 infection. *J Clin Endocrinol Metab*. (2020) 105:2367–70. doi: 10.1210/clinem/dgaa276
- Brancatella A, Ricci D, Cappellani D, Viola N, Sgrò D, Santini F, et al. Is subacute thyroiditis an underestimated manifestation of SARS-coV-2 infection? Insights from a case series. *J Clin Endocrinol Metab*. (2020) 105(10):e3742–6. doi: 10.1210/clinem/dgaa537
- Arefzadeh A. A review of thyroid dysfunction due to COVID-19. *Mini Rev Med Chem*. (2023) 24(3):265–71. doi: 10.2174/1389557523666230413090332
- Świstek M, Broncel M, Gorzelak-Pabiś P, Morawski P, Fabiś M, Woźniak E. Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality. *Endocrinol Pract*. (2022) 28:494–501. doi: 10.1016/j.eprac.2022.02.006
- Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol*. (2015) 3:816–25. doi: 10.1016/S2213-8587(15)00225-9
- Sparano C, Zago E, Morettini A, Nozzoli C, Yannas D, Adornato V, et al. Euthyroid sick syndrome as an early surrogate marker of poor outcome in mild SARS-CoV-2 disease. *J Endocrinol Invest*. (2022) 45:837–47. doi: 10.1007/s40618-021-01714-1
- Ahn J, Lee MK, Lee JH, Sohn SY. Thyroid hormone profile and its prognostic impact on the coronavirus disease 2019 in Korean patients. *Endocrinol Metab (Seoul)*. (2021) 36:769–77. doi: 10.3803/EnM.2021.1109
- Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity. *Clin Endocrinol (Oxf)*. (2021) 95:469–77. doi: 10.1111/cen.14476
- Vassiliadi DA, Ilias I, Pratikaki M, Jahaj E, Vassiliou AG, Detsika M, et al. Thyroid hormone alterations in critically and non-critically ill patients with SARS-CoV-2 infection. *Endocr Connect*. (2021) 10:646–55. doi: 10.1530/EC-21-0029
- Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the “euthyroid sick syndrome. *Endocr Rev*. (1982) 3:164–217. doi: 10.1210/edrv-3-2-164
- Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. *Front Endocrinol (Lausanne)*. (2020) 11:566439. doi: 10.3389/fendo.2020.566439
- Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. *J Endocrinol Invest*. (2021) 44:1031–40. doi: 10.1007/s40618-020-01460-w
- Lang S, Liu Y, Qu X, Lu R, Fu W, Zhang W, et al. Association between thyroid function and prognosis of COVID-19: A retrospective observational study. *Endocr Res*. (2021) 46:170–7. doi: 10.1080/07435800.2021.1924770
- Wilmar MW, Van den Berghe G. *Werner & Ingbar's the thyroid: a fundamental and clinical text*. 10th ed. Philadelphia: Lippincott Williams and Wilkins (2013) p. 203–17 p.
- Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JL, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1361479/full#supplementary-material>

Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. (2012) 22:1200–35. doi: 10.1089/thy.2012.0205

17. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. (2016) 26:1343–421. doi: 10.1089/thy.2016.0229

18. Commission NH. *Diagnosis and Treatment Plan for Covid-19 (Trial Version 9)*. China: National Health Commission of the People's Republic of China (2022).

19. Rossetti CL, Cazarin J, Hecht F, Beltrão FEL, Ferreira ACF, Fortunato RS, et al. COVID-19 and thyroid function: What do we know so far? *Front Endocrinol (Lausanne)*. (2022) 13:1041676. doi: 10.3389/fendo.2022.1041676

20. Zheng J, Cui Z, Shi N, Tian S, Chen T, Zhong X, et al. Suppression of the hypothalamic-pituitary-thyroid axis is associated with the severity of prognosis in hospitalized patients with COVID-19. *BMC Endocr Disord*. (2021) 21:228. doi: 10.1186/s12902-021-00896-2

21. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab*. (1998) 83:1827–34. doi: 10.1210/jcem.83.6.4763

22. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNFalpha in nonthyroidal illness syndrome induced by abdominal surgery. *J Clin Endocrinol Metab*. (2001) 86:4198–205. doi: 10.1210/jcem.86.9.7795

23. Wilmar MW, Van den Berghe G. *Werner & Ingbar's the thyroid: a fundamental and clinical text*. 10th ed. Philadelphia: Lippincott Williams and Wilkins (2015) p. 203–17 p.

24. Holland FW, Brown PS, Weintraub BD, Clark RE. Cardiopulmonary bypass and thyroid function: a “euthyroid sick syndrome. *Ann Thorac Surg*. (1991) 52:46–50. doi: 10.1016/0003-4975(91)91416-S

25. Girvent M, Maestro S, Hernández R, Carajol I, Monné J, Sancho JJ, et al. Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation. *Surgery*. (1998) 123:560–7. doi: 10.1067/msy.1998.87238

26. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: A retrospective study. *Thyroid*. (2021) 31:8–11. doi: 10.1089/thy.2020.0363

27. Li Z, Hou P, Mu S, Wang R, Miao H, Feng M, et al. Thyroxine changes in COVID-19 pandemic: A systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. (2023) 14:1089190. doi: 10.3389/fendo.2023.1089190

28. Moura Neto A, Parisi MC, Alegre SM, Pavin EJ, Tambascia MA, Zantut-Wittmann DE. Relation of thyroid hormone abnormalities with subclinical inflammatory activity in patients with type 1 and type 2 diabetes mellitus. *Endocrine*. (2016) 51:63–71. doi: 10.1007/s12020-015-0651-5

29. Fallahi P, Elia G, Ragusa F, Paparo SR, Patrizio A, Balestri E, et al. Thyroid autoimmunity and SARS-coV-2 infection. *J Clin Med*. (2023) 12(19):6365. doi: 10.3390/jcm12196365

30. Boelen A, Platvoet-Ter Schiphorst MC, Wiersinga WM. Association between serum interleukin-6 and serum 3,5,3'-triiodothyronine in nonthyroidal illness. *J Clin Endocrinol Metab*. (1993) 77:1695–9. doi: 10.1210/jcem.77.6.8263160

31. Mebis L, Paletta D, Debaveye Y, Ellger B, Langouche L, D'Hoore A, et al. Expression of thyroid hormone transporters during critical illness. *Eur J Endocrinol.* (2009) 161:243–50. doi: 10.1530/EJE-09-0290
32. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab.* (1999) 84:1311–23. doi: 10.1210/jcem.84.4.5636
33. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid.* (2014) 24:1456–65. doi: 10.1089/thy.2014.0201
34. Grondman I, de Nooijer AH, Antonakos N, Janssen NAF, Mouktaroudi M, Leventogiannis K, et al. The association of TSH and thyroid hormones with lymphopenia in bacterial sepsis and COVID-19. *J Clin Endocrinol Metab.* (2021) 106:1994–2009. doi: 10.1210/clinem/dgab148
35. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Pang P, et al. The independent association of TSH and free triiodothyronine levels with lymphocyte counts among COVID-19 patients. *Front Endocrinol (Lausanne).* (2021) 12:774346. doi: 10.3389/fendo.2021.774346
36. Sciacchitano S, De Vitis C, D'Ascanio M, Giovagnoli S, De Dominicis C, Laghi A, et al. Gene signature and immune cell profiling by high-dimensional, single-cell analysis in COVID-19 patients, presenting Low T3 syndrome and coexistent hematological Malignancies. *J Transl Med.* (2021) 19:139. doi: 10.1186/s12967-021-02805-6
37. Hodkinson CF, Simpson EE, Beattie JH, O'Connor JM, Campbell DJ, Strain JJ, et al. Preliminary evidence of immune function modulation by thyroid hormones in healthy men and women aged 55-70 years. *J Endocrinol.* (2009) 202:55–63. doi: 10.1677/JOE-08-0488
38. Schoenfeld PS, Myers JW, Myers L, LaRocque JC. Suppression of cell-mediated immunity in hypothyroidism. *South Med J.* (1995) 88:347–9. doi: 10.1097/00007611-199503000-00019



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Saira Rafaqat,
Lahore College for Women University,
Pakistan
Ahmet Fatih Durmusoglu,
Istanbul Medipol University, Türkiye
Bianca Leca,
University Hospitals Coventry and
Warwickshire NHS Trust, United Kingdom

*CORRESPONDENCE

Mingming Wang
✉ wmm@xzhmu.edu.cn

†These authors share first authorship

RECEIVED 17 May 2024

ACCEPTED 28 August 2024

PUBLISHED 04 October 2024

CITATION

Zhang S, Wu Y, Mprah R and Wang M (2024)
COVID-19 and persistent symptoms:
implications for polycystic ovary syndrome
and its management.
Front. Endocrinol. 15:1434331.
doi: 10.3389/fendo.2024.1434331

COPYRIGHT

© 2024 Zhang, Wu, Mprah and Wang. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

COVID-19 and persistent symptoms: implications for polycystic ovary syndrome and its management

Shanshan Zhang^{1†}, Yanqun Wu^{1†},
Richard Mprah² and Mingming Wang^{2,3*}

¹School of Biological Science, Jining Medical University, Rizhao, Shandong, China, ²Department of Physiology, School of Basic Medical Sciences, Xuzhou Medical University, Xuzhou, Jiangsu, China,

³China National Experimental Teaching Demonstration Center for Basic Medicine, Xuzhou Medical University, Xuzhou, Jiangsu, China

The COVID-19 pandemic has left a profound mark on global health, leading to substantial morbidity and mortality worldwide. Beyond the immediate symptoms of infection, the emergence of “long COVID”, the long-term effects of SARS-CoV-2, has become a significant public health concern. Long COVID is a multifaceted condition affecting various organs and systems, including the cardiovascular, digestive, nervous, and endocrine systems. Individuals diagnosed with polycystic ovary syndrome (PCOS) may face an increased risk of severe COVID-19 symptoms and infection. It is crucial to comprehend how long COVID affects PCOS patients to devise effective treatment and care strategies. Here, we review the detrimental effects of COVID-19 and its long-term effects on reproductive health, endocrine function, inflammation, metabolism, cardiovascular health, body composition, lifestyle, and mental health in patients with PCOS. We offer recommendations for the post-covid-19 management of PCOS, emphasizing the necessity of a comprehensive, multidisciplinary approach to patient care. Furthermore, we discuss prospective research directions, highlighting the significance of continued investigations and clinical trials to evaluate treatment approaches for long COVID and its ramifications in individuals with PCOS.

KEYWORDS

polycystic ovary syndrome, Long COVID, care strategies, treatment approaches, multidisciplinary management

1 Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2), has been declared a public health emergency of international concern (1). SARS-CoV-2 enters cells by interacting with spike protein S and angiotensin-converting enzyme 2 (ACE2), causing organ dysfunction (2).

The COVID-19 pandemic has taken a great toll worldwide, with profound consequences for individuals, organizations, and societies. While the initial focus was on the acute symptoms of the virus, more attention is now being paid to the long-term after-effects of COVID-19 (3).

Even after the virus becomes undetectable in COVID-19 patients, it can continue to replicate for up to four weeks following infection, potentially resulting in long-term effects on various organs and systems. This condition is commonly referred to as “Long COVID” (4) (Figure 1). The Centers for Disease Control has listed approximately 25 clinical laboratory abnormalities associated with an increase in COVID-19 prevalence, which affects the health-related quality of life and well-being of COVID-19 patients (5, 6). It is estimated that 10–20% of cases across all ages, including children, will develop long COVID (a complex disorder of multiple organ system dysfunction), with most cases occurring in people with mild acute illness (7, 8).

Several hypotheses for the pathogenesis of long COVID have been proposed (Figure 2), including the persistence of SARS-CoV-2 in tissues (9), pathological inflammation caused by persistent autoimmune responses and immune disorders (10, 11), long-term tissue damage (12), endothelial dysfunction and coagulation dysfunction (13), and the effects of SARS-CoV-2 on microbiota, including virome (10). Relevant risk factors may include female sex, type 2 diabetes, androgens, early dyspnoea, previous psychiatric disorders, and specific biomarkers (14). However, most of these

studies on the mechanism hypothesis are preliminary, and further studies on the pathophysiology of long COVID are urgently needed.

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting 5–20% of females of reproductive age (15). This syndrome can lead to infertility, insulin resistance (IR), obesity, type 2 diabetes, dyslipidaemia, cardiovascular problems, and a series of other health issues (16, 17). The overlap of many PCOS comorbidities with risk factors for severe COVID-19 progression has attracted research attention (Figure 3). Multiple studies have shown that women with PCOS are at a higher risk of contracting the SARS-CoV-2 virus and worsening COVID-19-related outcomes at all ages (18–20). A study of 21,000 patients with PCOS showed that women with PCOS had a 28% higher risk of developing COVID-19 (21). The clinical features of PCOS, such as hyperandrogenism, obesity, IR, chronic low-grade inflammation, and intestinal flora disturbance, may increase the risk of SARS-CoV-2 infection (18, 22). However, the impact of COVID-19 on patients with PCOS has not yet been explored. This review updates our knowledge on this issue, specifically examining the impact of COVID-19 and its subsequent effects on PCOS and its accompanying health issues.

To gain a comprehensive understanding of the health impact of COVID-19 and its long-term effects on patients with PCOS and to provide guidance for future research and clinical practice, we conducted an extensive literature search of reputable databases, including PubMed and Web of Science. The search terms involved “long-term COVID-19”, “polycystic ovary syndrome”,

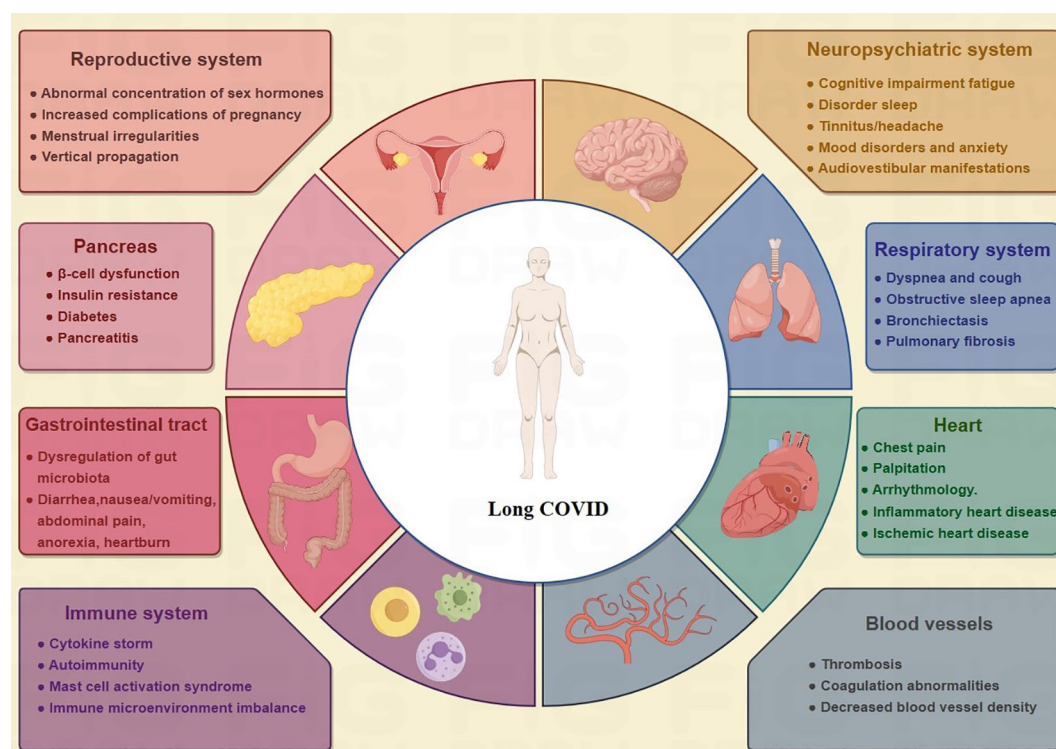


FIGURE 1

Multisystem symptoms/manifestations of long COVID. Among the various organ systems that long COVID can damage are the respiratory, cardiovascular, neuropsychological, digestive, circulatory, immune, and genitourinary systems, making it a truly multiorgan disease.

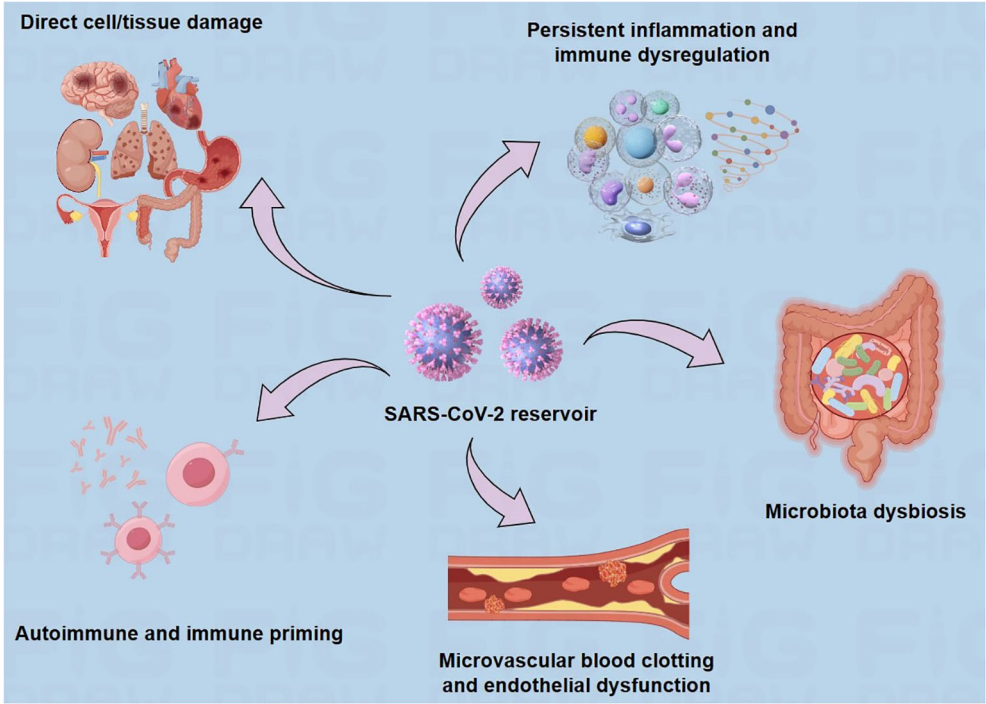


FIGURE 2
Suggested explanations for the underlying causes of long COVID. There are several hypothesized mechanisms for the pathogenesis of long COVID, including prolonged presence of the virus, direct cell/tissue damage, immune dysregulation, microbiome disruption, autoimmunity, coagulation, and endothelial abnormalities.

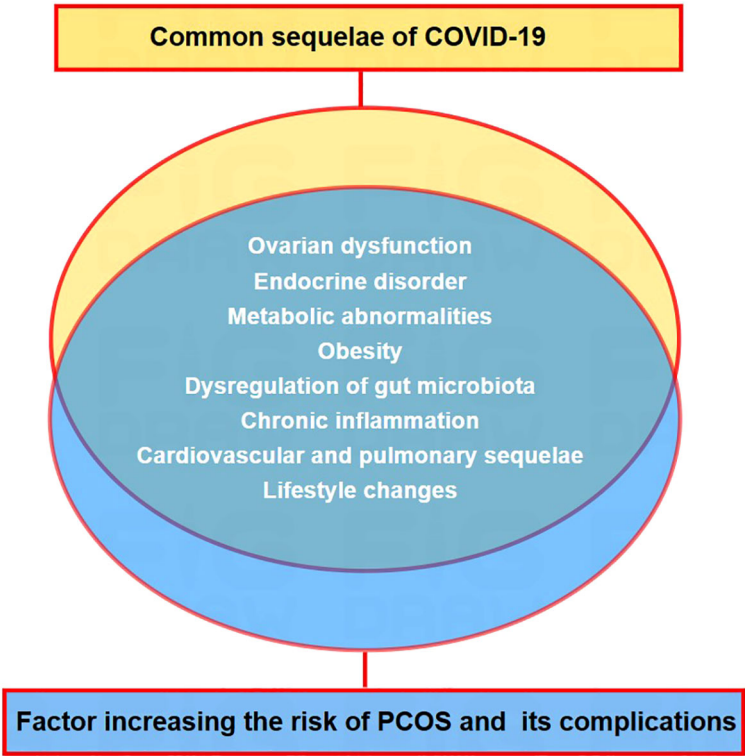


FIGURE 3
Convergence of post-covid-19 health issues and risk factors associated with PCOS and related problems. Overlapping factors between the common long-term outcomes of COVID-19 and risk indicators for PCOS and its associated health issues.

“epidemiology”, “symptoms”, “mechanism”, “management” and other related terms. Articles were selected based on their relevance to the topic identified in the abstract. The reference lists of articles were also searched to identify relevant literature.

2 Impacts of COVID-19 and its sequelae on PCOS

2.1 Reproductive health

2.1.1 Menstrual irregularities

The female reproductive endocrine system is commonly known to be susceptible to various viruses. Evidence from studies demonstrates that COVID-19 patients underwent different levels of temporary menstrual changes, including longer menstrual cycles and decreased menstrual blood volume (23, 24). Following the COVID-19 pandemic, a study of 1,031 women found that 53% suffered from more severe premenstrual symptoms, 18% experienced new menorrhagia, and 30% experienced new dysmenorrhea (25). One study revealed a link between menstrual disturbances and the gravity of COVID-19 (24). However, this change is temporary, and most patients return to normal within 1–2 months of discharge.

In addition to SARS-CoV-2 infection, the COVID-19 vaccine also affects the menstrual cycle (26). Studies have shown an increased incidence of changes in the menstrual cycle after COVID-19 vaccination, particularly in menstrual cycle length, menstrual pain, and flow of menstruation (27), which may be attributed to immunological processes (28, 29).

2.1.2 Ovarian dysfunction

To date, no significant studies have reported the influence of COVID-19 on the ovarian reserve, function, or follicular fluid properties. However, clinical studies have shown that ovarian damage can be observed in women with COVID-19, including decreased ovarian reserve and reproductive endocrine disruption. Certain patients exhibit irregular changes in their sex hormone levels, including elevated follicle-stimulating, luteinizing hormones, testosterone, prolactin, and reduced estradiol and progesterone levels, potentially suggesting ovarian suppression (23, 30–32). Elevated levels of luteinizing hormones would stimulate theca cells to secrete more testosterone, potentially leading to secondary ovulation dysfunction at a later time. This situation could be even more problematic for women with PCOS who already have underlying endocrine disorders. Anti-Müllerian hormone (AMH) is secreted by small antral follicles and is an important indicator for evaluating the ovarian reserve. It is not affected by the menstrual cycle, exogenous sex hormones or pregnancy (33). Studies on the effects of COVID-19 on AMH have shown mixed results, with some studies showing no difference in average AMH concentrations in COVID-19 patients compared to controls (23, 34); however, others suggest that COVID-19 infection can lead to ovarian reserve impairment by reducing AMH levels (32, 35).

When the body experiences acute stress, ovarian function is typically suppressed to maintain normal functioning of vital organs,

and cases of anovulation have been documented in numerous acute illnesses. SARS-CoV-2 has demonstrated the ability to invade host cells via either the ACE2/transmembrane serine protease 2 (TMPRSS2) pathway or the basigin/cathepsin L (BSG/CTSL) pathway (30). Public datasets have demonstrated that the coexistence of ACE2 and TMPRSS2 expression in ovaries is most prominent in oocytes, whereas a minor expression is also present in granulosa cells (36, 37). A comparison of ACE2-positive and ACE2-negative ovarian cells revealed greater enrichment of various viral infection-related pathways in the former (38), suggesting that SARS-CoV-2 specifically targets certain ovarian cells through the ACE2/TMPRSS2 pathway, thereby suppressing ovarian function.

2.2 Endocrine diseases

2.2.1 The hypothalamic-pituitary-thyroid axis (HPT)

Thyroid dysfunction can exacerbate metabolic disorders, dyslipidaemia, cardiovascular disease risk, and reproductive health disorders in patients (39–41). Endocrine conditions, including thyroid dysfunction, adrenal dysfunction, and hyperandrogenism, have been linked to increased vulnerability to and severity of SARS-CoV-2 infection. Notably, coronavirus directly affects the thyroid gland (42). According to reports, COVID-19 inpatients may experience clinical thyroid dysfunction, such as thyrotoxicosis, hypothyroidism, and subclinical thyroid dysfunction, with the level of thyroid-stimulating hormone indicating the presence of hyperthyroidism or hypothyroidism (43). A study reported that 87% of patients continued to suffer from hypothyroidism even after more than three months following their recovery from COVID-19 (44). Currently, there is no evidence of a direct or indirect effect of SARS-CoV-2 on thyroid function. However, given that SARS-CoV-2 appears to be capable of causing organ damage through autoimmune processes (45), COVID-19-induced thyroid damage via immune system dysregulation cannot be ruled out.

2.2.2 The hypothalamic-pituitary-adrenal axis (HPA)

HPA plays a crucial role in the female reproductive system, and adrenal cortex dysfunction often accompanies variations in reproductive system function (46). Multiple case studies and autopsy results have corroborated the deleterious effect of SARS-CoV-2 on the HPA axis (47–50). A study on the impact of SARS-CoV-2 on the HPA axis found that some COVID-19 patients had lower levels of dehydroepiandrosterone sulfate (DHEAS) and adrenocorticotrophic hormone (ACTH) in the morning (51–53). COVID-19 patients may experience central adrenal insufficiency (54). COVID-19, through its cytopathic actions, might enhance the degradation and necrotic processes affecting adrenal cortical cells (55). Physiological stress caused by diseases, such as infection, trauma, surgery, sepsis, and critical illness, can activate the HPA axis, decrease cortisol metabolism and binding proteins, and increase serum cortisol levels (56). An increase in cortisol can trigger many neuroendocrine and immune adaptive adjustments within the body, ultimately resulting in stress responses (57). The

pathological changes and physiological stress of the HPA caused by SARS-CoV2 may have negative effects on the reproductive system.

2.3 Metabolic abnormalities

2.3.1 Obesity

Globally, the COVID-19 crisis has profoundly affected both physical and mental health (58). The implementation of COVID-19 restrictions and lockdowns has been associated with weight gain, with nearly 30% of the population experiencing this effect (59). Since the inception of the COVID-19 pandemic, there has been a staggering increase in obesity rates among children aged 2–17 (60). One study indicated that during the pandemic, pre-existing differences in obesity in terms of race, ethnicity, and community socioeconomic status have widened.

Increased SARS-CoV-2 replication enhances the inflammatory immune response, which leads to fat inflammation and IR in obesity (61). Recent evidence suggests that SARS-CoV-2 directly infects human adipocytes and alters cell metabolism in a depot-specific and viral lineage-dependent manner (62). SARS-CoV-2 infection inhibits lipolysis in subcutaneous adipocytes and increases pro-inflammatory gene expression in visceral adipocytes (63, 64). *In vitro* models suggest that viral infection directly alters the morphology and function of adipocytes (65).

Obesity increases IR and compensatory hyperinsulinaemia, leading to hyperandrogenemia, which in turn increases lipogenesis and decreases lipolysis (66). Obesity can interfere with ovarian function through neuroendocrine mechanisms, leading to ovulation disorders (67). Many bioactive molecules released by adipose tissue interact with multiple molecular pathways involved in IR, inflammation, hypertension, cardiovascular risk, coagulation, and oocyte differentiation and maturation, thereby amplifying and worsening the metabolic and reproductive phenotypes of PCOS (68). Obesity is also an important factor leading to the presence and severity of PCOS in adolescents, and intractable pre-adolescent obesity with severe IR may predict later development of PCOS (69, 70). It is plausible that obesity due to the COVID-19 pandemic may increase the prevalence of PCOS, particularly among adolescents.

2.3.2 IR and β -cell dysfunction

PCOS is associated with severe IR and defective insulin secretion. IR and β -cell dysfunction are considered major drivers of PCOS pathophysiology and are involved in the occurrence of hyperandrogenemia and reproductive dysfunction through multiple mechanisms (71).

COVID-19 patients experience a cytokine storm, with a large number of inflammatory cells affecting the function of the skeletal muscle and liver, the two main insulin-responsive organs responsible for most insulin-mediated glucose uptake (72). Clinical studies have shown that severely ill patients with COVID-19 have a high demand for insulin during peak inflammatory responses, and this significant increase in insulin demand may be due to systemic inflammation and severe IR due to critical illness (73, 74). SARS-CoV-2 induces elevated cytokine levels that promote pancreatic β -cell over-stimulation and IR, resulting in fatigue and subsequent alterations in metabolism (75).

COVID-19 can significantly shorten the life expectancy of people with type 2 diabetes (76, 77). It can also cause β -cell dysfunction, IR, and abnormal control of glucose metabolism in COVID-19 patients who have never been diagnosed with diabetes (78). Glucose abnormalities can last for at least 2 months after disease onset (79). It is expected that COVID-19 will further exacerbate IR in patients with PCOS. Montefusco et al. reported hyperinsulinemia associated with COVID-19, suggesting that COVID-19 may lead to IR, which in turn leads to hyperglycemia (78). He et al. demonstrated that newly developed IR, rather than insulin deficiency, is the mechanism underlying hyperglycaemia after SARS-CoV-2 infection. Another study showed that COVID-19 increased the risk of IR in non-diabetic patients (80). Moreover, this IR condition persists even after the virus has cleared, meaning that COVID-19 patients may face long-term pathological effects. Taken together, the evidence suggests that COVID-19 exacerbates IR in patients with PCOS.

In reviewing the current literature, we found significant limitations and unexplored areas of research on the impact of COVID-19 on IR in PCOS patients. In particular, there have been few studies focusing on the specific effects of COVID-19 on PCOS patients, and few studies have explored its impact on IR, a core pathological process. Most studies have focused on the general clinical presentation of COVID-19, its induced complications, and how it affects a wide range of metabolic diseases, such as diabetes, but have overlooked the unique effects that may occur in this specific population of PCOS. In addition, the current understanding of how COVID-19 specifically acts on the mechanisms of IR in PCOS patients remains unclear. Although some studies have proposed that SARS-CoV-2 may affect insulin sensitivity by damaging islet beta cells and triggering cytokine storms, these hypothetical mechanisms need to be verified and refined by more empirical studies to build a more complete and accurate scientific picture.

2.4 Dysregulation of gut microbiota

Several pieces of scientific evidence strongly support that the microbiome significantly affects the aetiology and sustenance of PCOS, and changes in the intestinal flora may further aggravate metabolic disorders, cytokine storms, endocrine disorders, and hyperandrogenemia in women with PCOS (81, 82). In COVID-19 patients, the composition of the gut microbiota is altered, and in combination with inflammatory cytokines and blood indicators, it mirrors the gravity of illness and immune system dysfunction (83). ACE2 affects the expression of intestinal neutral amino acid transporters (84), thereby regulating the composition of the intestinal microbiota and regulating local and systemic immune responses (85). The ecological imbalance of intestinal flora lasted for up to 30 days after the resolution of the disease (79). The lingering presence of SARS-CoV-2 in the intestines of COVID-19 patients directly leads to the loss of the junction-dependent intestinal mucosal barrier in children with multisystem inflammatory syndrome (86), hinting at the possibility that the chronic presence of SARS-CoV-2 in the gastrointestinal tract can

provoke alterations in the intestinal microbiome, resulting in long-term outcomes. Sustained changes in the fecal microbiome of COVID-19 patients have been observed, with many bacteria associated with more proinflammatory cytokines and increased disease complications. Given the profound influence of intestinal flora on the pathophysiology of PCOS and changes in intestinal flora in COVID-19 patients, it is reasonable to speculate that the changes in intestinal flora induced by COVID-19 may exacerbate the symptoms and comorbidities of PCOS patients. The potential synergies between the two diseases warrant further investigation, as COVID-19 may exacerbate pre-existing PCOS-related metabolic and endocrine disturbances through dysregulation of the gut microbiome.

However, the literature on this intersecting field remains limited and is filled with gaps. First, there is a lack of studies that specifically examine the effects of COVID-19-induced changes in the gut microbiota of PCOS patients. Most studies have focused on either PCOS or COVID-19 alone, failing to bridge the link between the two diseases through the gut microbiota. Second, the long-term effects of changes in gut microbiota associated with COVID-19 in patients with PCOS are largely unknown. Although some studies have shown that intestinal dysbiosis can persist in the early stages of the disease, its impact on PCOS symptoms, fertility outcomes, and overall quality of life remains to be clarified. In addition, the mechanism of potential interactions between COVID-19, the gut microbiota, and PCOS is unclear. Although ACE2 and its role in regulating gut microbiome composition and immune response provide a promising avenue for exploration, the specific pathways linking COVID-19, gut dysbiosis, and PCOS outcomes require further investigation.

2.5 Low-grade chronic inflammation

Pro-inflammatory cytokines play a pivotal role in the pathophysiology of PCOS, potentially underpinning many of its metabolic abnormalities. These cytokines have been linked to dysfunction and inflammation within adipose tissue (87), IR, and the pathophysiology of diabetes (88) while exerting a regulatory influence on ovarian function and hyperandrogenemia.

In patients with SARS-CoV-2 infection, there is a notable depletion in the absolute number and functional vigor of antiviral cytotoxic lymphocytes (89, 90), alongside severe impairment of specific T-cell subtypes (91). The apparent hyperactivity of the immune system induced by the virus coupled with concurrent bacterial infection can overwhelm its capacity, leading to a chronic inflammatory state with lasting adverse effects. Even after recovery, this persistent inflammatory cascade may manifest as a spectrum of chronic symptoms, including profound fatigue, dyspnoea, and joint discomfort, as well as psychological distress, such as anxiety and depression (79). The COVID-19 cytokine storm is characterized by rapid proliferation and hyperactivation of macrophages and natural killer cells and the overproduction of >150 inflammatory cytokines and chemical mediators released by immune or nonimmune cells (92). Mast cell activation syndrome and lymphopenia (i.e. B-cell and T-cell lymphocyte deficiencies)

may be the cause of COVID-19 hyperinflammation and post-covid-19 illness (93, 94). Indeed, increased levels of pro-inflammatory markers (e.g. C-reactive protein, Interleukin-6, and D-dimer) and lymphopenia have been associated with long-term COVID (12).

It is plausible that the infection of SARS-CoV-2 in women with PCOS, who already harbor a background of low-grade inflammation, could further exacerbate this proinflammatory predisposition, thereby compounding various reproductive and metabolic dysfunctions.

2.6 Cardiopulmonary functional capacity

In terms of cardiopulmonary function, COVID-19 typically presents with cough and can precipitate a range of cardiovascular and pulmonary complications, such as diffuse alveolar injury and interstitial pulmonary fibrosis (95). Approximately 50% of patients continue to experience dyspnoea for months after recovery (96, 97). The pathophysiology of lung injury caused by SARS-CoV-2 includes its binding with ACE2 and cytokine storm (51). Decreased cardiorespiratory fitness and disrupted autonomic nervous system function, coupled with irregular heart rate recovery, could be contributing factors to the elevated cardiovascular risk observed in patients with PCOS (98). Concurrently, compromised lung function predisposes patients to glucose intolerance (51), IR (99), type 2 diabetes (100, 101), and cardiovascular diseases (102, 103). These adverse outcomes may stem from the direct impact of hypoxaemia on glucose and insulin regulation (104) as well as the inflammatory mediators and altered insulin signaling associated with pulmonary dysfunction (105, 106), potentially exacerbating the metabolic manifestations of PCOS.

2.7 Fertility outcomes

2.7.1 Assisted reproduction technology (ART)

PCOS is a multifaceted endocrine disorder that often intersects with challenges related to fertility and pregnancy. For many women with PCOS, the path to successful conception often involves ART. Recent investigations into the impact of COVID-19 on *in vitro* fertilization (IVF) cycles have yielded noteworthy insights. Notably, while COVID-19 did not seem to compromise patients' physical resilience or ovarian reserve during IVF procedures, there was a discernible decrease in the proportion of high-quality embryos (107). Furthermore, evidence suggests that while acute SARS-CoV-2 infection may not impede immediate ART outcomes, it could potentially exert adverse effects on oocyte production over the long term (i.e. beyond 180 days post-infection) (108). It has also been reported that the sperm concentration of couples was significantly reduced after exposure to COVID-19 (109). Hence, there should be at least three months (the time required for folliculogenesis and spermatogenesis) between a patient's recovery from COVID-19 and the resumption of IVF treatment.

The onset of the COVID-19 pandemic has precipitated unforeseen disruptions across various spheres, including the delivery of non-emergency healthcare services. Notably, both the

American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology independently recommend the temporary cessation of reproductive health care services (110). This suspension had profound repercussions for individuals and couples awaiting or undergoing fertility treatment. Delays resulting from the pandemic have forced some patients to face age-related limitations enforced by funding agencies, creating formidable barriers to treatment access, and prolonged waiting periods exacerbate anxiety, stress, and despondency among individuals grappling with infertility, consequently diminishing the success rates of ART (111, 112). A recent study revealed that postponing fertility treatment by a mere 12 months could lead to a substantial decrease in the likelihood of achieving a successful live birth through IVF among women aged 38–39 and 40–42, with percentages dropping by 18.8% and 22.4%, respectively (113). Furthermore, the economic and reproductive medicine response to the COVID-19 pandemic has reduced the affordability and accessibility of fertility care and has had a profound impact on IVF live birth rates (114–116).

2.7.2 Pregnancy complications

Epidemiological research has indicated that women with PCOS are more susceptible to COVID-19 than those without (19, 117). Contracting SARS-CoV-2 during pregnancy increases the risk of complications such as spontaneous abortion, premature delivery, intrauterine growth restriction, and maternal renal failure or disseminated intravascular coagulation (118). Furthermore, there is an elevated risk of stillbirth (119). Several preexisting conditions and demographic factors, including chronic hypertension, preexisting diabetes, advanced maternal age, high body mass index, and non-white ethnicity, increase the likelihood of severe COVID-19 during pregnancy. Pregnant women with COVID-19 are more prone to preterm birth, heightened rates of caesarean birth (120), and potentially heightened risks of maternal mortality and ICU admission (121), with newborns being more frequently admitted to neonatal units. Pregnant women with PCOS may fall within the high-risk category for pregnancy-related complications.

2.7.3 Vertical transmission

Vertical transmission, occurring when an infected pregnant woman passes the infection to her fetus or baby during pregnancy, delivery, or the postpartum period, is a significant concern. The transmission route can involve the placenta *in utero*, during delivery, or through breastfeeding during maternal-infant contact. ACE2, expressed in various maternal tissues including the placenta, human trophoblast ectoderm, fallopian tubes, ovaries, vagina, cervix, and endometrium, plays a role in this transmission process. Studies have reported a combined neonatal vertical transmission rate of SARS-CoV-2 at 3.2%, underscoring the potential for such transmission (122), with the severity of maternal illness linked to the likelihood of vertical foetal transmission (123).

Placental transmission likely serves as the primary mechanism of vertical transmission, with severe/critically ill mothers more prone to placental SARS-CoV-2 positivity (124). Another

mechanism briefly considered is the cervicovaginal vertical transmission route, which involves exposure of the newborn to infected cells during delivery (125). However, most studies testing vaginal fluids from infected pregnant women yielded negative results for the virus (126). While breast milk from mothers infected with SARS-CoV-2 (the virus that causes COVID-19) may contain minimal amounts of viral RNA, evidence suggests that breastfeeding rarely leads to transmission of the virus to newborns (127). According to previous reports, 93% (68 out of 73) of infants born to mothers who tested positive for COVID-19 were asymptomatic. However, a small fraction of these infants experiences adverse effects, such as gastric bleeding, multiple organ failure, and, in some cases, mortality (120). Although foetal and neonatal mortality due to COVID-19 during pregnancy is rare, adverse neonatal morbidity may be associated with maternal infection, including respiratory diseases and hyperbilirubinemia, as reported by Norman et al. (128).

2.8 Lifestyle

2.8.1 Physical activity

For patients with PCOS, managing weight is essential not only for symptom improvement and increasing the chances of pregnancy but also for overall health. However, owing to the challenging pathophysiology of PCOS, weight management is exceptionally difficult (129). The social distancing measures implemented during the COVID-19 pandemic, such as closures of social, educational, and recreational facilities, have resulted in behavioral changes that can negatively impact physical activity and promote sedentary behavior, potentially exacerbating chronic health conditions such as obesity (130, 131). The closure of sports and leisure facilities during the pandemic further disrupted weight management efforts in PCOS patients. Additionally, the lingering effects of COVID-19 on patients, including fatigue, respiratory issues, and joint pain, can hinder exercise routines and weight management (6, 132, 133).

2.8.2 Sleep patterns

Sleep patterns have also been significantly affected during the pandemic, with many women with PCOS reporting negative effects on sleep quality (134). Insomnia and poor sleep health are common issues in women with PCOS and are associated with mental health problems, such as anxiety and depression, which exacerbate stress levels (135, 136). Sleep deprivation can also lead to the secretion of proinflammatory cytokines (137), metabolic changes, and disruption of appetite regulation (138–140). These factors are closely linked to the pathogenesis of PCOS.

2.8.3 Dietary habits

Eating disorders and improper diets, especially those that are too low in plant protein and consume carbohydrates with a high glycaemic index, increase the risk of overweight adolescent girls with PCOS (141), causing inflammation, IR, and negatively affecting body composition. A diet lacking quality can lead to an

imbalance in the microbiome, subsequently causing intestinal permeability and endotoxaemia. These conditions can exacerbate hyperinsulinaemia, resulting in elevated insulin levels. Such high insulin levels stimulate increased androgen production within ovaries, disrupting the normal follicular development process. This, in turn, worsens the clinical severity of PCOS (142). Additionally, dietary and environmental factors play a pivotal role in the developmental programming of PCOS female susceptibility gene variants (143).

The stress and shopping restrictions caused by isolation lead to changes in people's eating habits, with a significant increase in sweet preference and frequency of eating (144). Stress causes subjects to overeat and consume super palatable convenience foods high in sugar and/or fat (145), replacing more nutrient-rich foods, and thus reducing dietary protein intake (146, 147). These foods can boost serotonin production, which has a positive effect on mood (148). However, it is associated with an increased risk of obesity, chronic inflammation, metabolic abnormalities, and cardiovascular disease (149), which have been shown to increase the risk of more serious complications from COVID-19 (150). Before the COVID-19 outbreak, the risk of eating disorders was more than four times higher in women with PCOS than in the control group (151). Given that people with PCOS are more prone to uncontrolled and emotional eating, the risk of eating disorders may be further elevated during the pandemic.

2.9 Healthcare systems

Despite the widespread occurrence of PCOS, its fundamental causes and biological mechanisms remain unclear. The approach to managing this condition in routine clinical settings is fragmented, with inconsistencies in the care provided by specialists such as general practitioners, endocrinologists, and gynaecologists (152). Furthermore, significant knowledge deficits persist among medical professionals concerning the diagnosis, treatment strategies, and comprehensive nature of PCOS manifestations (153–155). Previous studies have shown that PCOS patients are dissatisfied with the diagnosis and treatment they receive, and feel the need to seek specialist care for their condition (156). As a result, women with PCOS are often caught in the gap between relevant healthcare services, even without the enormous pressure that the COVID-19 pandemic is putting on clinical practice. Women with PCOS lack sufficient knowledge and access to contemporary healthcare services, a problem that has become even more apparent during the COVID-19 crisis (117).

The COVID-19 pandemic has placed enormous pressure on healthcare services, requiring the reorganization and reprioritization of resources and changes in healthcare delivery models. During the pandemic, PCOS patients face numerous challenges in accessing healthcare support, particularly when it comes to primary care physicians who serve as a crucial source of assistance (157–159). Contacting these professionals or scheduling face-to-face appointments is very challenging, compounding the stress and anxiety associated with PCOS (160–162). The limited availability of primary care, coupled with the suspension of specialized PCOS-

related medical services and the uncertainty surrounding their resumption, creates a significant burden for individuals with PCOS, further exacerbating their condition and overall well-being (163, 164). Thus, the role of healthcare workers during the peak of the COVID-19 pandemic cannot be underestimated. The COVID-19 pandemic puts healthcare workers at unprecedented risk and under increased stress due to work (5). Admittedly, the incidence of COVID-19 sequelae among healthcare workers affects their long-term performance, negatively affecting the healthcare environment.

The impact of COVID-19 on access to healthcare and PCOS management varies widely across countries, mainly because of differences in healthcare systems, resources, and pandemic response strategies. Developed countries with strong healthcare systems are generally better able to cope with the surge in COVID-19 cases; however, routine healthcare services have been disrupted even in these countries (165, 166). Telemedicine plays a vital role in maintaining continuity of care, enabling patients to access consultations, laboratory tests, and prescriptions without having to physically visit a healthcare facility (167, 168). Developing countries with weaker healthcare systems face tougher challenges, many of which struggle to provide basic COVID-19 care, let alone maintain services for chronic diseases such as PCOS (169–172). In resource-constrained settings, healthcare providers must prioritize COVID-19 cases over other diseases, and shortages of essential medicines needed for PCOS management are more common in developing countries, further exacerbating the problem for PCOS patients (171–174).

2.10 Psychological impacts

The mental health of women with PCOS is a critical concern, as studies have shown that they are more susceptible to depression, anxiety, and stress than are women without non-PCOS women (175). Recent international guidelines emphasize that women with PCOS are at a higher risk of developing mental health issues such as depression and anxiety, especially during the pandemic. The pandemic has exacerbated the emotional burden experienced by women with PCOS, leading to increased psychological distress (175).

The COVID-19 crisis has not only impacted the physical health of patients with PCOS but has also taken a toll on their mental well-being. Many individuals with PCOS have reported worsening mental health, including feelings of low mood, anxiety, and depression (164). The pandemic has also raised concerns regarding the potential impact of PCOS on the risk of severe COVID-19, causing heightened health anxiety among patients. During this period, it was discovered that conditions commonly associated with PCOS, such as obesity and diabetes, carry an increased risk of severe illness and mortality due to COVID-19. This uncertainty regarding the influence of PCOS on COVID-19 risk has led to significant health anxiety and depression among many patients.

Limited access to primary care and suspension of specialized medical services related to PCOS during the pandemic made patients feel neglected, exacerbating their distress and anxiety

(164). The suspension of fertility services caused severe anxiety, psychological stress, and a sense of isolation in some individuals struggling with PCOS (176).

Due to factors such as changes in sleep patterns, mandatory quarantine measures, and socioeconomic impacts, it is anticipated that global efforts to combat COVID-19 will have a negative effect on the mental well-being of the general population. However, individuals with PCOS who are already vulnerable may face potentially greater consequences for their mental health.

The impact of COVID-19 on the mental health of women with PCOS may vary depending on several factors. Women with PCOS often require regular medical follow-ups and symptom management. In countries where access to medical services is limited due to the outbreak, these women may face challenges in managing their condition, leading to increased anxiety and stress. In some countries, rapid response and efficient operation of health services have been achieved through the optimization of diagnosis and treatment processes and the introduction of intelligent management systems, and strong healthcare systems and telemedicine services may alleviate some of these challenges, thereby providing continuity of care and support during the pandemic (177, 178). Conversely, in countries with inefficient health services, patients may have to wait for long periods to access treatment, which not only exacerbates their physical suffering but can also trigger or worsen psychological problems (179–181). In countries with financial worries and limited or disrupted social support due to the pandemic, these women may feel more isolated and experience higher levels of anxiety and depression (182–184). In addition, the severity of the epidemic, awareness of PCOS, cultural attitudes, access to mental health services, and other factors in different countries will also have different impacts on the mental health of women with PCOS (185–187).

3 Interventions and management during the COVID-19 pandemic

3.1 Telemedicine and virtual care

The COVID-19 pandemic has overwhelmed healthcare systems worldwide, dramatically reducing or even eliminating the hospitalizations of individuals with other illnesses, particularly chronic conditions. Undoubtedly, the pandemic has changed the management of chronic diseases, such as PCOS, as well as the daily interactions between patients and healthcare providers. Telemedicine has been widely implemented during this period to effectively manage several chronic noncommunicable diseases, including arterial hypertension (188). Considerable evidence shows that telemedicine is an effective, safe, and satisfactory clinical option for day-to-day management of chronic diseases (114).

One of the most widely adopted areas of telemedicine is outpatient consultation or virtual clinics. Virtual consultations can avoid transportation to hospitals and unnecessary contact with waiting rooms, enabling continuity of care without exposing

patients or healthcare professionals to potential risks. Virtual clinics can also prevent unnecessary visits, thereby reducing the number of people in emergency departments and improving the efficiency of medical resource allocation. Clinical practice reports indicate that the consultation rate of virtual clinics is 60–95% of that of regular clinics, and various chronic diseases are satisfactorily controlled through virtual care (189, 190).

Since lifestyle changes are the first-line treatment for PCOS, most patients struggle with adherence to lifestyle management, and mobile services that provide education on lifestyle modifications can be beneficial in treating PCOS. Mobile health apps have been shown to improve body weight and oocyte quality in PCOS patients (191). This reflects the effectiveness of mobile apps in facilitating lifestyle changes in PCOS patients. Telepsychotherapy offers an important additional treatment option for PCOS patients experiencing anxiety and depression during the COVID-19 pandemic. Another study confirmed that mobile health apps based on cross-theoretical models can reduce BMI, anxiety, and depression in PCOS patients and improve exercise and dietary adherence in these individuals in the long term (192).

3.2 Adjustments in reproductive care guidelines

Patients with PCOS have a higher incidence of pregnancy complications, such as preterm labor, caesarean section, miscarriage, gestational diabetes mellitus, gestational hypertension, and preeclampsia. Anatomical, physiological, and immunological changes during pregnancy may lead to a higher risk of severe SARS-CoV-2 infection in pregnant women (193). To address these concerns and prevent potential complications, various fertility societies globally, including the American Society of Reproductive Medicine, Canadian Society of Fertility and Andrology, European Society of Human Reproduction and Embryology, and International Federation of Fertility Societies, issued guidelines during the pandemic (194). These guidelines emphasize the importance of implementing mitigation measures and infection control protocols in fertility care units. Most of these guidelines recommend a temporary halt for new fertility treatments, including ovulation induction, intrauterine insemination, *in vitro* fertilization, and non-urgent gamete cryopreservation. They also suggested postponing embryo transfers, elective surgeries, and non-emergency diagnostic procedures. A COVID-19 Task Force was established to monitor the situation and provide updated guidance in alignment with local health authorities. Enhanced monitoring of pregnant women with PCOS, particularly those with comorbid conditions, such as hypertension and diabetes, is recommended during prenatal and perinatal care (195).

3.3 Patient education and support

PCOS is a prevalent and intricate disorder linked to metabolic syndrome, obesity, eating disorders, depression, and sleep apnea (196, 197). Prior to the COVID-19 pandemic, a survey revealed that

women with PCOS felt that the existing information, resources, and education did not adequately address their needs. They expressed dissatisfaction with early diagnostic care and believed that clinicians lacked sufficient knowledge of their conditions (198, 199). There are evident knowledge gaps and discrepancies among residents and physicians in the diagnosis and treatment of PCOS (154, 155).

Epidemiological studies have shown that women with PCOS are more likely to be infected with SARS-CoV-2 than are women without PCOS (19). Risk factors for severe COVID-19 highly overlap with the common features of PCOS, and COVID-19 may have an impact on all aspects of PCOS care. Additionally, the accompanying hormonal disorders (such as IR or hyperandrogenemia) associated with COVID-19 may further complicate the clinical features of PCOS (19, 117). The elevated risk of COVID-19 poses challenges in accessing timely healthcare for patients with PCOS, making diagnosis and treatment more difficult.

Effective management of PCOS is crucial during the COVID-19 pandemic, necessitating closer monitoring and revision of care plans for this patient population. The challenges posed by the pandemic highlight the need for improved education, resources, and knowledge dissemination among healthcare professionals to ensure optimal care for patients with PCOS.

4 Impact of variants

COVID-19 and its evolving variants have demonstrated a significant impact on human health, especially in those with PCOS, which may in different ways exacerbate existing comorbidities in patients and introduce new health challenges.

Different variants of SARS-CoV-2 have been found to differ significantly in causing COVID-19-related symptoms and in severity (200, 201). Primordial strain infections are associated with a higher proportion of long-COVID symptoms and face a greater burden of disease and health costs than Alpha or Delta variants (202, 203).

Notably, some COVID-19 variants have shown increased transmissibility and virulence compared with the original SARS-CoV-2 strain (204, 205). This property could put people with PCOS - whose immune systems may already be compromised by comorbidities such as obesity, insulin resistance and chronic inflammation - at higher risk of infection.

In addition, SARS-CoV-2 mutants are not only more infectious than wild-type viruses but also have a particular tendency to infect obese individuals (206), which means that PCOS patients with symptoms of obesity need to be closely followed and actively treated.

Different variants can also trigger different immune responses, further affecting the balance of the immune system in PCOS patients (207). For example, certain variants may trigger intense autoantibody production or cytokine storms that exacerbate autoimmune symptoms associated with PCOS, such as hyperandrogenemia and chronic inflammation.

In summary, the impact of COVID-19 variants on PCOS patients is diverse, given their different manifestations of virulence, infectivity, and disruption to various physiological

systems (208). This difference may directly lead to further deterioration of reproductive health, metabolic status, mental health, cardiovascular health, and immune system functions. Therefore, it is important to continuously monitor the potential risks of novel COVID-19 variants in PCOS patients and develop personalized management strategies.

5 Future perspectives

As the COVID-19 pandemic continues, its long-term impact, particularly on PCOS patients, highlights the urgency of a multifaceted approach to care (Figure 4). Long COVID exacerbates several challenges faced by women with PCOS, including immune, endocrine, metabolic, neurological, cardiovascular, and gastrointestinal issues. Recognizing this complexity, future research must delve into the mechanisms linking COVID-19 and PCOS to develop tailored interventions.

One of the crucial aspects of long-term COVID-19 management is the recognition and treatment of psychological issues, such as depression and anxiety, that can arise from the traumatic experience of the pandemic. Seeking counseling and psychological support is vital in helping survivors overcome feelings of despair and anxiety, and in turn, improve their overall quality of life.

Given the heterogeneity of PCOS, personalized treatment regimens are critical (121). Healthcare providers must consider the impact of long COVID on PCOS symptoms and adjust interventions accordingly. Involving people with PCOS in research and clinical trials will contribute to a deeper understanding of the disease and its interactions with COVID-19 (209).

The International Evidence-based Guidelines for the Evaluation and Management of PCOS emphasize the importance of lifestyle interventions, such as diet, exercise, and sleep optimization, for overweight or obese women with PCOS (210). These interventions are essential to improve the metabolic, hormonal, and psychological aspects of the syndrome. However, many women with PCOS may struggle to follow diet and exercise guidelines, especially in the post-pandemic world, where COVID-19 restrictions and concerns about disease transmission continue to affect physical activity levels. Mobile technology can improve compliance with lifestyle management recommendations by providing support and monitoring tools for PCOS patients.

Future research should explore drug treatments that target both PCOS symptoms and boost the immune system or target the virus itself (211). Leveraging current infrastructure, developing scalable healthcare models, and integrating them across disciplines (212) are essential to address the complex interplay between long COVID and PCOS. Long-term follow-up studies and the development of effective treatments are urgently needed, with a focus on the evolving phase of the pandemic, possible complications, vaccination status, and the presence of new viral strains (213).

Improving the diagnosis and treatment of PCOS remains a significant challenge in the healthcare field. Health professionals, especially primary care professionals, must be educated about the standard diagnostic criteria and treatment options. A

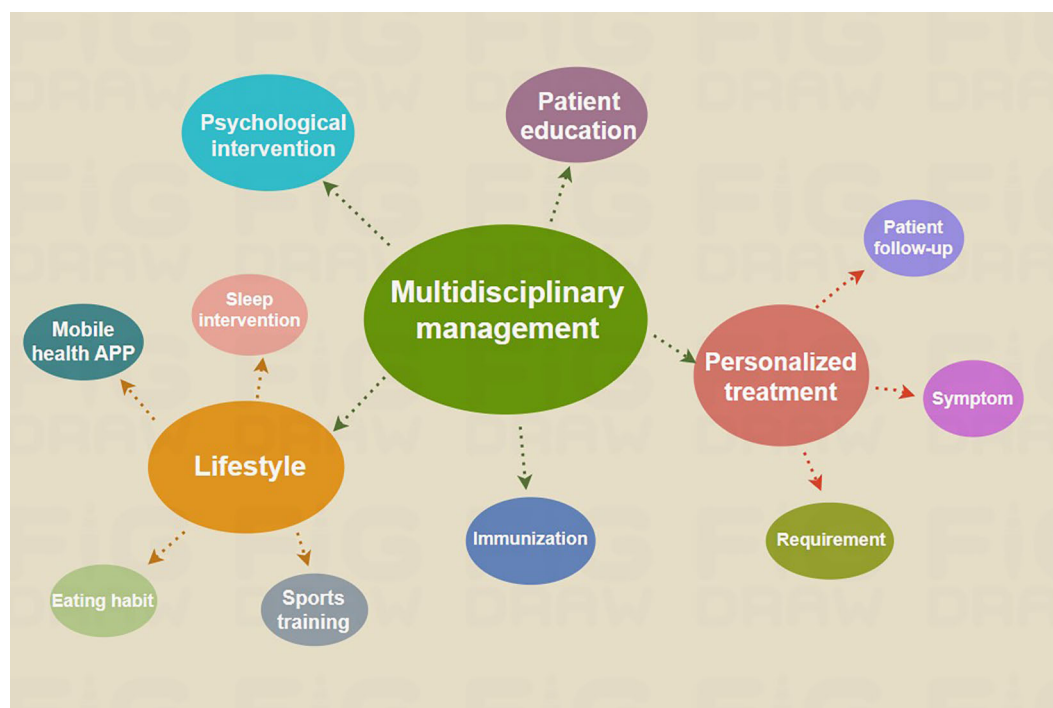


FIGURE 4

Therapeutic interventions for patients with PCOS affected by the sequelae of COVID-19. The complexity and wide-ranging impact of COVID-19 after-effects necessitate the use of a multidisciplinary care model for the optimal treatment of PCOS.

multidisciplinary collaborative approach involving specialists in gynaecology, endocrinology, family medicine, psychiatry, and nutrition should be implemented. Continuing education programs should be developed for healthcare professionals and patients, including workshops, webinars, and standardized educational materials (214).

Subsequent research priorities should include (i) assessing the long-term effects of COVID-19 in people with or without PCOS; (ii) elucidating the causal mechanisms of COVID-19 and its sequelae affecting PCOS and its complications, including endocrine, immune system, metabolism, and mental stress; (iii) developing and improving scalable diagnostic methods that are highly specific for COVID-19-related PCOS complications; (iv) assessing the effects of vaccination and immunotherapy on PCOS and its complications; (v) identifying new therapeutic solutions or repurposing older drugs that can protect or reverse COVID-19-associated PCOS and its complications; and (vi) testing the feasibility and effectiveness of mobile health applications to improve health-related behaviors in women with PCOS.

In conclusion, a comprehensive and collaborative approach involving health care professionals, researchers, and patients is key to effectively managing the long-term effects of COVID-19 and PCOS. By prioritizing individualized care, psychological support, and ongoing research efforts, we can improve the outcomes and quality of life for those grappling with the aftermath of the pandemic. This approach should encompass lifestyle interventions, innovative technologies, and targeted drug therapies to address the unique challenges posed by the convergence of these conditions. By integrating these strategies,

healthcare providers can better support patients in managing their health and well-being in the face of ongoing uncertainty and evolving healthcare needs.

6 Limitations

This review takes a multidisciplinary approach to provide patients with PCOS with a comprehensive perspective on understanding and managing the long-term effects of COVID-19. However, this method has several disadvantages. First, while the review cites a large number of studies, many of the studies on the relationship between long COVID and PCOS are still preliminary, leading to some conclusions that may not be deep or comprehensive enough. Second, the specific pathogenesis of long COVID is not fully understood at present, which limits the depth and accuracy of the review in exploring its mechanisms of influence. Finally, owing to the short duration of the COVID-19 outbreak, long-term follow-up data are relatively scarce, which has hindered the comprehensive assessment of the long-term impact of the long COVID.

7 Conclusion

The COVID-19 pandemic has significantly impacted global health, with long COVID emerging as a major concern. Long COVID affects multiple systems, posing a particular challenge for PCOS patients who may experience aggravated symptoms and complicated management. Current evidence indicates that

COVID-19 and its sequelae negatively impact reproductive health, endocrine function, inflammation, metabolism, cardiorespiratory health, body composition, lifestyle, and mental health in patients with PCOS. These mechanisms are multifactorial and include inflammation, lifestyle changes, and comorbidities. Given the lack of effective therapies for PCOS post-COVID-19, a comprehensive multidisciplinary approach is crucial for its management. Future research and clinical trials are needed to evaluate treatment and prevention strategies, emphasizing the importance of personalized care and risk assessment in patients with PCOS and COVID-19.

Author contributions

SZ: Writing – original draft. YQW: Writing – review & editing. RM: Writing – review & editing. MW: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was financially supported by the National Natural Science Foundation of China (Grant No.82401923) the Natural Science Research of Jiangsu Higher Education Institutions of China (Grant No. 22KJB180007), and Outstanding Talent Research Funding of Xuzhou Medical University (Grant No. RC20552029), the TaiShan Industrial Experts Programme (No. JYHL2022MS20), the Small-

and Medium-sized Enterprise Innovation Capability Enhancement Project of Shandong Province (No. 2023TSGC0549).

Acknowledgments

The authors would like to express their sincere gratitude to their respective institutions, Xuzhou Medical University and Jining Medical University, for their support in the literature research and collection. We appreciate the help of Yuanxin Wang, Siyuan Ye and Yinan Cao during the revision phase.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *New Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
- Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care (London England)*. (2020) 24:422. doi: 10.1186/s13054-020-03120-0
- Parotto M, Myatra SN, Munblit D, Elhazmi A, Ranzani OT, Herridge MS. Recovery after prolonged ICU treatment in patients with COVID-19. *Lancet Respir Med*. (2021) 9:812–4. doi: 10.1016/S2213-2600(21)00318-0
- Szabo S, Zayachivska O, Hussain A, Muller V. What is really 'Long COVID'? *Inflammopharmacology*. (2023) 31:551–7. doi: 10.1007/s10787-023-01194-0
- Shukla AK, Atal S, Banerjee A, Jhaj R, Balakrishnan S, Chugh PK, et al. An observational multi-centric COVID-19 sequelae study among health care workers. *Lancet regional Health Southeast Asia*. (2023) 10:100129. doi: 10.1016/j.lansea.2022.100129
- Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae in COVID-19 survivors in Wuhan, China: A single-centre longitudinal study. *Clin Microbiol Infect: Off Publ Eur Soc Clin Microbiol Infect Diseases*. (2021) 27:89–95. doi: 10.1016/j.cmi.2020.09.023
- The L. Long COVID: 3 years in. *Lancet (London England)*. (2023) 401:795. doi: 10.1016/S0140-6736(23)00493-2
- Lechner-Scott J, Levy M, Hawkes C, Yeh A, Giovannoni G. Long COVID or post-covid-19 syndrome. *Multiple sclerosis related Disord*. (2021) 55:103268. doi: 10.1016/j.msard.2021.103268
- Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, et al. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. *Clin Infect diseases: an Off Publ Infect Dis Soc America*. (2023) 76:e487–e90. doi: 10.1093/cid/ciac722
- Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. *Front Microbiol*. (2021) 12:698169. doi: 10.3389/fmicb.2021.698169
- Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol*. (2022) 23:210–6. doi: 10.1038/s41590-021-01113-x
- Yong SJ. Long COVID or post-covid-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (London England)*. (2021) 53:737–54. doi: 10.1080/23744235.2021.1924397
- Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, Kümpers P, et al. Persistent capillary rarefaction in long COVID syndrome. *Angiogenesis*. (2023) 26:53–61. doi: 10.1007/s10456-022-09850-9
- Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. (2023) 21:133–46. doi: 10.1038/s41579-022-00846-2
- March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod (Oxford England)*. (2010) 25:544–51. doi: 10.1093/humrep/dep399
- Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet (London England)*. (2007) 370:685–97. doi: 10.1016/S0140-6736(07)61345-2
- Patel S. Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. *J Steroid Biochem Mol Biol*. (2018) 182:27–36. doi: 10.1016/j.jsbmb.2018.04.008
- Morgante G, Troia L, De Leo V. Coronavirus Disease 2019 (SARS-CoV-2) and polycystic ovarian disease: Is there a higher risk for these women? *J Steroid Biochem Mol Biol*. (2021) 205:105770. doi: 10.1016/j.jsbmb.2020.105770
- Subramanian A, Anand A, Adderley NJ, Okoth K, Toulis KA, Gokhale K, et al. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. *Eur J endocrinology*. (2021) 184:637–45. doi: 10.1530/EJE-20-1163
- Jerzak M, Szafarowska M. Preliminary results for personalized therapy in pregnant women with polycystic ovary syndrome during the COVID-19 pandemic.

Archivum immunologiae therapiae experimentalis. (2022) 70:13. doi: 10.1007/s00005-022-00650-z

21. de Medeiros SF, Yamamoto MMW, de Medeiros MAS, Yamamoto A, Barbosa BB. Polycystic ovary syndrome and risks for COVID-19 infection: A comprehensive review: PCOS and COVID-19 relationship. *Rev endocrine Metab Disord.* (2022) 23:251–64. doi: 10.1007/s11554-022-09715-y
22. Ilias I, Goulas S, Zabulienė L. Polycystic ovary syndrome: Pathways and mechanisms for possible increased susceptibility to COVID-19. *World J Clin cases.* (2021) 9:2711–20. doi: 10.12998/wjcc.v9.i12.2711
23. Li K, Chen G, Hou H, Liao Q, Chen J, Bai H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. *Reprod biomedicine online.* (2021) 42:260–7. doi: 10.1016/j.rbmo.2020.09.020
24. Khan SM, Shilen A, Heslin KM, Ishimwe P, Allen AM, Jacobs ET, et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. *Am J obstetrics gynecology.* (2022) 226:270–3. doi: 10.1016/j.ajog.2021.09.016
25. Phelan N, Behan LA, Owens L. The impact of the COVID-19 pandemic on women's reproductive health. *Front endocrinology.* (2021) 12:642755. doi: 10.3389/fendo.2021.642755
26. Taşkalıran I, Vuraloğlu E, Bozkuş Y, Turhan İyidir Ö, Nar A, Başçıl Tütüncü N. Menstrual changes after COVID-19 infection and COVID-19 vaccination. *Int J Clin practice.* (2022) 2022:3199758. doi: 10.1155/2022/3199758
27. Aljehani AM, Banjar SA, Alawam HS, Alowais S, Aldraibi Y, BinSaif A, et al. The relationship between menstrual cycle irregularities and COVID-19 vaccination. *Cureus.* (2023) 15:e49841. doi: 10.7759/cureus.49841
28. Muharam R, Agiananda F, Budiman YF, Harahap JS, Prabowo KA, Azyati M, et al. Menstrual cycle changes and mental health states of women hospitalized due to COVID-19. *PLoS One.* (2022) 17:e0270658. doi: 10.1371/journal.pone.0270658
29. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual symptoms after COVID-19 vaccine: A cross-sectional investigation in the MENA region. *Int J women's Health.* (2022) 14:395–404. doi: 10.2147/IJWH.S352167
30. Ata B, Vermeulen N, Mocanu E, Gianaroli L, Lundin K, Rautakallio-Hokkanen S, et al. SARS-CoV-2, fertility and assisted reproduction. *Hum Reprod update.* (2023) 29:177–96. doi: 10.1093/humupd/dmac037
31. Wei L, Sun S, Zhang J, Zhu H, Xu Y, Ma Q, et al. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). *Biochem Cell Biol = Biochimie biologie cellulaire.* (2010) 88:723–30. doi: 10.1139/O10-022
32. Ding T, Wang T, Zhang J, Cui P, Chen Z, Zhou S, et al. Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in wuhan, China: an observational study. *Front Med.* (2021) 8:635255. doi: 10.3389/fmed.2021.635255
33. Iliodromiti S, Anderson RA, Nelson SM. Technical and performance characteristics of anti-Müllerian hormone and antral follicle count as biomarkers of ovarian response. *Hum Reprod update.* (2015) 21:698–710. doi: 10.1093/humupd/dmu062
34. Madendag IC, Madendag Y, Ozdemir AT. COVID-19 disease does not cause ovarian injury in women of reproductive age: an observational before-and-after COVID-19 study. *Reprod biomedicine online.* (2022) 45:153–8. doi: 10.1016/j.rbmo.2022.03.002
35. Ghaemi M, Hantoushadeh S, Shafiee A, Gargari OK, Fathi H, Eshraghi N, et al. The effect of COVID-19 and COVID-19 vaccination on serum anti-Müllerian hormone: A systematic review and meta-analysis. *Immunity Inflammation disease.* (2024) 12:e1136. doi: 10.1002/iid3.1136
36. Qi J, Zhou Y, Hua J, Zhang L, Bian J, Liu B, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to SARS-CoV-2 infection. *Int J Environ Res Public Health.* (2021) 18(1):284. doi: 10.3390/ijerph18010284
37. Hikmet F, Méar L, Edvinsson Å, Mücke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol.* (2020) 16:e9610. doi: 10.15252/msb.20209610
38. Wu M, Ma L, Xue L, Zhu Q, Zhou S, Dai J, et al. Co-expression of the SARS-CoV-2 entry molecules ACE2 and TMPRSS2 in human ovaries: Identification of cell types and trends with age. *Genomics.* (2021) 113:3449–60. doi: 10.1016/j.ygeno.2021.08.012
39. Fan H, Ren Q, Sheng Z, Deng G, Li L. The role of the thyroid in polycystic ovary syndrome. *Front endocrinology.* (2023) 14:1242050. doi: 10.3389/fendo.2023.1242050
40. Gabersček S, Zaletel K, Schwetz V, Pieber T, Obermayer-Pietsch B, Lerchbaum E. Mechanisms in endocrinology: thyroid and polycystic ovary syndrome. *Eur J endocrinology.* (2015) 172:R9–21. doi: 10.1530/EJE-14-0295
41. Trouva A, Alvarsson M, Calissendorff J, Åsvold BO, Vanky E, Hirschberg AL. Thyroid status during pregnancy in women with polycystic ovary syndrome and the effect of metformin. *Front endocrinology.* (2022) 13:772801. doi: 10.3389/fendo.2022.772801
42. Scappaticcio L, Pitoia F, Esposito K, Piccardi A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. *Rev endocrine Metab Disord.* (2021) 22:803–15. doi: 10.1007/s11554-020-09615-z
43. Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *J endocrinological Invest.* (2020) 43:1027–31. doi: 10.1007/s40618-020-01276-8
44. Brancatella A, Viola N, Rutigliano G, Sgrò D, Santini F, Latrofa F. Subacute thyroiditis during the SARS-CoV-2 pandemic. *J Endocrine Soc.* (2021) 5:bvab130. doi: 10.1210/endo/bvab130
45. Lyons-Weiler J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. *J Trans autoimmunity.* (2020) 3:100051. doi: 10.1016/j.jtauto.2020.100051
46. Wang F, Zhang ZH, Xiao KZ, Wang ZC. Roles of hypothalamic-pituitary-adrenal axis and hypothalamus-pituitary-ovary axis in the abnormal endocrine functions in patients with polycystic ovary syndrome. *Zhongguo yi xue ke xue yuan xue bao Acta Academiae Medicinae Sinicae.* (2017) 39:699–704. doi: 10.3881/j.issn.1000-503X.2017.05.017
47. Hashim M, Athar S, Gaba WH. New onset adrenal insufficiency in a patient with COVID-19. *BMJ Case Rep.* (2021) 14:e237690. doi: 10.1136/bcr-2020-237690
48. Sheikh AB, Javaid MA, Sheikh AAE, Shekhar R. Central adrenal insufficiency and diabetes insipidus as potential endocrine manifestations of COVID-19 infection: a case report. *Pan Afr Med J.* (2021) 38:222. doi: 10.11604/pamj.2021.38.222.28243
49. Freire Santana M, Borba MGS, Baia-da-Silva DC, Val F, Alexandre MAA, Brito-Sousa JD, et al. Case report: adrenal pathology findings in severe COVID-19: an autopsy study. *Am J Trop Med hygiene.* (2020) 103:1604–7. doi: 10.4269/ajtmh.20-0787
50. Zinserling VA, Semenova NY, Markov AG, Rybalchenko OV, Wang J, Rodionov RN, et al. Inflammatory cell infiltration of adrenals in COVID-19. *Hormone Metab Res = Hormon- und Stoffwechselforschung = Hormones métabolisme.* (2020) 52:639–41. doi: 10.1055/a-1191-8094
51. Alzahrani AS, Mukhtar N, Aljomaiah A, Aljamei H, Bakhsh A, AlSudani N, et al. The impact of COVID-19 viral infection on the hypothalamic-pituitary-adrenal axis. *Endocrine practice: Off J Am Coll Endocrinol Am Assoc Clin Endocrinologists.* (2021) 27:83–9. doi: 10.1016/j.eprac.2020.10.014
52. Ekinci I, Hursitoglu M, Tunc M, Kazezoglu C, Isiksacan N, Yurt S, et al. Adrenocortical system hormones in non-critically ill COVID-19 patients. *Acta endocrinologica.* (2021) 17:83–9. doi: 10.4183/aeb.2021.83
53. Kaya MG, Alanli R, Kucukay MB, Ulukaya FB, Bakir F. PITUITARY FUNCTIONS AFTER RECOVERY FROM COVID-19. *Acta endocrinologica (Bucharest Romania; 2005).* (2023) 19:314–8. doi: 10.4183/aeb.2023.314
54. Gonen MS, De Bellis A, Durcan E, Bellastella G, Cirillo P, Scappaticcio L, et al. Assessment of neuroendocrine changes and hypothalamo-pituitary autoimmunity in patients with COVID-19. *Hormone Metab Res = Hormon- und Stoffwechselforschung = Hormones métabolisme.* (2022) 54:153–61. doi: 10.1055/a-1764-1260
55. Wheatland R. Molecular mimicry of ACTH in SARS - implications for corticosteroid treatment and prophylaxis. *Med hypotheses.* (2004) 63:855–62. doi: 10.1016/j.mehy.2004.04.009
56. Téblick A, Langouche L, Van den Berghe G. Anterior pituitary function in critical illness. *Endocrine connections.* (2019) 8:R131–r43. doi: 10.1530/EC-19-0318
57. Nicolaides NC, Charmandari E, Kino T, Chrousos GP. Stress-related and circadian secretion and target tissue actions of glucocorticoids: impact on health. *Front endocrinology.* (2017) 8:70. doi: 10.3389/fendo.2017.00070
58. McGowan M, Lim S, O'Reilly SL, Harrison CL, Enticott J, Teede H, et al. Impact of COVID-19 restriction on weight, physical activity, diet and psychological distress on people with PCOS. *Nutrients.* (2023) 15(11):2579. doi: 10.3390/nu15112579
59. Bakaloudi DR, Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Chourdakis M. Impact of the first COVID-19 lockdown on body weight: A combined systematic review and a meta-analysis. *Clin Nutr (Edinburgh Scotland).* (2022) 41:3046–54. doi: 10.1016/j.clnu.2021.04.015
60. Jenssen BP, Kelly MK, Powell M, Bouchelle Z, Mayne SL, Fiks AG. COVID-19 and changes in child obesity. *Pediatrics.* (2021) 147(5):e2021050123. doi: 10.1542/peds.2021-050123
61. Tseng YH. Adipose tissue in communication: within and without. *Nat Rev Endocrinology.* (2023) 19:70–1. doi: 10.1038/s41574-022-00789-x
62. Sacco TD, Mousovich-Neto F, Ludwig RG, Carregari VC, Dos Anjos Souza AB, Dos Passos ASC, et al. SARS-CoV-2 infects adipose tissue in a fat depot- and viral lineage-dependent manner. *Nat Commun.* (2022) 13:5722. doi: 10.1038/s41467-022-33218-8
63. Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. *Obes (Silver Spring Md).* (2020) 28:1187–90. doi: 10.1002/oby.22856
64. Al Heialy S, Hachim MY, Senok A, Gaudet M, Abou Tayoun A, Hamoudi R, et al. Regulation of angiotensin- converting enzyme 2 in obesity: implications for COVID-19. *Front Physiol.* (2020) 11:555039. doi: 10.3389/fphys.2020.555039
65. Quaranta P, Scabia G, Storti B, Dattilo A, Quintino L, Perrera P, et al. SARS-CoV-2 infection alters the phenotype and gene expression of adipocytes. *Int J Mol Sci.* (2024) 25(4):2086. doi: 10.3390/ijms25042086
66. Glueck CJ, Goldenberg N. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. *Metabolism: Clin experimental.* (2019) 92:108–20. doi: 10.1016/j.metabol.2018.11.002
67. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod update.* (2003) 9:359–72. doi: 10.1093/humupd/dmg024
68. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. *Reprod Biol endocrinology: RB&E.* (2018) 16:22. doi: 10.1186/s12958-018-0336-z

69. Littlejohn EE, Weiss RE, Deplewski D, Edidin DV, Rosenfield R. Intractable early childhood obesity as the initial sign of insulin resistant hyperinsulinism and precursor of polycystic ovary syndrome. *J Pediatr Endocrinol Metabolism: JPEM*. (2007) 20:41–51. doi: 10.1515/JPEM.2007.20.1.41
70. Christensen SB, Black MH, Smith N, Martinez MM, Jacobsen SJ, Porter AH, et al. Prevalence of polycystic ovary syndrome in adolescents. *Fertility sterility*. (2013) 100:470–7. doi: 10.1016/j.fertnstert.2013.04.001
71. Goodarzi MO, Erickson S, Port SC, Jennrich RI, Korenman SG. beta-Cell function: a key pathological determinant in polycystic ovary syndrome. *J Clin Endocrinol Metab*. (2005) 90:310–5. doi: 10.1210/jc.2004-1006
72. Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, et al. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. *J Clin Invest*. (1989) 84:205–13. doi: 10.1172/JCI114142
73. Wu L, Giris CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. *Clin endocrinology*. (2020) 93:390–3. doi: 10.1111/cen.14288
74. Šestan M, Marinović S, Kavazović I, Cekinović Đ, Wueest S, Turk Wensveen T, et al. Virus-induced interferon- γ Causes insulin resistance in skeletal muscle and derails glycemic control in obesity. *Immunity*. (2018) 49:164–77.e6. doi: 10.1016/j.immuni.2018.05.005
75. de Carvalho Vidigal F, Guedes Cocate P, Gonçalves Pereira L, de Cássia Gonçalves Alfnas R. The role of hyperglycemia in the induction of oxidative stress and inflammatory process. *Nutricion hospitalaria*. (2012) 27:1391–8. doi: 10.3305/nh.2012.27.5.5917
76. Solerte SB, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: A multicenter, case-control, retrospective, observational study. *Diabetes Care*. (2020) 43:2999–3006. doi: 10.2337/dc20-1521
77. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care*. (2020) 43:1408–15. doi: 10.2337/dc20-0723
78. Montefusco L, Ben Nasr M, D'Addio F, Loretelli C, Rossi A, Pastore I, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab*. (2021) 3:774–85. doi: 10.1038/s42255-021-00407-6
79. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the mystery surrounding post-acute sequelae of COVID-19. *Front Immunol*. (2021) 12:686029. doi: 10.3389/fimmu.2021.686029
80. Chen M, Zhu B, Chen D, Hu X, Xu X, Shen WJ, et al. COVID-19 may increase the risk of insulin resistance in adult patients without diabetes: A 6-month prospective study. *Endocrine practice: Off J Am Coll Endocrinol Am Assoc Clin Endocrinologists*. (2021) 27:834–41. doi: 10.1016/j.eprac.2021.04.004
81. Tremellen K, Pearce K. Dysbiosis of Gut Microbiota (DOGMA)—a novel theory for the development of Polycystic Ovarian Syndrome. *Med hypotheses*. (2012) 79:104–12. doi: 10.1016/j.mehy.2012.04.016
82. Zhou L, Ni Z, Cheng W, Yu J, Sun S, Zhai D, et al. Characteristic gut microbiota and predicted metabolic functions in women with PCOS. *Endocrine connections*. (2020) 9:63–73. doi: 10.1530/EC-19-0522
83. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut*. (2021) 70:698–706. doi: 10.1136/gutjnl-2020-323020
84. Camargo SM, Singer D, Makrides V, Huggel K, Pos KM, Wagner CA, et al. Tissue-specific amino acid transporter partners ACE2 and collectrin differentially interact with harnput mutations. *Gastroenterology*. (2009) 136:872–82. doi: 10.1053/j.gastro.2008.10.055
85. Perlot T, Penninger JM. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes infection*. (2013) 15:866–73. doi: 10.1016/j.micinf.2013.08.003
86. Yonker LM, Gilboa T, Ogata AF, Senussi Y, Lazarovits R, Boribong BP, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *J Clin Invest*. (2021) 131(14):e149633. doi: 10.1172/JCI149633
87. Han MS, White A, Perry RJ, Camporez JP, Hidalgo J, Shulman GI, et al. Regulation of adipose tissue inflammation by interleukin 6. *Proc Natl Acad Sci United States America*. (2020) 117:2751–60. doi: 10.1073/pnas.1920004117
88. Sbierski-Kind J, Mai K, Kath J, Jurisch A, Streitz M, Kuchenbecker L, et al. Association between subcutaneous adipose tissue inflammation, insulin resistance, and calorie restriction in obese females. *J Immunol (Baltimore Md: 1950)*. (2020) 205:45–55. doi: 10.4049/jimmunol.2000108
89. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. (2020) 17:533–5. doi: 10.1038/s41423-020-0402-2
90. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol*. (2020) 17:541–3. doi: 10.1038/s41423-020-0401-3
91. De Biasi S, Meschiarri M, Gibellini L, Bellinazzi C, Borella R, Fidanza L, et al. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nat Commun*. (2020) 11:3434. doi: 10.1038/s41467-020-17292-4
92. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth factor Rev*. (2020) 53:38–42. doi: 10.1016/j.cytogfr.2020.04.002
93. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect diseases: IJID: Off Publ Int Soc Infect Diseases*. (2020) 100:327–32. doi: 10.1016/j.ijid.2020.09.016
94. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. *Sci (New York NY)*. (2022) 375:1122–7. doi: 10.1126/science.abm8108
95. Besnier F, Bérubé B, Malo J, Gagnon C, Grégoire CA, Juneau M, et al. Cardiopulmonary rehabilitation in long-COVID-19 patients with persistent breathlessness and fatigue: the COVID-rehab study. *Int J Environ Res Public Health*. (2022) 19(7):4133. doi: 10.3390/ijerph19074133
96. Carli A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *Jama*. (2020) 324:603–5. doi: 10.1001/jama.2020.12603
97. Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, et al. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA network Open*. (2021) 4:e2036142. doi: 10.1001/jamanetworkopen.2020.36142
98. Lenarcik A, Bidzińska-Speichert B. Cardiopulmonary functional capacity and the role of exercise in improving maximal oxygen consumption in women with PCOS. *Endokrynologia Polska*. (2010) 61:207–9. doi: 10.1016/j.ecl.2009.10.010
99. Lazarus R, Sparrow D, Weiss ST. Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *Eur Respir J*. (1998) 12:641–5. doi: 10.1183/09031936.98.12030641
100. Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care*. (2004) 27:2966–70. doi: 10.2337/diacare.27.12.2966
101. Zaigham S, Nilsson PM, Wollmer P, Engström G. The temporal relationship between poor lung function and the risk of diabetes. *BMC pulmonary Med*. (2016) 16:75. doi: 10.1186/s12890-016-0227-z
102. Engström G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Internal Med*. (2003) 253:574–81. doi: 10.1046/j.1365-2796.2003.01138.x
103. Jankowich M, Elston B, Liu Q, Abbasi S, Wu WC, Blackshear C, et al. Restrictive spirometry pattern, cardiac structure and function, and incident heart failure in african americans. *Jackson Heart Study Ann Am Thorac Society*. (2018) 15:1186–96. doi: 10.1513/AnnalsATS.201803-184OC
104. Braun B, Rock PB, Zamudio S, Wolf GE, Mazzeo RS, Muza SR, et al. Women at altitude: short-term exposure to hypoxia and/or alpha(1)-adrenergic blockade reduces insulin sensitivity. *J Appl Physiol (Bethesda Md: 1985)*. (2001) 91:623–31. doi: 10.1152/jappl.2001.91.2.623
105. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet (London England)*. (1999) 353:1649–52. doi: 10.1016/s0140-6736(99)01046-6
106. Semenza GL. Oxygen-regulated transcription factors and their role in pulmonary disease. *Respir Res*. (2000) 1:159–62. doi: 10.1186/rr27
107. Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. *Gynecological endocrinology: Off J Int Soc Gynecological Endocrinology*. (2021) 37:895–7. doi: 10.1080/09513590.2021.1918080
108. Youngster M, Avraham S, Yaakov O, Landau Rabbi M, Gat I, Yerushalmi G, et al. IVF under COVID-19: treatment outcomes of fresh ART cycles. *Hum Reprod (Oxford England)*. (2022) 37:947–53. doi: 10.1093/humrep/deac043
109. Wang M, Hu J, Huang B, Yang Q, Liu S, Li Z, et al. Investigating the impact of SARS-CoV-2 infection on basic semen parameters and *in vitro* fertilization/ intracytoplasmic sperm injection outcomes: a retrospective cohort study. *Reprod Biol endocrinology: RB&E*. (2022) 20:46. doi: 10.1186/s12958-022-00918-1
110. Veiga A, Gianaroli L, Ory S, Horton M, Feinberg E, Penzias A. Assisted reproduction and COVID-19: a joint statement of ASRM, ESHRE, and IFFS. *Global Reprod Health*. (2020) 5:10.1097. doi: 10.1093/hropen/hoaa033
111. Boivin J, Harrison C, Mathur R, Burns G, Pericleous-Smith A, Gameiro S. Patient experiences of fertility clinic closure during the COVID-19 pandemic: appraisals, coping and emotions. *Hum Reprod (Oxford England)*. (2020) 35:2556–66. doi: 10.1093/humrep/deaa218
112. Esposito V, Rania E, Lico D, Pedri S, Fiorenza A, Strati MF, et al. Influence of COVID-19 pandemic on the psychological status of infertile couples. *Eur J obstetrics gynecology Reprod Biol*. (2020) 253:148–53. doi: 10.1016/j.ejogrb.2020.08.025
113. Bhattacharya S, Maheshwari A, Ratna MB, van Eekelen R, Mol BW, McLernon DJ. Prioritizing IVF treatment in the post-covid 19 era: a predictive modelling study based on UK national data. *Hum Reprod (Oxford England)*. (2021) 36:666–75. doi: 10.1093/humrep/deaa339

114. Chandi A, Jain N. State of assisted reproduction technology in the coronavirus disease 2019 era and consequences on human reproductive system. *Biol reproduction*. (2021) 105:808–21. doi: 10.1093/biolre/iobab122
115. Lam JS, Shere M, Motamed N, Vilos GA, Abu-Rafea B, Vilos AG. Impact of the COVID-19 pandemic on access to fertility care: A retrospective study at a university-affiliated fertility practice. *J obstetrics gynaecology Canada: JOGC = J d'obstetrique gynecologie du Canada: JOGC*. (2022) 44:378–82. doi: 10.1016/j.jogc.2021.10.017
116. Gromski PS, Smith A, Lawlor DA, Sharara FI, Nelson SM. 2008 financial crisis versus 2020 economic fallout: how COVID-19 might influence fertility treatment and live births. *Reprod biomedicine Online*. (2021) 42:1087–96. doi: 10.1016/j.rbmo.2021.03.017
117. Kyrou I, Karteris E, Robbins T, Chatha K, Drenos F, Randeva HS. Polycystic ovary syndrome (PCOS) and COVID-19: an overlooked female patient population at potentially higher risk during the COVID-19 pandemic. *BMC Med*. (2020) 18:220. doi: 10.1186/s12916-020-01697-5
118. Li W, Yu N, Kang Q, Zeng W, Deng D, Chen S, et al. Clinical manifestations and maternal and perinatal outcomes with COVID-19. *Am J Reprod Immunol (New York NY: 1989)*. (2020) 84:e13340. doi: 10.1111/aji.13340
119. DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization - United States, march 2020-september 2021. *MMWR Morbidity mortality weekly Rep*. (2021) 70:1640–5. doi: 10.15585/mmwr.mm7047e1
120. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta obstetrica gynecologica Scandinavica*. (2020) 99:823–9. doi: 10.1111/aogs.13867
121. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. (2020) 370:m3320. doi: 10.1136/bmj.m3320
122. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. *Am J obstetrics gynecology*. (2021) 224:35–53.e3. doi: 10.1016/j.ajog.2020.07.049
123. Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. *Am J obstetrics gynecology MFM*. (2020) 2:100133. doi: 10.1016/j.ajogmf.2020.100133
124. Ashary N, Bhide A, Chakraborty P, Colaco S, Mishra A, Chhabria K, et al. Single-cell RNA-seq identifies cell subsets in human placenta that highly expresses factors driving pathogenesis of SARS-CoV-2. *Front Cell Dev Biol*. (2020) 8:783. doi: 10.3389/fcell.2020.00783
125. Egloff C, Vauloup-Fellous C, Picone O, Mandelbrot L, Roques P. Evidence and possible mechanisms of rare maternal-fetal transmission of SARS-CoV-2. *J Clin virology: Off Publ Pan Am Soc Clin Virology*. (2020) 128:104447. doi: 10.1016/j.jcv.2020.104447
126. Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, et al. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. *Rev Med virology*. (2021) 31:1–16. doi: 10.1002/rmv.2208
127. Kumar J, Meena J, Yadav A, Kumar P. SARS-CoV-2 detection in human milk: a systematic review. *J maternal-fetal neonatal medicine: Off J Eur Assoc Perinatal Medicine Fed Asia Oceania Perinatal Societies Int Soc Perinatal Obstet*. (2022) 35:5456–63. doi: 10.1080/14767058.2021.1882984
128. Norman M, Navé L, Söderling J, Ahlberg M, Hervius Askling H, Aronsson B, et al. Association of maternal SARS-CoV-2 infection in pregnancy with neonatal outcomes. *Jama*. (2021) 325:2076–86. doi: 10.1001/jama.2021.5775
129. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *J Clin Endocrinol Metab*. (2023) 108:2447–69. doi: 10.1210/clinem/dgad463
130. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J travel Med*. (2020) 27(2):taaa020. doi: 10.1093/jtm/taaa020
131. Khan MA, Moverley Smith JE. Covibesity,” a new pandemic. *Obes Med*. (2020) 19:100282. doi: 10.1016/j.obmed.2020.100282
132. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*. (2021) 76:399–401. doi: 10.1136/thoraxjnl-2020-216086
133. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-covid-19 symptom burden: what is long-COVID and how should we manage it? *Lung*. (2021) 199:113–9. doi: 10.1183/13993003.congress-2021.OA4189
134. Eyupoglu ND, Aksun S, Ozturk M, Yildiz BO. Impact of social isolation during COVID-19 pandemic on health behaviors and weight management in women with polycystic ovary syndrome. *Eating weight disorders: EWD*. (2022) 27:2407–13. doi: 10.1007/s40519-022-01369-8
135. Yang Y, Deng H, Li T, Xia M, Liu C, Bu XQ, et al. The mental health of Chinese women with polycystic ovary syndrome is related to sleep disorders, not disease status. *J Affect Disord*. (2021) 282:51–7. doi: 10.1016/j.jad.2020.12.084
136. Minkel JD, Banks S, Htaik O, Moreta MC, Jones CW, McGlinchey EL, et al. Sleep deprivation and stressors: evidence for elevated negative affect in response to mild stressors when sleep deprived. *Emotion*. (2012) 12:1015–20. doi: 10.1037/a0026871
137. Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab*. (2004) 89:2119–26. doi: 10.1210/jc.2003-031562
138. Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocrine Dev*. (2010) 17:11–21. doi: 10.1159/000262524
139. Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. *Ann New York Acad Sci*. (2008) 1129:287–304. doi: 10.1196/annals.1417.033
140. Van Cauter E, Holmback U, Knutson K, Leproult R, Miller A, Nedeltcheva A, et al. Impact of sleep and sleep loss on neuroendocrine and metabolic function. *Hormone Res*. (2007) 67 Suppl 1:2–9. doi: 10.1159/000097543
141. Mizgier M, Jarzabek-Bielecka G, Opydo-Szymaczek J, Wendland N, Więckowska B, Kędzia W. Risk factors of overweight and obesity related to diet and disordered eating attitudes in adolescent girls with clinical features of polycystic ovary syndrome. *J Clin Med*. (2020) 9(9):3041. doi: 10.3390/jcm9093041
142. Barrea L, Arnone A, Annunziata G, Muscogiuri G, Laudisio D, Salzano C, et al. Adherence to the mediterranean diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). *Nutrients*. (2019) 11(10):2278. doi: 10.3390/nul1102278
143. Parker J, O'Brien C, Gersh FL. Developmental origins and transgenerational inheritance of polycystic ovary syndrome. *Aust New Z J obstetrics gynaecology*. (2021) 61:922–6. doi: 10.1111/ajo.13420
144. Maestre A, Sospedra I, Martínez-Sanz JM, Gutierrez-Hervas A, Fernández-Saez J, Hurtado-Sánchez JA, et al. Assessment of spanish food consumption patterns during COVID-19 home confinement. *Nutrients*. (2021) 13(11):4122. doi: 10.3390/nul13114122
145. Gibson EL. Emotional influences on food choice: sensory, physiological and psychological pathways. *Physiol behavior*. (2006) 89:53–61. doi: 10.1016/j.physbeh.2006.01.024
146. Rodríguez-Martín BC, Meule A. Food craving: new contributions on its assessment, moderators, and consequences. *Front Psychol*. (2015) 6:21. doi: 10.3389/fpsyg.2015.00021
147. Rauber F, da Costa Louzada ML, Steele EM, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008–2014). *Nutrients*. (2018) 10(5):587. doi: 10.3390/nul10050587
148. Ma Y, Ratnasabapathy R, Gardiner J. Carbohydrate craving: not everything is sweet. *Curr Opin Clin Nutr Metab Care*. (2017) 20:261–5. doi: 10.1097/MCO.0000000000000374
149. Silva Meneguelli T, Viana Hinkelmann J, Hermsdorff HHM, Zulet M, Martínez JA, Bressan J. Food consumption by degree of processing and cardiometabolic risk: a systematic review. *Int J Food Sci Nutr*. (2020) 71:678–92. doi: 10.1080/09637486.2020.1725961
150. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Commentary: obesity: the “Achilles heel” for COVID-19? *Metabolism: Clin Exp*. (2020) 108:154251. doi: 10.1016/j.metabol.2020.154251
151. Lee I, Cooney LG, Saini S, Smith ME, Sammel MD, Allison KC, et al. Increased risk of disordered eating in polycystic ovary syndrome. *Fertility sterility*. (2017) 107:796–802. doi: 10.1016/j.fertnstert.2016.12.014
152. Ma R, Zou Y, Wang W, Zheng Q, Feng Y, Dong H, et al. Obesity management in polycystic ovary syndrome: disparity in knowledge between obstetrician-gynecologists and reproductive endocrinologists in China. *BMC endocrine Disord*. (2021) 21:182. doi: 10.1186/s12902-021-00848-w
153. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod (Oxford England)*. (2018) 33:1602–18. doi: 10.1093/humrep/dey256
154. Gibson-Helm M, Dokras A, Karro H, Piltonen T, Teede HJ. Knowledge and practices regarding polycystic ovary syndrome among physicians in europe, north america, and internationally: an online questionnaire-based study. *Semin Reprod Med*. (2018) 36:19–27. doi: 10.1055/s-0038-1667155
155. Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. *Fertility sterility*. (2017) 107:1380–6.e1. doi: 10.1016/j.fertnstert.2017.04.011
156. Tomlinson J, Pinkney J, Adams L, Stenhouse E, Bendall A, Corrigan O, et al. The diagnosis and lived experience of polycystic ovary syndrome: A qualitative study. *J advanced nursing*. (2017) 73:2318–26. doi: 10.1111/jan.13300
157. Jeong Y, Crowell T, Devon-Sand A, Sakata T, Sattler A, Shah S, et al. Building pandemic-resilient primary care systems: lessons learned from COVID-19. *J Med Internet Res*. (2024) 26:e47667. doi: 10.2196/47667
158. Williams S, Tsiligianni I. COVID-19 poses novel challenges for global primary care. *NPJ primary Care Respir Med*. (2020) 30:30. doi: 10.1038/s41533-020-0187-x
159. Lee IT, Sansone S, Irfan M, Copp T, Beidas R, Dokras A. Implementation of international guidelines for polycystic ovary syndrome: barriers and facilitators among

gynecologists and primary care providers. *FeS Rep.* (2022) 3:94–101. doi: 10.1016/j.xfre.2022.01.005

160. Hillman SC, Bryce C, Caleyachetty R, Dale J. Women's experiences of diagnosis and management of polycystic ovary syndrome: a mixed-methods study in general practice. *Br J Gen practice: J R Coll Gen Practitioners.* (2020) 70:e322–e9. doi: 10.3399/bjgp20X708881

161. Moreno C, Wykes T, Galderisi S, Nordentoft M, Crossley N, Jones N, et al. How mental health care should change as a consequence of the COVID-19 pandemic. *Lancet Psychiatry.* (2020) 7:813–24. doi: 10.1016/S2215-0366(20)30307-2

162. Sydora BC, Wilke MS, McPherson M, Chambers S, Ghosh M, Vine DF. Challenges in diagnosis and health care in polycystic ovary syndrome in Canada: a patient view to improve health care. *BMC women's Health.* (2023) 23:569. doi: 10.1186/s12905-023-02732-2

163. Kite C, Atkinson L, McGregor G, Clark CCT, Brown JE, Kyrou I, et al. Sleep disruption and depression, stress and anxiety levels in women with polycystic ovary syndrome (PCOS) during the lockdown measures for COVID-19 in the UK. *Front Global women's Health.* (2021) 2:649104. doi: 10.3389/fgwh.2021.649104

164. Atkinson L, Kite C, McGregor G, James T, Clark CCT, Randeve HS, et al. Uncertainty, anxiety and isolation: experiencing the COVID-19 pandemic and lockdown as a woman with polycystic ovary syndrome (PCOS). *J personalized Med.* (2021) 11(10):952. doi: 10.3390/jpm11100952

165. Giannopoulou I, Tsobanoglou GO. COVID-19 pandemic: challenges and opportunities for the Greek health care system. *Irish J psychol Med.* (2020) 37:226–30. doi: 10.1017/ipm.2020.35

166. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of covid-19. *New Engl J Med.* (2020) 382:2049–55. doi: 10.1056/NEJMs2005114

167. Craighead CG, Collart C, Frankel R, Rose S, Misra-Hebert AD, Tucker Edmonds B, et al. Impact of telehealth on the delivery of prenatal care during the COVID-19 pandemic: mixed methods study of the barriers and opportunities to improve health care communication in discussions about pregnancy and prenatal genetic testing. *JMIR formative Res.* (2022) 6:e38821. doi: 10.2196/38821

168. Dulaimy K, Pham RH, Farag A. The impact of COVID on health systems: the workforce and telemedicine perspective. *Semin ultrasound CT MR.* (2024) 45:314–317. doi: 10.1053/j.sult.2024.03.002

169. Dwomoh D, Yeboah I, Ndejo R, Kabwama SN, Aheto JM, Liu A, et al. COVID-19 outbreak control strategies and their impact on the provision of essential health services in Ghana: An exploratory-sequential study. *PloS One.* (2023) 18:e0279528. doi: 10.1371/journal.pone.0279528

170. Amu H, Dowou RK, Boateng LA, Tarkang EE. Implications of COVID-19 for the management of chronic non-communicable diseases in sub-Saharan Africa: application of the chronic care model. *Pan Afr Med J.* (2020) 35:94. doi: 10.11604/pamj.supp.2020.35.24047

171. Aborode AT, Fajemisin EA, Aiyenuro EA, Alakitan MT, Ariwoola MO, Imisioluwa JO, et al. Neglected tropical diseases (NTDs) and COVID-19 pandemic in africa: special focus on control strategies. *Combinatorial Chem High throughput screening.* (2022) 25:2387–90. doi: 10.2174/1386207325666220427123349

172. Beyene DT, Lemma KT, Sultan SA, Sinbiro IA. Perceived impact of COVID-19 on routine care of patients with chronic non-communicable diseases: a cross-sectional study. *Pan Afr Med J.* (2022) 43:212. doi: 10.11604/pamj.2022.43.212.32769

173. Owopetu O, Fasehun LK, Abakporo U. COVID-19: implications for NCDs and the continuity of care in Sub-Saharan Africa. *Global Health promotion.* (2021) 28:83–6. doi: 10.1177/1757975921992693

174. Wright A, Salazar A, Mirica M, Volk LA, Schiff GD. The invisible epidemic: neglected chronic disease management during COVID-19. *J Gen Internal Med.* (2020) 35:2816–7. doi: 10.1007/s11606-020-06025-4

175. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ, Moran LJ. Depression, anxiety and perceived stress in women with and without PCOS: a community-based study. *psychol Med.* (2019) 49:1510–20. doi: 10.1017/S0033291718002076

176. Tippet A. Life on pause: An analysis of UK fertility patients' coping mechanisms after the cancellation of fertility treatment due to COVID-19. *J Health Psychol.* (2022) 27:1583–600. doi: 10.1177/1359105321999711

177. Ramezani M, Takian A, Bakhtiari A, Rabiee HR, Ghazanfari S, Sazgarnejad S. Research agenda for using artificial intelligence in health governance: interpretive scoping review and framework. *BioData mining.* (2023) 16:31. doi: 10.1186/s13040-023-00346-w

178. Jonnagaddala J, Godinho MA, Liaw ST. From telehealth to virtual primary care in Australia? A Rapid scoping review. *Int J Med informatics.* (2021) 151:104470. doi: 10.1016/j.ijmedinf.2021.104470

179. Byrne A, Barber R, Lim CH. Impact of the COVID-19 pandemic – a mental health service perspective. *Prog Neurol Psychiatry.* (2021) 25:27–33b. doi: 10.1002/pnp.708

180. Walker A, Alkasaby MA, Baingana F, Bosu WK, Abdulaziz M, Westerveld R, et al. Challenges and opportunities for mental health and psychosocial support in the COVID-19 response in africa: A mixed-methods study. *Int J Environ Res Public Health.* (2022) 19(15):9313. doi: 10.3390/ijerph19159313

181. Shuib S, Arif N, Nahidi M, Rumiyya K, Swed S, Yusha'u Armiya'u A. Nagorno-Karabakh conflict: Mental health repercussions and challenges in Azerbaijan. *Asian J Psychiatry.* (2022) 73:103095. doi: 10.1016/j.ajp.2022.103095

182. Charlson F, van Ommeren M, Flaxman A, Cornett J, Whiteford H, Saxena S. New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. *Lancet (London England).* (2019) 394:240–8. doi: 10.1016/S0140-6736(19)30934-1

183. Burki T. The indirect impact of COVID-19 on women. *Lancet Infect diseases.* (2020) 20:904–5. doi: 10.1016/S1473-3099(20)30568-5

184. Aksunger N, Vernot C, Littman R, Voors M, Meriggi NF, Abajobir A, et al. COVID-19 and mental health in 8 low- and middle-income countries: A prospective cohort study. *PloS Med.* (2023) 20:e1004081. doi: 10.1371/journal.pmed.1004081

185. Moitra M, Owens S, Hailemariam M, Wilson KS, Mensa-Kwao A, Gonesse G, et al. Global mental health: where we are and where we are going. *Curr Psychiatry Rep.* (2023) 25:301–11. doi: 10.1007/s11920-023-01426-8

186. Zhang Y, Lange KW. Coronavirus disease 2019 (COVID-19) and global mental health. *Global Health J (Amsterdam Netherlands).* (2021) 5:31–6. doi: 10.1016/j.jglhj.2021.02.004

187. Semo BW, Frissa SM. The mental health impact of the COVID-19 pandemic: implications for sub-saharan africa. *Psychol Res Behav management.* (2020) 13:713–20. doi: 10.2147/PRBM.S264286

188. Ruzzenenti G, Maloberti A, Giani V, Biolcati M, Leidi F, Monticelli M, et al. Covid and cardiovascular diseases: direct and indirect damages and future perspective. *High Blood Pressure Cardiovasc prevention: Off J Ital Soc Hypertension.* (2021) 28:439–45. doi: 10.1007/s40292-021-00464-8

189. Hemingway JF, Singh N, Starnes BW. Emerging practice patterns in vascular surgery during the COVID-19 pandemic. *J Vasc surgery.* (2020) 72:396–402. doi: 10.1016/j.jvs.2020.04.492

190. Blue R, Yang AI, Zhou C, De Ravin E, Teng CW, Arguelles GR, et al. Telemedicine in the era of coronavirus disease 2019 (COVID-19): A neurosurgical perspective. *World neurosurgery.* (2020) 139:549–57. doi: 10.1016/j.wneu.2020.05.066

191. Boyle JA, Xu R, Gilbert E, Kuczynska-Burggraf M, Tan B, Teede H, et al. Ask PCOS: identifying need to inform evidence-based app development for polycystic ovary syndrome. *Semin Reprod Med.* (2018) 36:59–65. doi: 10.1055/s-0038-1667187

192. Wang L, Liu Y, Tan H, Huang S. Transtheoretical model-based mobile health application for PCOS. *Reprod Health.* (2022) 19:117. doi: 10.1186/s12978-022-01422-w

193. Narang K, Enninga EAL, Gunaratne M, Ibiroba ER, Trad ATA, Elrefaei A, et al. SARS-coV-2 infection and COVID-19 during pregnancy: A multidisciplinary review. *Mayo Clinic Proc.* (2020) 95:1750–65. doi: 10.1016/j.mayocp.2020.05.011

194. Pountoukidou A, Potamiti-Komi M, Sarri V, Papapanou M, Routsis E, Tsatsiani AM, et al. Management and prevention of COVID-19 in pregnancy and pandemic obstetric care: A review of current practices. *Healthcare (Basel Switzerland).* (2021) 9(4):467. doi: 10.3390/healthcare9040467

195. Ismayilova M, Yaya S. What can be done to improve polycystic ovary syndrome (PCOS) healthcare? Insights from semi-structured interviews with women in Canada. *BMC women's Health.* (2022) 22:157. doi: 10.1186/s12905-022-01734-w

196. Dokras A, Stener-Victorin E, Yildiz BO, Li R, Ottey S, Shah D, et al. Androgen Excess- Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome. *Fertility therapy.* (2018) 109:888–99. doi: 10.1016/j.fertnstert.2018.01.038

197. Helvacı N, Karabulut E, Demir AU, Yildiz BO. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. *Endocrine connections.* (2017) 6:437–45. doi: 10.1530/EC-17-0129

198. Lin AW, Bergomi EJ, Dollahite JS, Sobal J, Hoeger KM, Lujan ME. Trust in physicians and medical experience beliefs differ between women with and without polycystic ovary syndrome. *J Endocrine Society.* (2018) 2:1001–9. doi: 10.1210/js.2018-00181

199. Soucie K, Samardzic T, Schramer K, Ly C, Katzman R. The diagnostic experiences of women with polycystic ovary syndrome (PCOS) in ontario, Canada. *Qual Health Res.* (2021) 31:523–34. doi: 10.1177/1049732320971235

200. Park S, Lim SY, Kim JY, Park H, Lim JS, Bae S, et al. Clinical and virological characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-coV-2) B.1.617.2 (Delta) variant: A prospective cohort study. *Clin Infect diseases: an Off Publ Infect Dis Soc America.* (2022) 75:e27–34. doi: 10.1093/cid/ciac239

201. Hoang VT, Colson P, Levasseur A, Delerice J, Lagier JC, Parola P, et al. Clinical outcomes in patients infected with different SARS-CoV-2 variants at one hospital during three phases of the COVID-19 epidemic in Marseille, France. *Infection Genet evolution: J Mol Epidemiol evolutionary Genet Infect diseases.* (2021) 95:105092. doi: 10.1016/j.meegid.2021.105092

202. Fernández-de-Las-Peñas C, Cancela-Cilleruelo I, Rodríguez-Jiménez J, Gómez-Mayordomo V, Pellicer-Valero OJ, Martín-Guerrero JD, et al. Associated-onset symptoms and post-covid-19 symptoms in hospitalized COVID-19 survivors infected with wuhan, alpha or delta SARS-coV-2 variant. *Pathog (Basel Switzerland).* (2022) 11(7):725. doi: 10.3390/pathogens11070725

203. Menges D, Ballouz T, Anagnostopoulos A, Aschmann HE, Domenghino A, Fehr JS, et al. Burden of post-covid-19 syndrome and implications for healthcare service planning: A population-based cohort study. *PloS One.* (2021) 16:e0254523. doi: 10.1371/journal.pone.0254523

204. Kannan SR, Spratt AN, Cohen AR, Naqvi SH, Chand HS, Quinn TP, et al. Evolutionary analysis of the Delta and Delta Plus variants of the SARS-CoV-2 viruses. *J autoimmunity.* (2021) 124:102715. doi: 10.1016/j.jaut.2021.102715

205. Chen J, Wang R, Wang M, Wei GW. Mutations strengthened SARS-CoV-2 infectivity. *J Mol Biol.* (2020) 432:5212–26. doi: 10.1016/j.jmb.2020.07.009
206. Ningombam SS, Kumar R, Tanwar P. Mutant strains of SARS-CoV-2 are more prone to infect obese patient: a review. *Wiener klinische Wochenschrift.* (2021) 133:383–92. doi: 10.1007/s00508-021-01819-w
207. Alefishat E, Jelinek HF, Mousa M, Tay GK, Alsafar HS. Immune response to SARS-CoV-2 variants: A focus on severity, susceptibility, and pre-existing immunity. *J infection Public Health.* (2022) 15:277–88. doi: 10.1016/j.jiph.2022.01.007
208. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol.* (2019) 17:181–92. doi: 10.1038/s41579-018-0118-9
209. Mongioi LM, Barbagallo F, Condorelli RA, Cannarella R, Aversa A, La Vignera S, et al. Possible long-term endocrine-metabolic complications in COVID-19: lesson from the SARS model. *Endocrine.* (2020) 68:467–70. doi: 10.1007/s12020-020-02349-7
210. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertility sterility.* (2018) 110:364–79. doi: 10.1016/j.fertnstert.2018.05.004
211. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* (2020) 20:363–74. doi: 10.1038/s41577-020-0311-8
212. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med.* (2021) 27:601–15. doi: 10.1038/s41591-021-01283-z
213. Wu Q. Understanding the burden of post-covid-19 condition. *BMJ (Clinical Res ed).* (2023) 381:932. doi: 10.1136/bmj.p932
214. Teoh WS, Ramu D, Indran IR, Chua MWJ, Thu WPP, Yong EL. Diagnosis and management of polycystic ovary syndrome: Perspectives of clinicians in Singapore. *Ann Acad Medicine Singapore.* (2022) 51:204–12. doi: 10.47102/annals-acadmedsg.



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Dana Manuela Savulescu,
Science and Medical Writer, Canada
Avraham Ishay,
Technion Israel Institute of Technology, Israel

*CORRESPONDENCE

Douglas D. Fraser
✉ douglas.fraser@lhsc.on.ca
Victor K. M. Han
✉ victor.han@lhsc.on.ca

RECEIVED 04 July 2024

ACCEPTED 01 October 2024

PUBLISHED 22 October 2024

CITATION

Iosef C, Matusa AM, Han VKM and Fraser DD
(2024) Endocrine dysregulation in COVID-19:
molecular mechanisms and insights.
Front. Endocrinol. 15:1459724.
doi: 10.3389/fendo.2024.1459724

COPYRIGHT

© 2024 Iosef, Matusa, Han and Fraser. This is
an open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

Endocrine dysregulation in COVID-19: molecular mechanisms and insights

Cristiana Iosef^{1,2,3}, Andrei M. Matusa¹, Victor K. M. Han^{1,2,3*}
and Douglas D. Fraser^{1,2,3*}

¹Children's Health Research Institute, London, ON, Canada, ²Lawson Health Research Institute, London, ON, Canada, ³Department of Pediatrics, Western University, London, ON, Canada

This review describes the impact of COVID-19 on the endocrine system, focusing on cortisol signaling and growth factor-induced endocrine resistance. As expected, SARS-CoV-2 infection induces systemic inflammation, resulting in stimulation of the adrenal glands leading to elevated cortisol levels with normal adrenocorticotrophic hormone (ACTH) levels. The cytokine storm could also stimulate cortisol production. However, in some instances, cortisol levels rise independently of ACTH due to a phenomenon known as “pseudo-Cushing's syndrome,” where adrenal glands become less responsive to ACTH. Plasma proteomic analyses showed that this pattern was variably observed among COVID-19 patients, potentially involving calcium dysregulation and GNAS-regulated activities, ultimately impacting the regulation of microvascular permeability. COVID-19 also exhibited a syndrome resembling endocrine resistance, governed by receptor tyrosine kinase signaling pathways. Mild cases displayed elevated activity of EGFR and MMP9, along with increased expression of survival factors like Bax and Bcl2. In contrast, more severe cases involved IGFR-I and enhanced NOTCH signaling, with altered expression of Bcl2, AKT1, and MAPK8. In summary, these findings describe the complex interplay between COVID-19 and endocrine pathology, particularly endocrine resistance. These insights suggest potential endocrine targets for therapeutic interventions to improve short- and long-term outcomes for COVID-19 patients.

KEYWORDS

endocrine, COVID-19, cortisol, adrenal glands, disease management

Endocrine profiles in COVID-19

To date, over 400,000 scientific reports on COVID-19 have been published worldwide and indexed in PubMed, with only a small percentage (~0.5%) addressing the impact of SARS-CoV-2 infection on the endocrine system. Severe COVID-19 is typically characterized by significant respiratory distress, low blood oxygen levels, the need for ventilation, and/or multi-organ dysfunction. Notably, obesity and diabetes have been

identified as risk factors for severe infection since the early stages of the pandemic and have been extensively studied (1–4). Furthermore, it is increasingly acknowledged that patients with severe COVID-19 may experience adverse endocrine outcomes, including altered glucose metabolism, thyroid dysfunction, and adrenal insufficiency (1). This short review aims to outline the complex interactions between COVID-19 and the endocrine system disorders by synthesizing the current scientific knowledge obtained by targeted plasma proteomics and envisioning future research considerations. It is important to note that among the plethora of COVID-19 publications, only 0.08% of the cases refer to plasma proteomic profiles from different viewpoints, all excluding the endocrine complications. Our studies characterized the plasma proteomic profiles of patients with mild and severe COVID-19 by Olink targeted proteomics technologies exploring 3,072 proteins simultaneously (5, 6). We observed and predicted three categories of endocrine effects associated with the adrenocortical system: (i) calcium dysregulation that may lead to hormonal hypersecretion; (ii) novel actions of the guanine nucleotide binding protein (GNAS); and (iii) fluctuations in circulating growth factors.

SARS-CoV-2 has been detected in endocrine tissues (7), and the inflammatory processes that develop post-infection could directly or indirectly affect the endocrine tissues and their functions. Such observations have been made globally (8), with therapeutic strategies currently being developed to address the consequences (9). COVID-19 has been shown to affect various components of the endocrine system; recently, the hypothalamic-pituitary-adrenal (HPA) axis has gained interest along with the renin-angiotensin-aldosterone system (RAAS), and the thyroid system (1–4, 10). Disturbance of the RAAS due to viral infection can affect aldosterone and renin levels, leading to electrolyte disturbances and hypertension (11–13). Similarly, SARS-CoV-2 infection may lead to dysregulation of the HPA axis and alterations in cortisol levels. Some patients with severe COVID-19 may exhibit adrenal insufficiency or adrenal crisis, while others may have elevated cortisol levels due to the stress response and inflammation (1, 14, 15). Interestingly, the angiotensin-converting enzyme 2 (ACE2) receptor, which mediates SARS-CoV-2 viral entry into cells, is expressed in various tissues, including the adrenal glands and the pancreas, and has been implicated in the disturbance of the endocrine homeostasis. Additionally, SARS-CoV-2 infection can alter thyroid function, reflected by changes in the thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels (16, 17). Some COVID-19 patients have also reported thyroid dysfunction, such as subacute thyroiditis or non-thyroidal illness syndrome (also known as ‘euthyroid sick syndrome’). Lastly, COVID-19 may also impact sex hormone levels, perhaps through changes in the functionality of the vascular supply to the primary sex organs (11, 18). In men, low testosterone levels have been linked to a more severe course of COVID-19, while in women, higher testosterone levels are associated with a stronger immune response (19).

COVID-19 impacts the insulin system by targeting, in part, the insulin-like growth factors (IGFs), as they utilize the same class of receptor tyrosine kinases (RTKs). In certain conditions, the RTKs can be shared by IGFs and insulin systems, and vice-versa. With regards to the insulin system, hyperglycemia, insulin resistance and new-onset diabetes are observed in some patients, particularly those who suffered

severe COVID-19 (20–27). The exact mechanisms underlying these metabolic changes are not fully understood but may involve systemic inflammation, a stress response and the direct effects of the virus on the pancreatic beta cells (27, 28). COVID-19 may also affect the growth hormone/insulin-like growth factor (GH-IGF-1) axis and the gonadotropin-releasing hormone (GnRH) axis. Although we recently showed a comprehensive profile of the growth factors and their binding proteins based on the Olink plasma proteomics (5, 6), the changes in the IGFs system, the magnitude, and the significance of these alterations in COVID-19 patients require further investigation, especially with regards to the possible competition between IGF and insulin signaling mentioned above (20–22). The endocrine profile in COVID-19 is complex and can vary depending on factors such as the severity of illness, pre-existing hormonal disorders and individual patient characteristics (18).

When investigating the endocrine status of current and recovered COVID-19 patients, reports suggest that some individuals may exhibit features resembling Cushing’s syndrome (29–31). As presented in Figure 1, one of the main causes of Cushing’s-like syndrome could be the use of exogenous glucocorticoids as a primary treatment for severe COVID-19. Patients with severe COVID-19 may receive glucocorticoids, such as Dexamethasone, to counteract systemic inflammation and the cytokine storm. In this context, treatment with glucocorticoids could lead to Cushing’s syndrome-like features, including hypertension, glucose intolerance, and muscle weakness (32–36). Shacham and Ishay (36) examined immune activation resulting from chronic endogenous glucocorticoid excess in Cushing’s syndrome and explored how coronavirus infection might improve outcomes for COVID-19 patients treated with glucocorticoids. They concluded that a comprehensive understanding of the molecular and cellular mechanisms associated with both endogenous and exogenous glucocorticoids is crucial. This includes factors such as the timing of administration, dosage, duration of treatment, and specific formulations of these medications. While the exact mechanisms underlying these manifestations in COVID-19 are not yet known, pathology may vary, underscoring the potential for SARS-CoV-2 to affect adrenal function and cortisol metabolism. It is important to note that the Cushing’s syndrome-like manifestations observed in some COVID-19 patients may be transient and reversible, particularly in cases where they are associated with exogenous glucocorticoid administration or acute stress response (31–39). As glucocorticoid therapy is reduced with clinical improvement, these manifestations may improve or resolve. Some of the COVID-19 patients may still experience endogenous hypercortisolism as a result of viral infection, and thus the dysregulated cortisol production may persist. Again, this dysregulation can occur due to various factors, such as the stress-induced activation of the HPA axis, cytokine-mediated stimulation of adrenal cortisol synthesis, or direct effects of the virus on adrenal glands (31, 32). HPA axis can also be affected by systemic ionic dysbalance (39). Electrolyte disorders, such as potassium abnormalities, have been frequently reported as clinical manifestations of COVID-19. SARS-CoV-2 could affect potassium equilibrium via altered epithelial sodium channels (ENaC) activity (39). The incidence of hyperkalemia is due to the key role of furin which is hijacked by the virus, thus the decreased activity of ENaC would be expected, which causes retention of potassium ions and

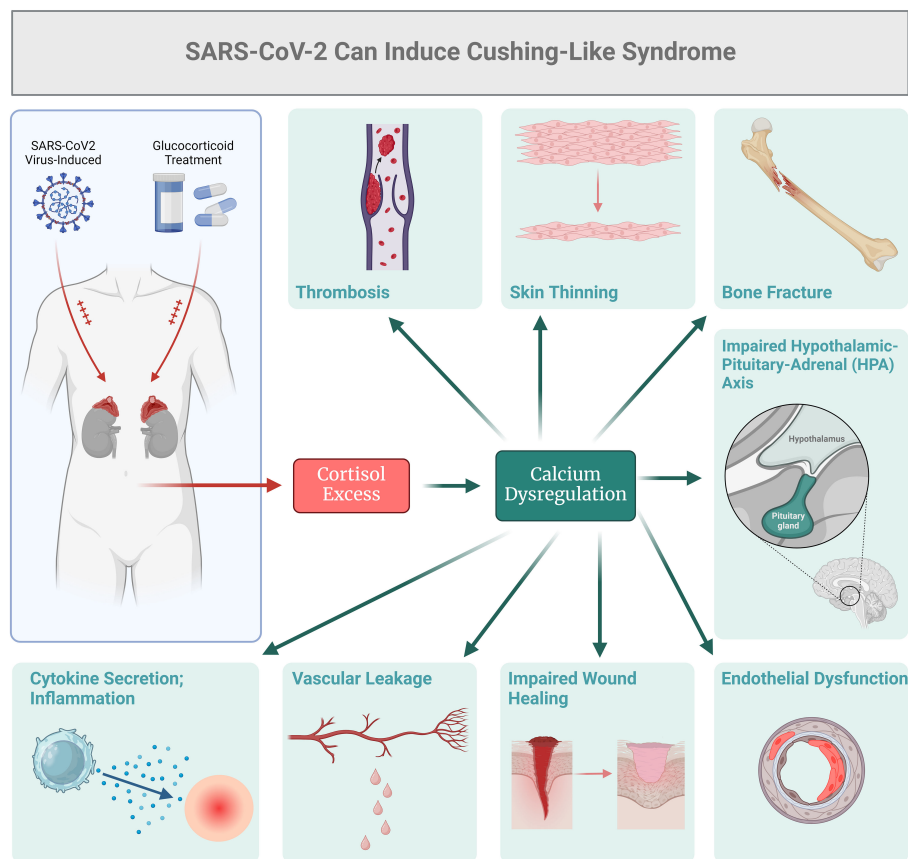


FIGURE 1
SARS-Cov2 can induce cortisol excess and Cushing's-like syndrome.

hyperkalemia (39). On the other hand, the envelope (E) protein of the SARS-CoV-2 virus forms cation-conducting channels in the endoplasmic reticulum Golgi intermediate compartment of infected cells (40). In this context, the calcium channel activity of E protein is associated with the inflammatory responses of COVID-19 (40).

Dysregulated calcium signaling pathway (KEGG: hsa04020) was notably significant across all COVID-19 datasets that we have analyzed using enrichment algorithms with Bonferroni correction (3–6). The three receptors involved in calcium signaling were: i) G Protein-Coupled Receptor (GPCR), which acts through Gs Alpha Subunit (GNAS) and affects parathyroid hormone receptor (PTHr) signaling, ii) Growth factors Receptor Tyrosine Kinase (RTK), which operates through Phospholipase C Gamma (PLC γ), Inositol 1,4,5-Trisphosphate Receptor (IP3R), and phosphatidylinositol (PI3), and iii) Voltage-Gated Calcium Channel (CaV1), which functions through Calmodulin and its associated kinases. These signaling pathways impact calcium homeostasis, cell proliferation, metabolism, tight junctions, and cell movement. One key mechanism that emerges from all our studies, and is relevant to endocrine function, involves the GNAS protein. Its role in cyclic adenosine monophosphate (cAMP) signaling is crucial for the regulation of calcium levels in the body in association with PTH.

Plasma proteomics associated with SARS-CoV-2 infection may reflect an altered endocrine activity

In the past four years, our group has performed extensive plasma-targeted proteomics studies using the Olink technology on COVID-19 patients (3–6). The data suggests that, in addition to cortisol, growth factors, and other possible endocrinopathies, COVID-19 could potentially alter calcium homeostasis and the novel endocrine-related-proteins such as GNAS, which can potentially lead to further disruptions in calcium homeostasis and dysregulation of vascular permeability. All of this could be related to endocrine resistance due to SARS-CoV-2 induced complex pathology.

The GNAS gene, otherwise known for being involved in clinical phenotypes including pseudo-hypoparathyroidism (PHP) and pseudo-pseudo-hypoparathyroidism (PPHP), helps stimulate the activity of adenylate cyclase that controls the production of several hormones and regulates the activity of endocrine glands such as the thyroid, pituitary gland, ovaries and testes (gonads), and adrenal glands (41–44). GNAS-controlled activities that may be related to endocrine responses may affect, per se, hormone receptor signaling pathways, and hypothetically lead to endocrine resistance. For

instance, GNAS signaling intersects with several pathways involved in hormone action, including cAMP/PKA and MAPK pathways, which are crucial for hormonal responses (41–44).

During viral infection, cellular calcium dynamics could be highly affected as dysregulation of host cell signaling cascades is elicited by SARS-CoV-2 (45). Calcium ions act as critical secondary messengers in cellular signaling pathways, including those involved in hormone receptor signaling and cell survival. Proper calcium levels are crucial for maintaining vascular integrity and permeability (45). Dysregulation of calcium homeostasis can lead to increased vascular permeability, which is associated with inflammatory processes, potentially leading to endocrine resistance (45). Moreover, alterations in calcium equilibrium and vascular permeability can disturb the microenvironment of hormone-sensitive cells, affecting their response to hormones in natural conditions and to hormone therapies. In addition, increased permeability may alter drug distribution and cellular signaling, potentially contributing to resistance mechanisms (45).

Vascular dysfunction in COVID-19 can also be associated with endocrine pathology that may lead to complications, including endothelial dysfunction, increased vascular permeability and thrombosis. An important example includes leaky blood vessels, which may impact hormone delivery and signaling in hormone-sensitive tissues, directly inducing inflammation with inflammatory cytokine release and direct effects on endothelial cells and other tissues (3–6).

The observed alterations in calcium channel function and GNAS-controlled activities could lead to disruptions in the regulation of vascular permeability, which may, in turn, induce endocrine resistance in the context of COVID-19. These disruptions affect intracellular signaling pathways crucial for hormonal responses and create an environment that hampers the effectiveness of endocrine therapies. Understanding these molecular and cellular changes can provide insights into endocrine resistance mechanisms in COVID-19 and inform potential therapeutic strategies to overcome resistance.

Pathogenesis of Cushing's-like syndrome in COVID-19

Conditions or factors that mimic Cushing's syndrome without primary adrenal pathology are termed Cushing's-like syndrome, and they may be observed in some COVID-19 patients. Again, precipitating factors may include direct viral infection, the cytokine storm and/or treatment with exogenous glucocorticoids. The GNAS-controlled activities, calcium balance, and vascular permeability could contribute to the clinical manifestations of Cushing's-like syndrome, either directly or indirectly, through excessive cortisol or related hormonal imbalances (41–44). Calcium dysregulation can contribute to various symptoms seen in Cushing's syndrome, such as muscle weakness and fatigue. On the other hand, GNAS mutations can also contribute to Cushing's-like syndrome since they are associated with various endocrine disorders, including certain subtypes of Cushing's syndrome, such

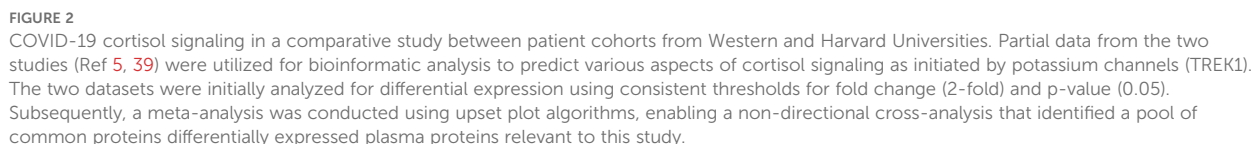
as McCune-Albright syndrome (41–44). Dysregulated GNAS signaling can potentially lead to excessive production of cortisol or alterations in adrenal gland function, contributing to the development of this disease (41–44). Furthermore, calcium homeostatic effects and vascular permeability can be potentially observed in conditions associated with cortisol excess, including Cushing's syndrome. This phenomenon acts as a feed-forward loop, where high cortisol levels can lead to alterations in calcium metabolism and induce changes in vascular permeability, thus resulting in multiple organ dysfunctions.

Cortisol pathway activation in COVID-19: a comparative study between Western and Harvard University databases

There are many studies describing genomics, epigenomics, transcriptomics, and proteomics profiles in COVID-19 (46–48), but very few have investigated the plasma proteome associated with this disease. Studies by our group, and that from Harvard Medical School (48), demonstrated similar changes in the cortisol signaling pathway in COVID-19 (5, 6) (Figure 2). Utilizing our own bioinformatics pipeline we compared our data with the repository published by Filbin et al.

The same comparative analysis also highlighted the activation of the angiotensin I (AGT1) 1/AT1 receptor system. Angiotensin I is usually cleaved by angiotensin-converting enzyme (ACE) to generate the active product angiotensin II, which is involved in maintaining blood pressure, body fluid and electrolyte homeostasis, as well as playing a role in the pathogenesis of essential hypertension and preeclampsia (48–50). In COVID-19, ACE acts as a pathological target, directly inducing smooth muscle cell vasoconstriction, influencing cardiac contractility and heart rate through the sympathetic nervous system, and altering kidney functions such as renal sodium and water absorption, concurrently stimulating the zona glomerulosa cells from the adrenal cortex to synthesize and secrete aldosterone (50). In Figure 2, we can further speculate that melanocortin receptors (MC2R) can be selectively activated by the adrenocorticotrophic hormone ACTH in COVID-19, and TREK1 could activate phospholipase C (PLC beta), which catalyzes the formation of inositol 1,4,5-trisphosphate and diacylglycerol from phosphatidylinositol 4,5-bisphosphate. This latter enzymatic reaction requires calcium as a cofactor, and calcium plays a critical role in the intracellular transduction of many extracellular signals. PLC beta can be activated by two G-protein alpha subunits, thereby regulating the function of the endothelial barrier. Lastly, in the same Figure 2, it can be observed that the cortisol signaling pathway is predicted to exhibit high activation of the CREB/cytochrome P450 system (CYP).

Calcium regulation is critical for cellular homeostasis especially with infections such as SARS-CoV-2 (51, 52). When calcium channels open, they allow influx of calcium into the cells. Intracellular calcium levels modulate the inflammatory response,



Furthermore, calcium ions themselves are secondary messengers for different signal transduction pathways especially when they can activate downstream signaling molecules such as calmodulin, calcineurin, and numerous kinases which in turn may regulate growth factor receptor (GF) signaling (53). Protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase (CaMK), are two of the kinases that can phosphorylate GF

Potential cortisol signaling-associated effectors driven by growth factors

In the study described above, GNAS was found to be a key factor upregulated almost 2-fold (Figure 3). This stimulatory G-protein alpha subunit peptide is an important element of the signal transduction pathway that links receptor-ligand interactions to the activation of adenylyl cyclase and a variety of cellular responses (41–43).

As mentioned above, GNAS is generally regarded as a ubiquitously expressed protein involved in several pathologies such as pseudo-hypoparathyroidism type 1a, fibrous dysplasia of bone, and even several pituitary tumors (41–43). GNAS functions downstream of several G protein receptors, including beta-adrenergic receptors, and alters the secretion of PTH, GHRH, ACTH, TSH, or gonadotrophins. In addition, GNAS, which regularly binds to angiotensin (AGT), can possibly interact with CREB molecules (41–43). Finally, we predict that GNAS may interact with Proopiomelanocortin (POMC), a protein synthesized in corticotroph cells of the anterior pituitary associated with ACTH. In tissues, including the hypothalamus, placenta, and epithelium, these peptides have roles in pain and energy homeostasis, melanocyte stimulation, and immune modulation, especially inflammation. Overall, GNAS-related proteins could be proposed to interact with the cortisol signaling in COVID-19.

GNAS is normally associated with RAS and KRAS activity in cancers (44). We observed that functions of GNAS could also be associated with programmed cell death in COVID-19 (Figure 4), possibly due to overlapping growth factor signals that may affect RAS signaling (Figure 5). In another study by Zhou S et al. (45), GNG7 (Guanine nucleotide-binding protein G) and GNAS proteins were also found to play “a non-ignorable role in the progression of COVID-19”. In this context, a consequence of overlapping signals can be Bax and Bcl2

dysregulation, which can also be part of the RTK signaling, ultimately regulating apoptosis under inflammatory conditions induced by SARS-CoV-2 (54, 55). Bax is a pro-apoptotic factor, while Bcl2 is anti-apoptotic, and the balance between these factors determines cell survival or apoptosis. We can speculate that in the context of COVID-19-associated *endocrine resistance*, elevated Bcl2 expression can help cells evade the apoptotic signals that would typically result from hormone therapy, thus contributing to *resistance*. It is clear that COVID-19 can disrupt various hormonal pathways through inflammatory responses and direct viral effects on endocrine organs, even creating local memory (1, 55). However, many effects could be a consequence of the anti-COVID-19 therapy (53). As such, endocrine disruptions would lead directly to hormonal resistance.

As we elaborated on RAS signaling we observed that stress and inflammation caused by COVID-19 can even induce a state of amplified cellular survival, proliferation and migration signaling, as evidenced also by the elevated EGFR, MMP9, and other survival factors. These changes can mirror the mechanisms underlying endocrine resistance by creating an environment where cells become less responsive to hormonal regulation and more reliant on alternative survival pathways. This environment can mimic the conditions that lead to endocrine resistance, where hormone-sensitive cells become less responsive to hormonal signals due to the activation of alternative survival and growth pathways. This observation can lead to

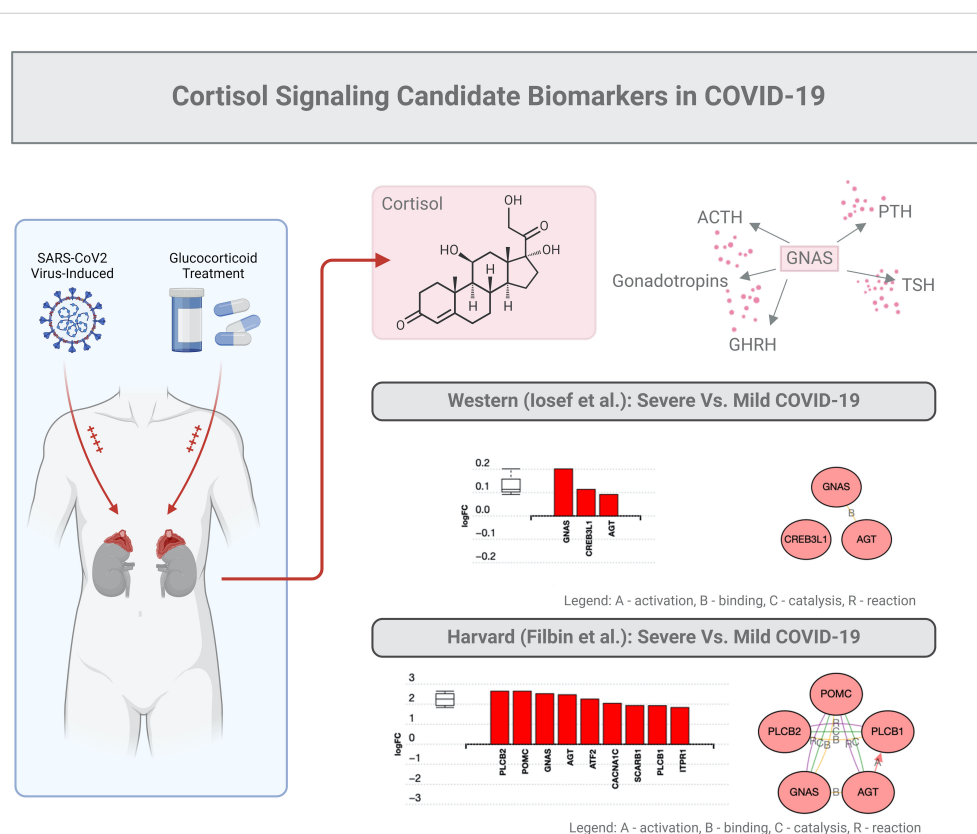
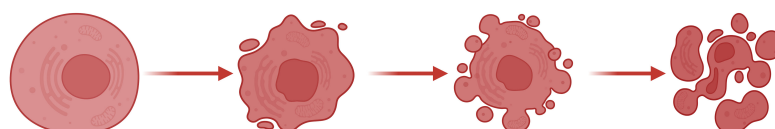


FIGURE 3

Cortisol signaling: candidate biomarkers in COVID-19. The same subset of data (201 proteins) described in the legend of Figure 2 was used for an in-depth bioinformatic analysis focusing on the GNAS protein marker. This specific protein stimulates the activity of adenylate cyclase, an enzyme that plays a crucial role in regulating the production of several hormones that influence the function of endocrine glands, including the thyroid, pituitary gland, ovaries, testes, and adrenal glands.

Candidate Biomarkers for Endocrine Resistance in COVID-19



Apoptosis Regulation

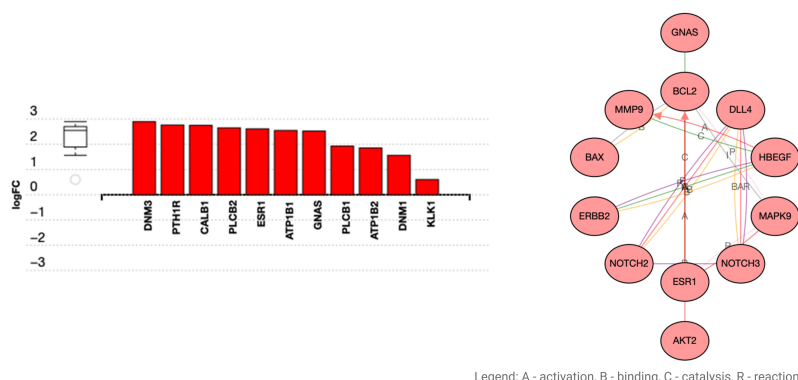


FIGURE 4
Candidate biomarkers for COVID-19 endocrine resistance.

understanding the broader implications of COVID-19 on endocrine health and resistance to endocrine therapies.

Alterations of growth factor signaling in mild COVID-19

In mild COVID-19 cases (hospitalized for oxygen therapy only), we observed elevated activity of epithelial growth factor receptor (EGFR) and metalloproteinase (MMP9), along with increased expression of survival factors like Bax and Bcl2, which can be related to endocrine resistance through several mechanisms. Endocrine resistance, *per se*, refers to the reduced response of hormone-sensitive cells to endocrine therapies, often seen in, but not exclusive to, conditions such as certain cancers. EGFR is a receptor tyrosine kinase (RTK) that, when activated, initiates a cascade of downstream signaling pathways supporting cell proliferation, survival, and differentiation (56). The impact of EGFR on endocrine signaling is manifested by chronic activation of EGFR, which can alter the normal signaling balance within cells and potentially lead to reduced sensitivity to hormonal signals. As EGFR activation can stimulate pathways (e.g., MAPK, PI3K/Akt) that overlap or interfere with hormone receptor pathways, it thereby promotes resistance to hormone-based therapies (56). The EGF-EGFR axis may also have a role in tissue remodeling and inflammation, affecting metalloproteinase-9 (MMP9), an enzyme involved in the breakdown of extracellular matrix

components (57, 58), which could potentially influence hormone receptors. Elevated MMP9 may lead to increased degradation of extracellular matrix components and growth factor receptors, and alter the cellular microenvironment that affects hormone receptor expression and function, contributing to endocrine resistance. Moreover, MMP9 could release growth factors sequestered in the matrix, further activating signaling pathways like EGFR and exacerbating the resistance mechanisms. Through MMP9 activities and aberrant release of growth factors, these molecules can cause signaling competition by overlapping induction of RTKs. It is important to note that future research should investigate the role of EGFR in COVID-19 management, particularly as clinical trials are already exploring the repurposing of EGFR inhibitors for treatment. For example, nimotuzumab, an anti-cancer monoclonal antibody targeting EGFR, has been repurposed for COVID-19 and studied for its potential to modulate the immune response and reduce inflammation. Nimotuzumab may help mitigate severe inflammatory responses in COVID-19 patients, potentially improving clinical outcomes (59). However, research remains limited, and more comprehensive clinical trials are needed to establish its efficacy and safety specifically for COVID-19 treatment.

Endocrine profile in severe COVID-19

Unlike in mild COVID-19, the severe cases of COVID-19 that were admitted to intensive care units (3–6) and showed the

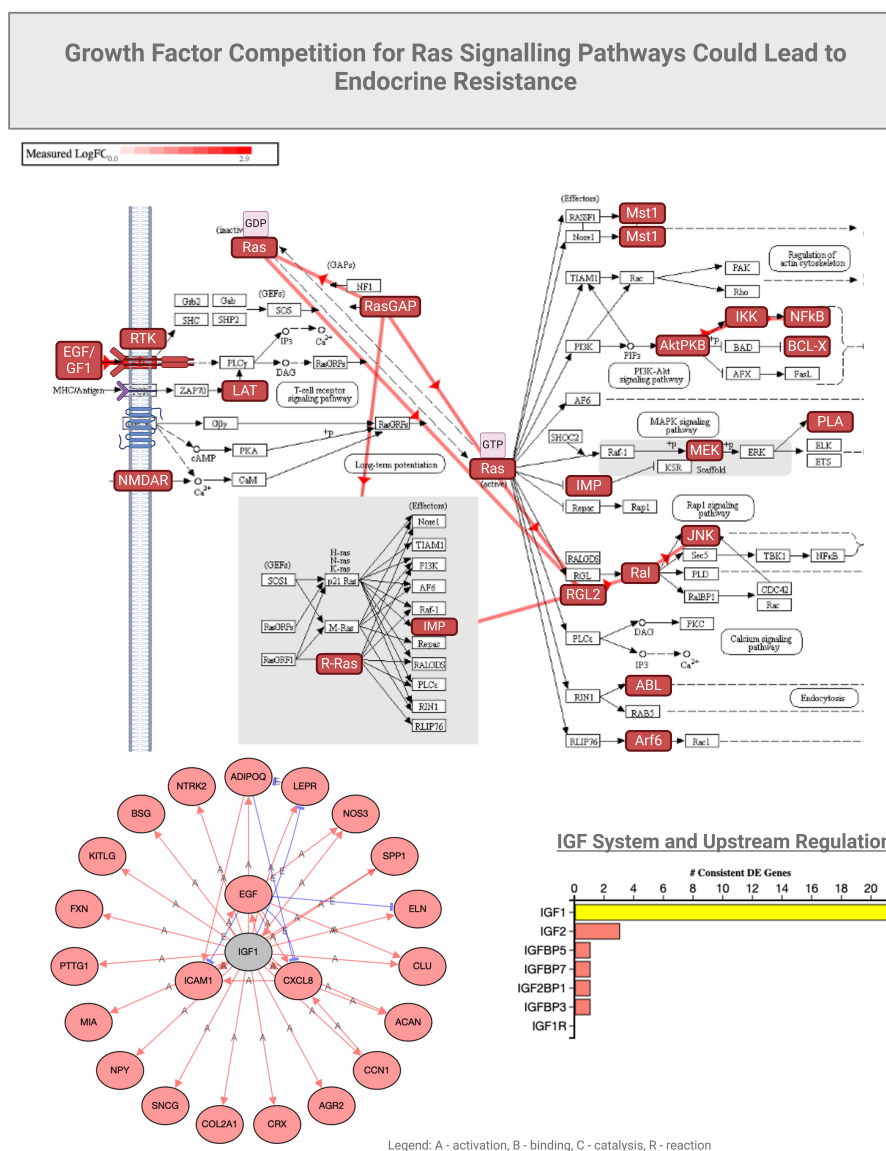


FIGURE 5
Growth factor competition for Ras signaling could lead to endocrine resistance.

involvement of insulin-like growth factor receptor I (IGF-IR), enhanced NOTCH signaling, along with altered expression levels of Bcl2, AKT1, and MAPK8 that can lead to endocrine resistance through various intricate mechanisms (Figure 5). IGF-IR is a receptor that, when activated by insulin-like growth factors (IGFs), triggers downstream signaling pathways that promote cell growth, survival, and metabolism; these factors have been studied in COVID-19 in association with clinical parameters (60–63). Enhanced IGF-IR signaling may lead to increased cellular survival and proliferation, similar to EGFR activation. The result is a reduced efficacy of hormone-based therapies due to the activation of alternative survival pathways (e.g., PI3K/Akt and MAPK pathways), which can interfere with, or bypass, hormone receptor signaling.

Our studies also indicated that NOTCH signaling can be crucial in cell differentiation, proliferation, and apoptosis. Enhanced NOTCH signaling could potentially lead to changes in cell fate and survival. Increased NOTCH signaling would also contribute to endocrine resistance by making cells less responsive to apoptotic signals induced by hormone therapies. In addition, NOTCH signaling can interact with other pathways, such as AKT and MAPK, to further complicate the cellular response to hormonal treatments (64).

Similar to the EGFR state observed in mild COVID-19, we also detected altered expression of Bcl2, AKT1, and MAPK8. Again, increased levels of Bcl2 promote cell survival by inhibiting apoptosis, making cells resistant to treatments that rely on inducing cell death. AKT1, part of the PI3K/Akt pathway, is

crucial for cell survival, growth, and metabolism in COVID-19 (65). Increased AKT1 activity can enhance cell survival, resistance to apoptosis, and contributes to endocrine resistance. In addition, MAPK8 (JNK, Stress-Activated Protein Kinase) is usually involved in stress responses and can influence apoptosis and cell proliferation. Altered MAPK8 signaling would not only affect the cellular response to stress and apoptosis, but also contribute to resistance mechanisms. It is thus predicted that endocrine disruptions leading to resistance may involve increased activation of IGFR-I and NOTCH pathways, along with altered levels of Bcl2, AKT1, and MAPK8 creating a cellular environment that promotes survival and proliferation (64, 66). Such an environment can reduce the efficacy of hormone therapies by promoting alternative pathways that support cell survival, independent of the presence of endocrine treatments.

In summary, the activation of IGFR-I and enhanced NOTCH signaling, coupled with altered expression of Bcl2, AKT1, and MAPK8 in severe COVID-19 may lead to an environment that favors cell survival and proliferation. These observed changes could lead to endocrine resistance by promoting pathways that bypass or interfere with hormone receptor signaling, making cells less responsive to hormone therapies. Understanding these interactions can provide insights into how acute COVID-19 influences endocrine health and resistance mechanisms, and provide clinical guidance towards more effective treatment strategies.

Methodological limitations

There are very few studies available for comparison, with the notable exception of the research conducted by Filbin et al. (39) at Harvard University, which makes our data sets unique. Both Filbin et al. and Iosef et al. (5) analyzed patients at Day 0/1, 3, and 7 post-admission with severe COVID-19, all of whom presented with severe disease characterized by bilateral pneumonia. For our cross-comparison aimed at identifying pathways related to endocrine dysfunction, we utilized data from Day 3 for both studies.

In Filbin et al.'s study, there were 109 patients with severe COVID-19 and 78 COVID-negative controls, while Iosef et al. examined 22 patients with severe COVID-19 and 22 healthy controls. A notable distinction between the two studies lies in the technology employed: Filbin et al. used the Olink Explore 1536 platform, whereas Iosef et al. utilized the Olink Explore 3072, which allows for the analysis of a greater number of differentially expressed proteins.

We acknowledge that confounding factors and publication biases may influence our results; however, our primary aim was to conduct a meta-analysis using algorithms that facilitate a comprehensive comparison of data sets derived from Olink technology, specifically analyzing plasma samples from patients with severe COVID-19. We maintained consistent thresholds for p-values and fold change (FC) in our analysis. While the patient

numbers varied, recruitment was age- and sex-matched in both studies, and the criteria for severe COVID-19 were similar.

After aligning and meta-analyzing the data sets, we identified 1,780 differentially expressed proteins in our dataset and 783 in the Harvard dataset. The difference in numbers arises from the distinct panels of markers used for targeted proteomics in each study. Notably, we found that 201 markers were common between the two studies, forming the basis for our comparative analysis. Clinical parameters, including age, sex, comorbidities (such as hypertension, COPD, cancer, and chronic kidney disease), baseline medication, and laboratory parameters (like blood counts and X-ray findings) were also comparable across the studies, including confirmation of sepsis and administered intervention drugs.

Conclusions

This review examines the endocrine implications of COVID-19, focusing on cortisol signaling and growth factor-induced endocrine resistance, highlighting the impact of SARS-CoV-2 on the endocrine system. COVID-19 often causes elevated cortisol levels with normal ACTH levels due to systemic inflammation, illness-induced stress, and cytokine storms. Sometimes, cortisol levels rise independently of ACTH, resembling “pseudo-Cushing’s syndrome.” Plasma proteomics suggests this variation may involve calcium dysregulation and GNAS-controlled activities, affecting vascular permeability. COVID-19 also presents endocrine resistance syndromes through activation of receptor tyrosine kinase pathways. Mild cases show elevated EGFR and MMP9 activity, while severe cases involve IGF-1R and enhanced NOTCH signaling, altering Bcl2, AKT1, and MAPK8 expression. The medical conclusion is that COVID-19 potentially impacts the endocrine system, particularly described here, through altered cortisol signaling and endocrine resistance mechanisms. These changes include elevated cortisol levels with normal ACTH levels, resembling “pseudo-Cushing’s syndrome,” and variations in receptor tyrosine kinase pathways, with different patterns in mild and severe cases. These endocrine alterations should be considered when developing targeted therapeutic interventions to improve patient outcomes. Developing interventions aimed at preventing severe cases could be a crucial direction for future research and clinical practice.

Author contributions

CI: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. AMM: Software, Visualization, Writing – review & editing. VKMH: Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing. DDF: Conceptualization, Funding

acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. VKMH was supported by the Children's Health Foundation and DDF by the AMOSO Innovation Fund.

Acknowledgments

OpenAI and Grammarly software were used to correct grammar and spelling in the English language.

References

- Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *J Endocrinological Invest.* (2020) 43:1027–31. doi: 10.1007/s40618-020-01276-8
- Sathish T, Cao Y, Kapoor N. Association of sex, age, and comorbidities with mortality in COVID-19 patients: a systematic review and meta-analysis. *Int J Infect Dis.* (2021) 104:447–59. doi: 10.1159/000512592
- Patel MA, Knauer MJ, Nicholson M, Daley M, Van Nynatten LR, Cepinskas G, et al. Organ and cell-specific biomarkers of Long-COVID identified with targeted proteomics and machine learning. *Mol Med.* (2023) 29:26. doi: 10.1186/s10020-023-00610-z
- Fraser DD, Cepinskas G, Patterson EK, Slessarev M, Martin C, Daley M, et al. Novel outcome biomarkers identified with targeted proteomic analyses of plasma from critically ill coronavirus disease 2019 patients. *Crit Care Explor.* (2020) 2:e0189. doi: 10.1097/CCE.0000000000000189
- Iosef C, Knauer MJ, Nicholson M, Van Nynatten LR, Cepinskas G, Draghici S, et al. Plasma proteome of Long-COVID patients indicates HIF-mediated vasculo-proliferative disease with impact on brain and heart function. *J Transl Med.* (2023) 21:377. doi: 10.1186/s12967-023-04149-9
- Iosef C, Martin CM, Slessarev M, Gillio-Meina C, Cepinskas G, Han VKM, et al. COVID-19 plasma proteome reveals novel temporal and cell-specific signatures for disease severity and high-precision disease management. *J Cell Mol Med.* (2023) 27:141–57. doi: 10.1111/jcmm.17622
- Poma AM, Bonuccelli D, Giannini R, Macerola E, Vignali P, Ugolini C, et al. COVID-19 autopsy cases: detection of virus in endocrine tissues. *J Endocrinol Invest.* (2022) 45:209–14. doi: 10.1007/s40618-021-01628-y
- Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement Eur Soc Endocrinology. *Endocrine.* (2020) 68:2–5. doi: 10.1007/s12020-020-02294-5
- Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. *Acta Pharmacol Sin.* (2023) 44:695–709. doi: 10.1038/s41401-022-00998-0
- Marazuela M, Giustina A, Puig-Domingo M, Endocrinology, D. G. O. T. S. COVID-19 and the endocrine system: a comprehensive review. *Eur J Endocrinol.* (2020) 183:R153–67. doi: 10.3390/jem10132920
- Khan S, Karim M, Gupta V, Goel H, Jain R. A comprehensive review of COVID-19-associated endocrine manifestations. *South Med J.* (2023) 116:350–4. doi: 10.14423/SMJ.00000000000001542
- Abdel-Moneim A, Hosni A. Insights into the possible impact of COVID-19 on the endocrine system. *Arch Physiol Biochem.* (2023) 129:998–1006. doi: 10.1080/13813455.2021.1890131
- Clarke SA, Abbata A, Dhillon WS. Impact of COVID-19 on the endocrine system: A mini-review. *Endocrinology.* (2022) 163:bqab203. doi: 10.1210/endo/bqab203
- Guo Z, Shi M, Feng Y, Zou X, Chen Y. Characteristics of thyroid function test in COVID-19 patients: a systematic review and meta-analysis. *Front Endocrinol.* (2021) 12:676810. doi: 10.7759/cureus.40628
- Nieman LK. Approach to the patient with endocrine disorders caused by COVID-19. *J Clin Endocrinol Metab.* (2020) 105:dga615. doi: 10.1016/j.dsx.2020.05.050
- Oguz SH, Yildiz BO. Endocrine disorders and COVID-19. *Annu Rev Med.* (2023) 74:75–88. doi: 10.1146/annurev-med-043021-033509
- Bandara T, Deshmukh HA, Abdalla M, Sathyapalan T. Metabolic and endocrine complications of long-COVID-19: A review. *Exp Clin Endocrinol Diabetes.* (2023) 131:367–74. doi: 10.1055/a-2063-8697
- Zhao Y, Wu X. Influence of COVID-19 vaccines on endocrine system. *Endocrine.* (2022) 78:241–6. doi: 10.1007/s12020-022-03119-3
- Stasi VD, Rastrelli G. The role of sex hormones in the disparity of COVID-19 outcomes based on gender. *J Sex Med.* (2021) 18:1950–4. doi: 10.1016/j.jsxm.2021.09.003
- Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *Lancet Diabetes Endocrinol.* (2018) 6:743–52. doi: 10.1016/S2213-8587(18)30110-4
- D'Souza A, Spicer D, Lu J. Overcoming endocrine resistance in metastatic hormone receptor-positive breast cancer. *J Hematol Oncol.* (2018) 11:80. doi: 10.1186/s13045-018-0620-6
- Jeanrenaud B, Halimi S, van de Werve G. Neuro-endocrine disorders seen as triggers of the triad: obesity–insulin resistance–abnormal glucose tolerance. *Diabetes Metab Rev.* (1985) 1:261–91. doi: 10.1002/dmr.5610010303
- Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO, Endocrine, B. M. T. S. F. E. C. O. t. E. S. f. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol.* (2020) 16:297–8. doi: 10.1038/s41574-020-0353-9
- Mak IWY, Chu CM. Acute and prolonged endocrine complications in COVID-19: a systematic review and meta-analysis. *J Diabetes Invest.* (2021) 12:191–207. doi: 10.1530/EC-21-0184
- Konda A, Shah SP, Rabiee A. Acute and post-acute COVID-19 endocrine manifestations: a systematic review. *J Endocrine Soc.* (2021) 5:bvab048. doi: 10.1055/a-2063-8697
- Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract.* (2020) 164:108166. doi: 10.1016/j.diabres.2020.108166
- Capaldo B, Annuzzi G, Creanza A, Giglio C, De Angelis R. Blood glucose control during lockdown for COVID-19: CGM metrics in Italian adults with type 1 diabetes. *Diabetes Care.* (2020) 43:e88–9. doi: 10.2337/dc20-1127
- Scherer PE, Kirwan JP, Rosen CJ. Post-acute sequelae of COVID-19: A metabolic perspective. *Elife.* (2022) 11:e78200. doi: 10.7554/eLife.78200
- Gorthi RS, Sastry N, Kumar PS. Cushing's syndrome in a COVID-19 patient. *Indian J Endocrinol Metab.* (2020) 24:547–9. doi: 10.1530/EDM-21-0182
- Bacaner MB, Ata B. ACTH-dependent Cushing's syndrome in a patient with severe COVID-19 pneumonia: a case report. *Endocrine.* (2021) 72:220–1. doi: 10.1007/s12020-021-02674-5
- Reddy P, Nguyen K, Banga N, Zaloga G. Post COVID-19 syndrome (PCS) and adrenal axis suppression: the hidden battle after the war. *Am J Med Sci.* (2020) 360:740–1. doi: 10.3390/medicina57101087
- Yasir M, Goyal A, Sonthalia S. Corticosteroid adverse effects. In: *StatPearls*. StatPearls Publishing, Treasure Island (FL) (2023).
- Alzahrani AS, Mukhtar N, Aljomaiah A, Aljamei H, Bakhsh AR. Severe Cushing's syndrome with adrenal insufficiency precipitated by COVID-19 pneumonia: a case report and literature review. *J Endocrine Soc.* (2021) 5:bvab010. doi: 10.1507/endo/crj20-0613

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

34. Kadian M, Gupta A, Gautam G, Yadav P, Garg P. Cushing's syndrome in a patient with COVID-19 infection. *Indian J Endocrinol Metab.* (2021) 25:104–6. doi: 10.1016/S2213-8587(20)30215-1
35. Benetti C, Cosma C, Fracassi E, Ferrari M, Storici P. Glucocorticoid-induced Cushing syndrome in a patient with severe COVID-19 pneumonia. *Endocrine Pract.* (2021) 27:e384–7. doi: 10.1016/j.eprac.2022.07.006
36. Shacham EC, Ishay A. New insights on effects of glucocorticoids in patients with SARS-CoV-2 infection. *Endocr Pract.* (2022) 28:1100–6. doi: 10.1016/j.eprac.2022.07.006
37. Lui DTW, Lee CH, Chow WS, Lee ACH. Exogenous Cushing syndrome in a patient with severe COVID-19 pneumonia. *Endocrine Pract.* (2021) 27:e313–6. doi: 10.3389/fendo.2022.889928
38. Alataki A, Dowsett M. Human epidermal growth factor receptor-2 and endocrine resistance in hormone-dependent breast cancer. *Endocr Relat Cancer.* (2022) 29:R105–22. doi: 10.1530/ERC-21-0293
39. Noori M, Nejadghaderi SA, Sullman MJM, Carson-Chahhoud K, Ardalan M, Kolahi AA, et al. How SARS-CoV-2 might affect potassium balance via impairing epithelial sodium channels? *Mol Biol Rep.* (2021) 48:6655–61. doi: 10.1007/s11033-021-06642-0
40. Medeiros-Silva J, Dregni AJ, Somberg NH, Duan P, Hong M. Atomic structure of the open SARS-CoV-2 E viroporin. *Sci Adv.* (2023) 9:eadi9007. doi: 10.1126/sciadv.adi9007
41. Dejkhamron P, Ittiwut C, TangNgam H, Sunkonkit K, Natesirinilkul R, Suphateetiporn K, et al. A novel GNAS mutation causing isolated infantile cushing's syndrome. *Horm Res Paediatr.* (2019) 92:196–202. doi: 10.1159/000501169
42. Haldeman-Englert CR, Hurst ACE, Levine MA. Disorders of GNAS inactivation. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews®*. University of Washington, Seattle, WA (2017). p. 1993–2024.
43. Bastepe M, Jüppner H. GNAS locus and pseudo-hypoparathyroidism. *Horm Res.* (2005) 63:65–74. doi: 10.1159/000083895
44. Kawabata H, Ono Y, Tamamura N, Oyama K, Ueda J, Sato H, et al. Mutant GNAS limits tumor aggressiveness in established pancreatic cancer via antagonizing the KRAS-pathway. *J Gastroenterol.* (2022) 57:208–20. doi: 10.1007/s00535-021-01846-4
45. Zhou Y, Xue S, Yang JJ. Calcium and viruses. In: Kretsinger RH, Uversky VN, Permyakov EA, editors. *Encyclopedia of Metalloproteins*. Springer, New York, NY, USA (2013). p. 415–24.
46. Zhou S, Zhang J, Xu J, Zhang F, Li P, He Y, et al. An epigenome-wide DNA methylation study of patients with COVID-19. *Ann Hum Genet.* (2021) 85:221–34. doi: 10.1111/ahg.12440
47. Chakraborty C, Sharma AR, Bhattacharya M, Zayed H, Lee SS. Understanding gene expression and transcriptome profiling of COVID-19: an initiative towards the mapping of protective immunity genes against SARS-CoV-2 infection. *Front Immunol.* (2021) 12:724936. doi: 10.3389/fimmu.2021.724936
48. Filbin MR, Mehta A, Schneider AM, Kays KR, Guess JR, Gentili M, et al. Longitudinal proteomic analysis of severe COVID-19 reveals survival-associated signatures, tissue-specific cell death, and cell-cell interactions. *Cell Rep Med.* (2021) 2:100287. doi: 10.1016/j.xcrim.2021.100287
49. Suleiman A, Qaswal AB, Alnouti M, Yousef M, Suleiman B, Jarbeh ME, et al. Sedating mechanically ventilated COVID-19 patients with volatile anesthetics: insights on the last-minute potential weapons. *Sci Pharm.* (2021) 89:6. doi: 10.3390/scipharm89010006
50. Shirbhatte E, Pandey J, Patel VK, Kamal M, Jawaid T, Gorain B, et al. Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. *Pharmacol Rep.* (2021) 73:1539–50. doi: 10.1007/s43440-021-00303-6
51. Surya W, Tavares-Neto E, Sanchis A, Queralt-Martín M, Alcaraz A, Torres J, et al. The complex proteolipidic behavior of the SARS-CoV-2 envelope protein channel: weak selectivity and heterogeneous oligomerization. *Int J Mol Sci.* (2023) 24:12454. doi: 10.3390/ijms241512454
52. Chimote AA, Alshwimi AO, Chirra M, Gawali VS, Powers-Fletcher MV, Hudock KM, et al. Immune and ionic mechanisms mediating the effect of dexamethasone in severe COVID-19. *Front Immunol.* (2023) 14:1143350. doi: 10.3389/fimmu.2023.1143350
53. Chatterjee B, Thakur SS. SARS-CoV-2 infection triggers phosphorylation: potential target for anti-COVID-19 therapeutics. *Front Immunol.* (2022) 13:829474. doi: 10.3389/fimmu.2022.829474
54. Simpson DS, Pang J, Weir A, Kong IY, Fritsch M, Rashidi M, et al. Interferon- γ primes macrophages for pathogen ligand-induced killing via a caspase-8 and mitochondrial cell death pathway. *Immunity.* (2022) 55:423–441.e9. doi: 10.1016/j.immuni.2022.01.003
55. Silvestri Y, Clemente F, Moschetti G, Maioli S, Carelli E, Espadas de Arias A, et al. SARS-CoV-2 specific t-cells in patients with thyroid disorders related to COVID-19 are enriched in the thyroid and acquire a tissue-resident memory phenotype. *Clin Immunol.* (2023) 254:109684. doi: 10.1016/j.clim.2023.109684
56. Vagapova ER, Lebedev TD, Prassolov VS. Viral fibrotic scoring and drug screen based on MAPK activity uncovers EGFR as a key regulator of COVID-19 fibrosis. *Sci Rep.* (2021) 11:11234. doi: 10.1038/s41598-021-90701-w
57. Klein J, Wood J, Jaycox JR, Dhodapkar RM, Lu P, Gehlhausen JR, et al. Distinguishing features of long COVID identified through immune profiling. *Nature.* (2023) 623:139–48. doi: 10.1038/s41586-023-06651-y
58. Mohamed AA, Nour AA, Mosbah NM, Wahba ASM, Esmail OE, Eysa B, et al. Evaluation of circulating insulin-like growth factor-1, heart-type fatty acid-binding protein, and endotrophin levels as prognostic markers of COVID-19 infection severity. *Virol J.* (2023) 20:94. doi: 10.1186/s12985-023-02057-4
59. Londres HD, Armada JJ, Martínez AH, Abdo Cuza AA, Sánchez YH, Rodríguez AG, et al. Blocking EGFR with nimotuzumab: a novel strategy for COVID-19 treatment. *Immunotherapy.* (2022) 14:521–30. doi: 10.2217/imt-2022-0027. Erratum in: *Immunotherapy.* 2022 Oct;14(14):1181. doi: 10.2217/imt-2022-0027c1.
60. Feizollahi P, Matin S, Roghani SA, Mostafaei S, Safarzadeh E, Taghadosi M. Evaluation serum levels of Insulin Growth Factor-1 (IGF-1) and its association with clinical parameters in severe COVID-19. *Inflammopharmacology.* (2022) 30:199–205. doi: 10.1007/s10787-021-00908-6
61. Hazrati E, Gholami M, Farahani RH, Ghorban K, Ghayomzadeh M, Rouzbahani NH. The effect of IGF-1 plasma concentration on COVID-19 severity. *Microb Pathog.* (2022) 164:105416. doi: 10.1016/j.micpath.2022.105416
62. Kelesidis T, Mantzoros CS. Cross-talk between SARS-CoV-2 infection and the insulin/IGF signalling pathway: Implications for metabolic diseases in COVID-19 and for post-acute sequelae of SARS-CoV-2 infection. *Metabolism.* (2022) :134:155267. doi: 10.1016/j.metabol.2022.155267
63. Fan X, Yin C, Wang J, Yang M, Ma H, Jin G, et al. Pre-diagnostic circulating concentrations of insulin-like growth factor-1 and risk of COVID-19 mortality: results from UK Biobank. *Eur J Epidemiol.* (2021) 36:311–8. doi: 10.1007/s10654-020-00709-1
64. Breikaa RM, Lilly B. The notch pathway: A link between COVID-19 pathophysiology and its cardiovascular complications. *Front Cardiovasc Med.* (2021) 8:681948. doi: 10.3389/fcvm.2021.681948
65. Basile MS, Cavalli E, McCubrey J, Hernández-Bello J, Muñoz-Valle JF, Fagone P, et al. The PI3K/Akt/mTOR pathway: A potential pharmacological target in COVID-19. *Drug Discovery Today.* (2022) 27:848–56. doi: 10.1016/j.drudis.2021.11.002
66. Lorente L, Martín MM, González-Rivero AF, Pérez-Cejas A, Argüeso M, Perez A, et al. Blood concentrations of pro-apoptotic sFas and anti-apoptotic Bcl2 and COVID-19 patient mortality. *Expert Rev Mol Diagn.* (2021) 21:837–44. doi: 10.1080/14737159.2021.1941880



OPEN ACCESS

EDITED BY

Kamrar Asadipooya,
University of Kentucky, United States

REVIEWED BY

Charlotte Steenblock,
Technical University Dresden, Germany
Lohanna Palhinha,
Oswaldo Cruz Foundation (Fiocruz), Brazil

*CORRESPONDENCE

Nazarii Kobylak
✉ nazarii.kobylak@gmail.com

RECEIVED 03 July 2024

ACCEPTED 27 November 2024

PUBLISHED 11 December 2024

CITATION

Matviichuk A, Yerokhovych V, Zemskov S,
Ilkiv Y, Gurianov V, Shaienko Z, Falalyeyeva T,
Sulaieva O and Kobylak N (2024) Unveiling
risk factors for post-COVID-19 syndrome
development in people with type 2 diabetes.
Front. Endocrinol. 15:1459171.
doi: 10.3389/fendo.2024.1459171

COPYRIGHT

© 2024 Matviichuk, Yerokhovych, Zemskov,
Ilkiv, Gurianov, Shaienko, Falalyeyeva, Sulaieva
and Kobylak. This is an open-access article
distributed under the terms of the [Creative
Commons Attribution License \(CC BY\)](#). The
use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Unveiling risk factors for post-COVID-19 syndrome development in people with type 2 diabetes

Anton Matviichuk¹, Viktoriia Yerokhovych¹, Sergii Zemskov¹,
Yeva Ilkiv¹, Vitalii Gurianov¹, Zlatoslava Shaienko²,
Tetyana Falalyeyeva^{3,4}, Oksana Sulaieva^{4,5}
and Nazarii Kobylak^{1,4*}

¹Department of Endocrinology, Bogomolets National Medical University, Kyiv, Ukraine, ²Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine, ³Department of Fundamental Medicine, Educational-Scientific Center "Institute of Biology and Medicine" Taras Shevchenko National University of Kyiv, Kyiv, Ukraine, ⁴Scientific Department, Medical Laboratory CSD, Kyiv, Ukraine, ⁵Department of Pathology, Kyiv Medical University, Kyiv, Ukraine

Introduction: Post-COVID-19 syndrome (PCS) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-associated chronic condition characterized by long-term violations of physical and mental health. People with type 2 diabetes (T2D) are at high risk for severe COVID-19 and PCS.

Aim: The current study aimed to define the predictors of PCS development in people with T2D for further planning of preventive measures and improving patient outcomes.

Materials and methods: The data were collected through the national survey targeting persons with T2D concerning the history of COVID-19 course and signs and symptoms that developed during or after COVID-19 and continued for more than 12 weeks and were not explained by an alternative diagnosis. In total, 469 patients from different regions of Ukraine were enrolled in the study. Among them, 227 patients reported PCS development (main group), while 242 patients did not claim PCS symptoms (comparison group). Stepwise multivariate logistic regression and probabilistic neural network (PNN) models were used to select independent risk factors.

Results: Based on the survey data, 8 independent factors associated with the risk of PCS development in T2D patients were selected: newly diagnosed T2D (OR 4.86; 95% CI 2.55–9.28; $p < 0.001$), female sex (OR 1.29; 95% CI 0.86–1.94; $p = 0.220$), COVID-19 severity (OR 1.35 95% CI 1.05–1.70; $p = 0.018$), myocardial infarction (OR 2.42 95% CI 1.26–4.64; $p = 0.002$) and stroke (OR 3.68 95% CI 1.70–7.96; $p = 0.001$) in anamnesis, HbA1c above 9.2% (OR 2.17 95% CI 1.37–3.43; $p = 0.001$), and the use of insulin analogs (OR 2.28 95% CI 1.31–3.94; $p = 0.003$) vs human insulin (OR 0.67 95% CI 0.39–1.15; $p = 0.146$). Although obesity aggravated COVID-19 severity, it did not impact PCS development. In ROC analysis, the 8-factor multilayer perceptron (MLP) model exhibited better performance (AUC 0.808; 95% CI 0.770–0.843), allowing the prediction of the risk of PCS development with a sensitivity of 71.4%, specificity of 76%, PPV of 73.6% and NPV of 73.9%.

Conclusions: Patients who were newly diagnosed with T2D, had HbA1c above 9.2%, had previous cardiovascular or cerebrovascular events, and had severe COVID-19 associated with mechanical lung ventilation were at high risk for PCS.

KEYWORDS

post-COVID-19 Syndrome, long COVID-19, COVID-19 infection, SARS-CoV-2, type 2 diabetes

Introduction

Approximately 95% of people with diabetes worldwide have type 2 diabetes (T2D). A 3% increase in age-standardized mortality rates from diabetes was recorded from 2000 to 2019 (1). T2D is a group of metabolic diseases caused by insulin resistance (IR) and altered insulin secretion by β -cells of the pancreas (2, 3).

The 2019 coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global concern (4–6). T2D is one of the most common comorbidities in patients infected with the SARS-CoV-2 virus, with a relatively high incidence of severe COVID-19 (7, 8). T2D has a bidirectional relationship with COVID-19 (9). Poorly controlled, decompensated T2D exacerbates the severity of COVID-19 and leads to an increased risk of hospitalization and mortality (10, 11). Potential mechanisms contributing to enhanced susceptibility to SARS-CoV-2 infection and poorer prognosis in people with T2D include a proinflammatory state, weakened innate immune response, possibly elevated levels of angiotensin-converting enzyme 2 (ACE2), vascular dysfunction and a prothrombotic state (12–14). On the other hand, an extreme systemic immune response (“cytokine storm”), direct attack of pancreatic β -cells by SARS-CoV-2 by binding to ACE2, and an unbalanced immune response can, in turn, lead to glycemic profile disorders, uncontrolled hyperglycemia, and progression of IR in persons with T2D (15, 16).

COVID-19 combined with T2D enhances the risk of hospitalization and the need for mechanical ventilation, increasing the probability of post-COVID-19 syndrome development. Post-COVID-19 syndrome (PCS; long COVID-19, post-acute COVID-19, long-term effects of COVID-19) has become an emerging health problem in people recovering from COVID-19 infection (17–19). PCS condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis (20). Common symptoms include rapid fatigue, weakness, headaches, memory loss, distraction, depression, prolonged cough or shortness of breath, insomnia, heart palpitations, bone and joint aches, myalgias, gastrointestinal disorders, and insensitivity to smells and tastes (20). Symptoms

may be new onset, following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time (20).

One of the consequences of lung damage in patients with SARS-CoV-2 infection, namely, pulmonary fibrosis, which can manifest as persistent shortness of breath requiring oxygen supplementation in the PCS period, is more common in people with poorly controlled diabetes (18). Not surprisingly, the bidirectional association between diabetes and PCS has been at the top of scientific discussions (21, 22). Some evidence suggests that diabetes may be a risk factor for the development of PCS (22, 23). Recent data also indicate that new-onset diabetes might be a complication of COVID-19 and represents the metabolic clinical phenotype of PCS (18, 24). However, the particular links between T2D and PCS are still under debate. Limited research exists on PCS incidence and prevalence in low- and middle-income countries.

The current study aimed to define the predictors of PCS development in people with T2D for further planning of preventive measures and improving patient outcomes.

Materials and methods

Ethics statement

The study protocol was approved by the Ethics Committee at Bogomolets National Medical University (protocol number: 171/2023) and was conducted according to the guidelines of the 1975 Declaration of Helsinki. Individuals with T2D were enrolled in the study during visits to endocrinologists at outpatient clinics. The purpose and methodology of the study were fully explained to the participants by the researchers, and all patients were asked to provide signed informed consent before data collection.

Study design

To gather data concerning the outcomes of COVID-19 in T2D persons, a questionnaire was developed. The following clinical and demographic data were collected: age, sex, anthropometric indicators, T2D duration and age at onset, T2D complications,

history of COVID-19, COVID-19 severity and treatment, PCS symptoms, duration of PCS and hypoglycemic therapy. According to the WHO classification, COVID-19 was categorized as mild, moderate or severe. Mild COVID-19 was defined as respiratory symptoms without evidence of pneumonia or hypoxia, while moderate or severe infection required the presence of clinical and radiological evidence of pneumonia. In moderate cases, SpO₂ ≥90% on room air, while one of the following was required to define severe cases: respiratory rate >30 breaths/min or SpO₂ <90% on room air (25, 26). The data were collected and registered by a professional endocrinologist during the follow-up visits of patients to outpatient clinics. Medical data were also retrieved from the medical records of the participants.

The inclusion criteria were as follows: age over 18 years and the presence of T2D and COVID-19 confirmed by a positive RT–PCR test. The exclusion criteria included type 1 diabetes or secondary diabetes, autoimmune diseases, inflammatory diseases, other than T2D metabolic diseases and active malignancy. The data from 469 patients who suffered from COVID-19 infection were collected in different regions of Ukraine. According to the responses, patients were divided into 2 groups depending on the outcomes for up to 6 months after COVID-19 infection: the PCS group (main group, n=227) and patients who didn't develop PCS (comparison group, n=242).

Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the participant's height in meters (weight/height²). The waist (narrowest diameter between the xiphoid process and iliac crest) circumference (WC) was also measured.

As obesity itself is an immunometabolic disorder, facilitating pro-inflammatory cytokines secretion, reducing insulin sensitivity (27) and modulating SARS-Cov2 retention (28) we provided a sub-analysis for assessing the effect of obesity on PCS development and COVID-19 severity. Patients were divided into two sub-groups including individuals with BMI<30kg/m² (n=110) and patients with obesity (BMI≥30kg/m², n=117).

In addition, cases of new-onset T2D were assessed separately. New-onset T2D in PCS group was defined when occur during or after acute COVID-19 phase within 3 months (n=43). From comparison group we included in sub analysis patients with onset of T2D before 3 months to COVID-19 (n=17).

Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software v. 22.026 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2024) and STATISTICA Neural Networks R.4.0 C (StatSoft, Inc. 1998-1999). To test the normality of the distribution, the Shapiro–Wilk test was used. Quantitative variables are presented as the median and interquartile range (Me, Q_I – Q_{III}), and qualitative variables are presented as %. To estimate the difference in the incoming qualitative data, the χ^2 test or Fisher's exact test was used; for quantitative data, the Mann–Whitney test was used. Univariate

logistic regression analysis was applied to assess variables associated with PCS development in patients with T2D.

Stepwise multivariate logistic regression and probabilistic neural network (PNN) models were used to select independent risk factors associated with PCS development. In the first stage, a minimal set of variables associated with PCS risk was selected. To select independent risk factors for multivariate logistic regression models, stepwise inclusion/exclusion of variables (stepwise with $p_{\text{enter}} < 0.1$ and $p_{\text{remove}} > 0.2$) was performed, and the genetic algorithm (GA) method of selection was used for the PNN models. For the PNN models, all patients were randomly (using a random number generator) divided into 3 sets: training (which was used to build the model and calculate weight coefficients of the neural network, n=369), test (used to prevent overtraining of the mathematical model, n=60) and verification (used to test the predictive ability of the mathematical model on new data for controlling model retraining, n=40) sets.

The diagnostic performance of the models was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) and its 95% confidence interval (CI) were calculated. A p value < 0.05 was considered to indicate statistical significance in all tests. Optimal cutoff values were chosen to maximize the sum of sensitivity and specificity. Positive predictive values (PPVs) and negative predictive values (NPVs) were computed for these cutoff values (29).

Results

Patient characteristics

The baseline clinical parameters, COVID-19 and T2D histories of the surveyed patients are presented in Table 1. Among the study subjects, the ages in the main group were 61 (54 – 67) and 60 (54 – 68) years (p=0.900), respectively. The main group comprised more patients over 60 years old (59% vs 53.7% in the comparison group), although these differences were not significant (p=0.264) (Table 1). There were 124 females (54.6%) in the PCS group, while the proportion of women was lower among patients with no PCS (115 out of 242, 47.5); however, sex differences were not significant between the groups (p=0.139). We also did not find differences in patient weight (p=0.994) or BMI (p=0.881) (Table 1).

By assessing the clinical phenotypes of PCS among T2D patients, we found that fatigue was the most often observed manifestation of PCS (59.5%). It was followed by muscle aches (49.3%), headache (44.1%), shortness of breath (39.2%), new or persistent cough (31.7%), loss or change of smell (31.3%), dyssomnia (28.8%), arrhythmia (23.3%), gastrointestinal disorders (19.8%), and depression (16.7%) (Figure 1A).

Medical history of diabetes and beyond – the links to PCS

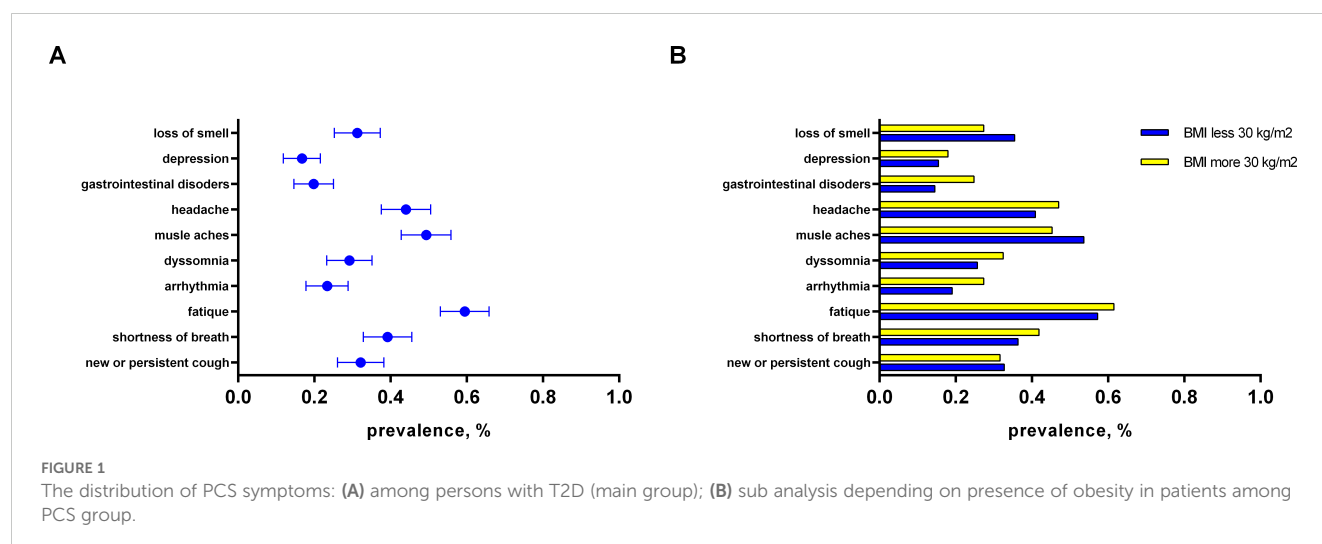
The subjects who suffered from PCS reported a medical history of poor glycemic control during anamnesis and had higher values of

TABLE 1 Baseline clinical parameters and COVID-19 and T2D history in surveyed patients.

Parameter	Comparison group (no PCS) (n=242)	Main group (PCS) (n=227)	p
Age, years	60 (54 – 68)	61 (54 – 67)	0.900
Age over 60 years, n (%)	130 (53.7)	134 (59)	0.264
Females, n (%)	115 (47.5)	124 (54.6)	0.139
T2D duration, years	11 (7 – 16)	10 (3 – 15)	0.015
Newly diagnosed diabetes, n (%)	17 (7.0)	43 (18.9)	<0.001
Weight, kg	88 (80 – 98)	88 (78 – 100)	0.994
Height, cm	169 (165 – 176)	168 (163 – 177)	0.384
BMI, kg/m ²	29.8 (27.500 – 33.8)	30.7 (26.925 – 34)	0.881
HbA1C before, %	7.9 (7 – 9)	8.2 (7.2 – 10)	0.005
Poor glycemic control (HbA1c>7.5), n (%)	154 (63.6)	160 (70.5)	0.118
T2D chronic complication			
Diabetic nephropathy, n (%)	71 (29.3)	54 (23.8)	0.210
Diabetic neuropathy, n (%)	160 (66.1)	147 (64.8)	0.771
Diabetic retinopathy, n (%)	119 (49.2)	98 (43.2)	0.196
Diabetic foot, n (%)	43 (17.8)	26 (11.5)	0.067
Myocardial infarction, n (%)	19 (7.9)	31 (13.7)	0.051
Stroke, n (%)	11 (4.5)	27 (11.9)	0.004
No complication, n (%)	51 (21.1)	60 (26.4)	0.120
T2D treatment			
No medical treatment, n (%)	8 (3.3)	18 (7.9)	0.042
Metformin, n (%)	161 (66.5)	156 (68.7)	0.623
Sulfonylureas, n (%)	86 (35.5)	68 (30)	0.203
DPP-4 inhibitors, n (%)	20 (8.3)	10 (4.4)	0.093
GLP-1 agonists, n (%)	9 (3.7)	13 (5.7)	0.383
SGLT-2 antagonists, n (%)	21 (8.7)	33 (14.5)	0.059
PPAR-γ agonists, n (%)	3 (1.2)	0 (0)	0.249
Human insulin, n (%)	58 (24)	36 (15.9)	0.029
Insulin analogs, n (%)	30 (12.4)	53 (23.3)	0.002
COVID-19 history			
COVID-19 severity (WHO), n (%)			
Mild	107 (44.2)	85 (37.4)	<0.001
Moderate without hospitalization	91 (37.6)	55 (24.2)	
Moderate with hospitalization	40 (16.5)	65 (28.6)	
Severe	4 (1.7)	22 (9.7)	
No treatment, n (%)	23 (9.5)	14 (6.2)	0.230
Supplements/NSAIDs, n (%)	203 (83.9)	190 (83.7)	0.999
Antibiotics, n (%)	157 (64.9)	152 (67)	0.697
O ₂ therapy, n (%)	61 (25.2)	71 (31.3)	0.152
Steroids, n (%)	61 (25.2)	97 (42.7)	<0.001
Mechanical ventilation, n (%)	1 (0.4)	16 (7)	<0.001

The data are presented as the Me (Q_I - Q_{III}) or n (%); BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; WHO, World Health Organization; PCS, post-COVID-19 syndrome.

Bold values indicate significant changes.



HbA1c than did those in the comparison group (8.2% (7.2 – 10) vs 7.9% (7 – 9); $p=0.005$) (Table 1). Surprisingly, the mean duration of T2D was lower in the main group 10 (3–15) years as compared to the comparison group – 11 (7 – 16) years ($p=0.015$) (Table 1). This finding was explained by the increased incidence of newly diagnosed T2D during the COVID-19 pandemic, representing one of the clinical phenotypes of PCS. The number of patients with newly developed T2D was 43 out of 224 patients in the main group (18.9%), while only 17 individuals with newly diagnosed T2D were identified in the comparison group (7.0%; $p<0.001$) (Table 1). In sub analysis patient with new-onset T2D from PCS group characterized with more aggressive presentation as compared to matched patient from comparison group (7.0 (6.5 – 8.8) vs 7.8% (6.5 – 9.4); $p=0.344$). We did not find significant differences in the age of patients with new T2D between groups (57.0 (47.5 – 69.0) vs 58.0 (45.0 – 64.0) years, $p=0.582$). Surprisingly, patients with new-onset T2D in PCS group had lower weight (88.0 (80.0 – 96.0) vs 97.0 (85.0 – 109.0) kg; $p=0.043$) and BMI (28.4 (25.2 – 31.2) vs 31.5 (28.4 – 38.1) kg/m²; $p=0.021$) as compared to those with no PCS.

It is also worth noting that patients with PCS had a greater incidence of diabetic macrovascular complications: 13.7% and 11.9% of PCS patients reported myocardial infarction and stroke, respectively, during anamnesis (Table 1). In patients without PCS, a significantly lower prevalence of cardiovascular events was reported in their medical history: 7.9% for myocardial infarction ($p=0.051$) and 4.5% for stroke ($p=0.004$). The incidence of microvascular T2D complications did not differ significantly between the groups (Table 1).

PCS was associated with a greater rate of hospitalization and a more severe COVID-19 course. By comparing the COVID-19 course, we found that in the comparison group, most patients demonstrated mild (107; 44.2%) or moderate COVID-19 without hospitalization (91; 37.6%), and only a relatively small portion of the group had a moderate course of hospitalization (40; 16.5%) or suffered from severe COVID-19 (4; 1.7%) (Table 1). In contrast, approximately 40% of the main group reported severe (22; 9.7%) or

moderate disease, with hospitalization (65; 28.6%) impacting further PCS development ($p<0.001$) (Table 1).

To what extent can treatment affect the risk of PCS?

Importantly, PCS development was associated with a higher rate of noncompliance with antidiabetic medications: 7.9% of patients in the main group didn't follow treatment recommendations, while the percentages were less than half in the comparison group (3.3%; $p=0.042$) (Table 1). We also found a difference in the rate of insulin and its analog administration between the observed groups: patients without PCS were more often administered human insulin than were those in the main group (24% vs 15.9%; $p=0.029$), where insulin analogs were used more often (23.3% vs 12.4%; $p=0.002$) (Table 1). In terms of the treatment of T2D, we did not find significant differences among the prescribed anti-diabetic drugs (ADDs) between the groups (Table 1).

There were also peculiarities related to COVID-19 treatment. Considering the increased rate of hospital admission and severe COVID-19 history, the PCS group reported a significantly increased rate of steroid prescription (42.7% vs 25.2%; $p<0.001$) and mechanical ventilation (7% vs 0.4%; $p<0.001$) due to the severity of COVID-19. At the same time, we did not find differences in the prescription of NSAIDs, antibiotics or O₂ therapy between the groups (Table 1).

Is there a link between obesity and PCS?

Obese people with T2D were more frequently diagnosed with moderate and severe forms of COVID-19 infection as compared to patients with BMI<30 (46.1% vs 30.0%, $p=0.011$; Table 2). Besides, glucocorticoid prescription was more frequent in obese patients

TABLE 2 The sub analysis for distribution of clinical parameters, COVID-19 and T2D history depending on presence of obesity in patients of PCS group.

Parameter	BMI $\leq$ 30 kg/m ² (n=110)	BMI>30 kg/m ² (n=117)	p
Age, years	61.0 (53.0 – 66.3)	62.0 (55.0 – 68.0)	0.308
Age over 60 years, n (%)	61 (55.5)	73 (62.4)	0.288
Females, n (%)	63 (57.3)	61 (52.1)	0.437
T2D duration, years	8.5 (2.8 – 14.0)	11.0 (5.0 – 17.0)	0.013
Newly diagnosed diabetes, n (%)	27 (24.5)	16 (13.7)	0.037
Weight, kg	78.0 (68.0 – 87.0)	99.0 (89.5 – 110.0)	<0.001
Height, cm	172.0 (165.0 – 179.0)	167.0 (162.5 – 176.0)	0.042
BMI, kg/m ²	26.9 (24.0 – 28.0)	33.7 (32.0 – 37.1)	<0.001
HbA1C before, %	8.2 (7.2 – 10.0)	8.3 (7.2 – 10.0)	0.991
T2D chronic complication			
Diabetic nephropathy, n (%)	24 (21.8)	30 (25.6)	0.499
Diabetic neuropathy, n (%)	65 (59.1)	82 (70.1)	0.083
Diabetic retinopathy, n (%)	45 (40.9)	53 (45.3)	0.505
Diabetic foot, n (%)	11 (10.0)	15 (12.8)	0.505
Myocardial infarction, n (%)	13 (11.8)	18 (15.4)	0.434
Stroke, n (%)	16 (14.5)	11 (9.4)	0.232
No complication, n (%)	31 (28.2)	29 (24.8)	0.562
T2D treatment			
No medical treatment, n (%)	9 (8.2)	9 (7.7)	0.891
Metformin, n (%)	68 (61.8)	87 (74.4)	0.090
Sulfonylureas, n (%)	31 (28.2)	37 (31.6)	0.572
DPP-4 inhibitors, n (%)	5 (4.5)	5 (4.3)	0.921
GLP-1 agonists, n (%)	3 (2.7)	10 (8.5)	0.059
SGLT-2 antagonists, n (%)	18 (16.4)	15 (12.8)	0.449
Human insulin, n (%)	14 (12.7)	22 (18.8)	0.210
Insulin analogs, n (%)	31 (28.2)	22 (18.8)	0.095
COVID-19 history			
COVID-19 severity (WHO), n (%)			
Mild	51 (46.4)	34 (29.1)	0.011
Moderate without hospitalization	26 (23.6)	29 (24.8)	
Moderate with hospitalization	28 (25.5)	37 (31.6)	
Severe	5 (4.5)	17 (14.5)	
No treatment, n (%)	8 (7.3)	6 (5.1)	0.488
Supplements/NSAIDs, n (%)	94 (85.5)	96 (82.1)	0.502
Antibiotics, n (%)	70 (63.6)	82 (70.1)	0.302
O ₂ therapy, n (%)	28 (25.5)	43 (36.8)	0.067
Steroids, n (%)	34 (30.9)	63 (53.8)	<0.001
Mechanical ventilation, n (%)	2 (1.8)	4 (3.4)	0.452

The data are presented as the Me (Q_I - Q_{III}) or n (%); BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; WHO, World Health Organization; PCS, post-COVID-19 syndrome.

Bold values indicate significant changes.

with T2D (53.8% vs 30.9%; $p < 0.001$; **Table 2**) during the COVID-19 course. The data representing clinical parameters, COVID-19 and T2D history in PCS group with respect to obesity are presented in **Table 2**. Important that T2D duration in normal/overweight patients was significantly shorter as compared to obese (8.5 (2.8 – 14.0) vs 11.0 (5.0 – 17.0) years, $p = 0.013$). This finding can be explained by the higher occurrence of newly onset T2D in PCS group (**Table 2**). The profile of T2D complication and anti-diabetic treatment didn't differ significantly between subgroups (**Table 2**). Moreover, there were no significant differences in PCS symptoms in T2D patients regarding obesity (**Figure 1B**).

It is worth noting that patients with and without PCS did not differ in BMI (**Table 1**). Similarly, there were no differences in the incidence of obesity between PCS and comparison groups. The shares of people with obesity comprised 51.5% (117 of 227) among the PCS group being comparable with the value in the comparison group (116 of 242; 47.8%; $p = 0.435$). Finally, among 233 T2D patients with comorbid obesity, about half (117; 50.2%) reported PCS symptoms while the rest – no, demonstrating no impact of obesity on PCS development in the observed cohort.

Thus, comorbid obesity aggravated COVID-19 severity but did not impact PCS development in patients with T2D.

Uncovering the prognostic factors contributing to PCS

Univariate logistic regression analysis revealed the following independent predictors of PCS development in patients with T2D: newly diagnosed T2D ($p < 0.001$), poor glycemic control with an HbA1c above 9.2% ($p < 0.001$), history of myocardial infarction ($p = 0.044$) or stroke ($p = 0.005$), treatment of T2D with insulin analogs ($p = 0.002$), moderate-to-severe COVID-19 course ($p < 0.001$), history of treating COVID-19 with glucocorticoids ($p < 0.001$) and mechanical ventilation ($p = 0.005$). In contrast, the use of human insulin (OR 0.598; 95% CI 0.377–0.950; $p = 0.029$) had a protective effect on PCS development (**Table 3**).

To select the most informative risk factors, multifactorial logistic regression analysis was applied. As a result of the selection, the following 8 independent factors associated with the risk of PCS development in T2D patients were selected: newly diagnosed T2D (OR 4.86; 95% CI 2.55 – 9.28; $p < 0.001$), female sex (OR 1.29; 95% CI 0.86 – 1.94; $p = 0.220$), COVID-19 severity (OR 1.35 95% CI 1.05 – 1.70; $p = 0.018$), presence of myocardial infarction (OR 2.42 95% CI 1.26 – 4.64; $p = 0.002$) and stroke (OR 3.68 95% CI 1.70 – 7.96; $p = 0.001$) in anamnesis, HbA1c above 9.2% (OR 2.17 95% CI 1.37 – 3.43; $p = 0.001$), use of insulin analogs (OR 2.28 95% CI 1.31 – 3.94; $p = 0.003$) vs human insulin (OR 0.67 95% CI 0.39 – 1.15; $p = 0.146$), as specified in **Table 4**. The AUROC of the model was 0.74 (95% CI 0.697 – 0.779; $p < 0.001$) (**Figure 2A**). This model demonstrated modest accuracy, as presented in **Table 5**.

In the second stage, we built PNN models based on nonlinear relationships between variables and outcomes. We used a multilayer perceptron (MLP) with one hidden layer. The architecture of the

hidden layer had 3 neurons with a logistic activation function. According to the ROC analysis, the AUC for the MLP model was 0.808 (95% CI 0.770 – 0.843, $p < 0.001$) (**Figure 2B**). The cutoff value for this model was chosen based on the Youden index (> 0.490). When applying the optimal threshold, the following characteristics of the model were detected: sensitivity, 71.4% (95% CI 65.0 – 77.2%); specificity, 76.0% (95% CI 70.1 – 81.3%); PPV, 73.6% (95% CI 68.7 – 78.0%); and NPV, 73.9% (95% CI 69.5 – 77.9%) (**Table 5**). The forecasting results using neural networks were significantly better than those of the logistic model ($p < 0.001$). The results of pairwise comparisons of the ROC curves are presented in **Figure 2C**. This indicates the presence of nonlinearity in the relationship between PCS risk and factor attributes that cannot be taken into account in a simple regression model.

Discussion

Although high BMI and diabetes have been recognized as risk factors for developing severe COVID-19 and PCS, there are still no clearly articulated predictors of PCS development in T2D patients who restrict preventive measures for improving patient outcomes and quality of life (30). This study revealed the key risk factors associated with the risk of PCS development in T2D patients.

By applying various types of logistic regression analysis and PNN, we identified risk factors, including female sex, COVID-19 severity and corresponding mechanical ventilation experience, newly diagnosed during COVID-19 diabetes and an HbA1c higher than 9.2%, as well as myocardial infarction or stroke in medical history, as key risk factors for PCS prediction. Various studies of PCS prognosis have also revealed the prognostic role of different factors. Despite the variability of the results, the ability of core factors, including female sex and COVID-19 severity, to predict PCS has been underscored in different studies. Maglietta et al. in systematic review demonstrated the role of female sex and acute disease severity (31). Lemhöfer et al. reported that female sex, preexisting coagulation disorders and coronary artery disease were associated with a higher PCS rate (32). Similarly, in multivariate analysis, Zemni et al. showed that female sex, preexisting comorbidities, duration of acute COVID-19 illness, hospitalization, number of COVID-19 episodes and vaccination against SARS-CoV-2 are important in defining the risk of PCS development (33). These data obtained from the whole population analysis are consistent with our findings supporting the role of sex and acute viral infection severity. In this study, involving exclusively T2D patients, additional factors, including T2D severity and insulin treatment, were found to be essential for estimating the probability of PCS.

Diabetes is associated with a high risk of adverse outcomes of COVID-19 infection and PCS (30). On the other hand, the current study did not confirm that the presence of T2D was a risk factor for long-term symptoms of PCS (34). According to the obtained results, patients with and without T2D who recovered from COVID-19 at 7.2 (SD 0.6) months after hospital discharge had similar incidence

TABLE 3 Univariate logistic regression analysis.

Variables		Event/Total	Odds ratio	95% CI	p
Diab foot	No	201/400	0.599	0.354-1.012	0.055
	Yes	26/69			
Diabetic nephropathy	No	173/344	0.752	0.498-1.135	0.175
	Yes	54/125			
Diabetic retinopathy	No	129/252	0.785	0.546-1.130	0.193
	Yes	98/217			
Diabetic neuropathy	No	80/162	0.942	0.643-1.378	0.757
	Yes	147/307			
Age	<=60 Y	93/205	1.241	0.861-1.790	0.247
	>60 Y	134/264			
T2D duration	Long-term	184/409	3.093	1.707-5.604	<0.001
	New onset	43/60			
Gender	Male	103/230	1.33	0.925-1.912	0.124
	Female	124/239			
No complication	No	167/358	1.346	0.878-2.063	0.173
	Yes	60/111			
Myocardial infarction	No	196/419	1.856	1.016-3.391	0.044
	Yes	31/50			
HbA1c	>9.2	148/342	2.157	1.421-3.276	<0.001
	<=9.2	79/127			
Stroke	No	200/431	2.835	1.371-5.860	0.005
	Yes	27/38			
T2D treatment					
PPAR-γ agonists	No	227/466	0.15	0.0077-2.928	0.191
	Yes	0/3			
DPP-4 inhibitors	No	217/439	0.512	0.234-1.118	0.093
	Yes	10/30			
Human insulin	No	191/375	0.598	0.377-0.950	0.029
	Yes	36/94			
Sulfonylureas	No	159/315	0.776	0.527-1.143	0.199
	Yes	68/154			
Metformin	No	71/152	1.098	0.745-1.618	0.635
	Yes	155/316			
GLP-1 agonists	No	214/447	1.573	0.659-3.754	0.308
	Yes	13/22			
SGLT-2 inhibitors	No	194/415	1.79	1.002-3.198	0.051
	Yes	33/54			
Insulin analogs	No	174/386	2.152	1.318-3.516	0.002
	Yes	53/83			

(Continued)

TABLE 3 Continued

Variables		Event/Total	Odds ratio	95% CI	p
T2D treatment					
No treatment	No	209/443	2.519	1.073-5.914	0.034
	Yes	18/26			
COVID-19 history					
No treatment	No	213/432	0.626	0.314-1.249	0.184
	Yes	14/37			
Supplements/NSAIDs	No	37/76	0.987	0.604-1.613	0.957
	Yes	190/393			
Antibiotics	No	75/160	1.097	0.749-1.608	0.476
	Yes	152/309			
O ₂ therapy	No	156/337	1.35	0.902-2.022	0.145
	Yes	71/132			
Steroids	No	130/311	2.214	1.497-3.275	<0.001
	Yes	97/158			
COVID severity	<=2	140/338	2.796	1.833-4.266	<0.001
	>2	87/131			
Mechanical ventilation	No	211/452	18.275	2.403-138.973	0.005
	Yes	16/17			

Bold values indicate significant changes.

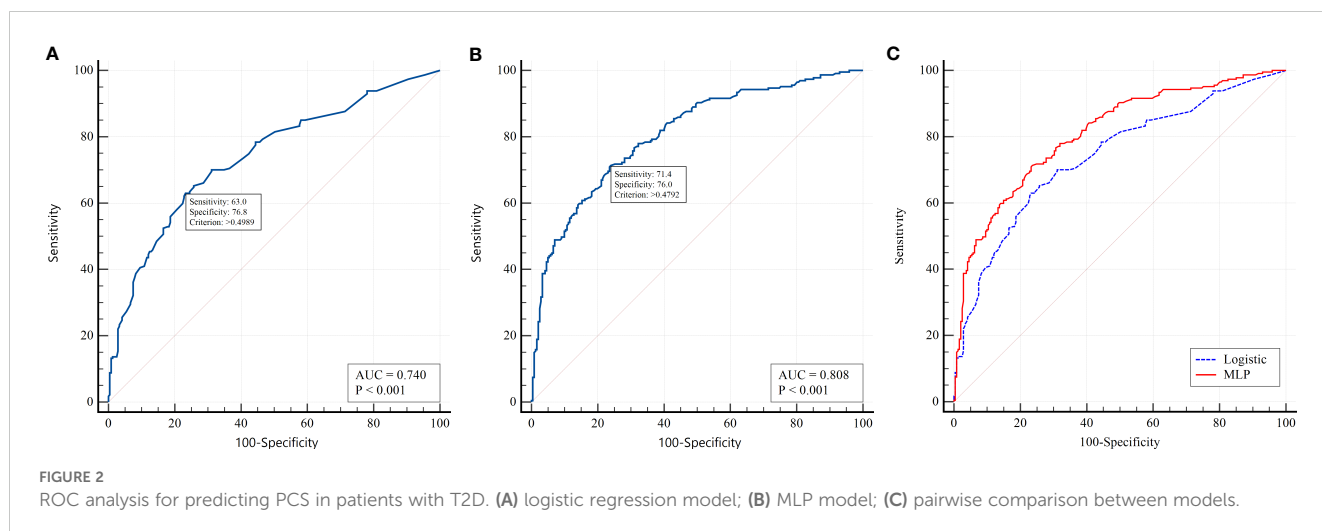
rates of PCS symptoms (1.06, 95% CI 0.92-1.24; $p=0.372$) (34). Therefore, additional factors influencing the outcome of COVID-19 infection should be investigated.

Another challenge which is actively debated is assessment of preadmission use of different ADD for on COVID-19 adverse

outcomes, mortality as well PCS development and severity. Recent studies revealed that pretreatment with metformin, GLP-1RA, and SGLT-2i was associated with a lower mortality rate, main adverse outcomes and hospitalization in patients with COVID-19 and T2D (35, 36). DPP-4i use was associated with a statistically

TABLE 4 Coefficients of the 8-factor logistic regression model for PCS risk prediction.

Factor		$b \pm m$	p	OR (95% CI)
COVID severity		0.29 ± 0.12	0.018	1.35 (1.05 – 1.70)
Mechanical ventilation		2.85 ± 1.08	0.008	17.4 (2.11 – 143)
Myocardial infarction		0.88 ± 0.33	0.008	2.42 (1.26 – 4.64)
Gender (female vs male)		0.25 ± 0.21	0.220	1.29 (0.86 – 1.94)
Stroke		1.30 ± 0.39	0.001	3.68 (1.70 – 7.96)
HbA1c (>9.2 vs ≤9.2)		0.77 ± 0.23	0.001	2.17 (1.37 – 3.43)
T2D duration	Long-term	Reference		
	New onset	1.58 ± 0.33	<0.001	4.86 (2.55 – 9.28)
Insulin	No insulin	Reference		
	Human insulin	-0.40 ± 0.28	0.146	0.67 (0.39 – 1.15)
	Insulin analogs	0.82 ± 0.28	0.003	2.28 (1.31 – 3.94)



significant increase in the risk of hospitalization, admission (35) to the ICU and mortality (36). Treatment with insulin is a risk factor for hospitalization and increased mortality (36, 37). The effects of sulfonylurea, thiazolidinedione, and alpha-glucosidase inhibitors on mortality are neutral (36). In contrast, the current study did not find a significant association between at-home ADD administration and mortality or adverse outcomes in patients with T2D admitted for COVID-19 (38). Recent data regarding the association between common T2D treatments and PCS development are scarce and limited to several reports on the protective effects of metformin (39–41). For instance, a recent multicenter, randomized, quadruple-blind, parallel-group, phase 3 trial demonstrated that outpatient treatment with metformin reduced the PCS incidence by approximately 41% (42). In our study, we noticed that insulin analogs significantly increased the risk of PCS development; in contrast, the use of human insulin had a protective effect. The other types of ADDs were neutral.

TABLE 5 Diagnostic accuracy of the proposed models for predicting PCS.

Parameter	8-factors logistic	8-factors MLP
Cutoff value	>0.4989	>0.4792
Sensitivity, % (95% CI)	63.0 (56.4 - 69.3)	71.4 (65.0 - 77.2)
Specificity, % (95% CI)	76.8 (70.9 - 81.9)	76.0 (70.1 - 81.3)
NPV, % (95% CI)	68.8 (64.7 - 72.6)	73.9 (69.5 - 77.9)
PPV, % (95% CI)	71.9 (66.5 - 76.6)	73.6 (68.7 - 78.0)
-LR, (95% CI)	0.48 (0.40 - 0.58)	0.38 (0.30 - 0.47)
+LR, % (95% CI)	2.71 (2.11 - 3.48)	2.98 (2.34 - 3.78)
AUC	0.740	0.808
95% CI	0.697 - 0.779	0.770 - 0.843
p (AUC)	<0.001	<0.001

NPV, negative predictive value; PPV, positive predictive value; LR, likelihood ratio; AUC, area under the ROC curve; 95% CI, 95% confidence interval for the AUC.

A close association between T2D and COVID-19 emerged early during the pandemic and is still active (43–45). A history of diabetes in subjects with acute SARS-CoV-2 infections was shown to worsen all outcomes and increase mortality (46). Although the respiratory system is the primary target of SARS-CoV-2, many other organs and cells can be affected by the virus, including the endothelium, cardiomyocytes, immune cells and β -cells of the pancreas. In fact, diabetes and SARS-CoV-2 infection share two essential commonalities - inflammatory pathway activation and multiorgan involvement in pathological processes (47, 48). This can result in manifestations of various severe pathologies, including acute cardiovascular dysfunction, digestive system disorders, neurological complications and metabolic disturbances.

Both severe COVID-19 and inefficient glucose control aggravated PCS development in T2D patients. However, there is a bidirectional interplay between COVID-19 and T2D (43), establishing a vicious cycle that facilitates the development of complications (49). SARS-CoV-2 infection and diabetes share two fundamental features: an inflammatory state and multiorgan involvement and damage (50). Notably, the close relationship between immunity and the endocrine system impacts immune cell functionality and the response to viruses. For instance, insulin can directly regulate immune cells, including T-lymphocytes, which are responsible for antiviral immunity (51). Both CD4+ and CD8+ T cells express insulin receptors, which are involved in facilitating glucose uptake and promoting glycolytic metabolism during T-cell activation (52). Moreover, an acute decrease in insulin levels impairs CD8+ T-cell responses to infection, whereas the injection of basal insulin increases the antiviral potential of these cells (53). Hyperglycemia directly undermines the key function of immune cells (54). High blood glucose is related to impaired cytotoxicity of CD8+ and NK cells, as well as abnormal cytokine production by CD4+ T cells, in patients with T2D following infection (55). In addition, HbA1c was shown to positively correlate with the course of infections induced by different pathogens, impacting both disease duration and severity (51). This mechanism could be related to the stimulatory effect of hyperglycemia on the replication of several pathogens (54), impeding the ability of the immune system to fight infectious agents. Thus, our findings showed that poor glycemic

control or the use of insulin analogs instead of human insulin increased the risk of PCS development in T2D patients after COVID-19.

We also found that a history of myocardial infarction or stroke can significantly increase the risk of PCS. This finding is consistent with previous findings demonstrating the impact of coronary artery disease on increasing the rate of PCS. Similarly, cardiovascular comorbidities and cerebrovascular events were also shown to enhance the probability of PCS (56). Both myocardial infarction and stroke have common mechanisms in their pathogenesis based on the compromised regulation of the blood clotting system (platelet aggregation and coagulation cascades), endothelial dysfunction, mild long-term inflammation and oxidative stress (57). Importantly, most of these pathophysiological processes interact with theories about the mechanisms underlying PCS development. In addition to persisting viral reservoirs and sustained inflammation, with autoimmune components, dysfunction of the endothelium and corresponding alterations in blood clotting have been underscored in PCS pathogenesis (58, 59). Notably, endothelial dysfunction, inflammation and blood clotting are closely related to myocardial infarction and stroke. These mechanisms are also main players in diabetic progression and complication development. Therefore, patients who experience myocardial infarction and stroke are at high risk for PCS and should be considered for preventing PCS complications. Thus, patients who experience severe COVID-19, especially those on mechanical ventilation, are at greater risk for long-term PCS, which can affect both their physical and mental health.

Finally, we found that patients with T2D manifested during acute COVID-19 infections more frequently observed in normal/overweight persons and characterized with more aggressive presentation as compared to matched patient with onset of T2D before COVID-19. This finding addresses recent scientific discussions of a new specific type of diabetes. It's still debatable if this phenomenon represents abrupt onset of classical type 1 and type 2 diabetes or a new type of diabetes? Preliminary studies have provided evidence that β -cell infection may be involved in COVID-19 pathogenesis or, alternatively, that pancreatic infection may impact β cells by changing their local microenvironment. The precise underlying mechanisms are not clearly defined, the existing research studies suggests that the pathogenesis of new-onset diabetes due to COVID-19 might be linked to direct viral effects on pancreatic islets as well as systemic inflammatory responses that disrupt glucose metabolism (60). SARS-CoV-2 uses ACE2 to enter human cells and TMPRSS2 for 'priming' (61). Both proteins are highly expressed in gastrointestinal epithelial cells, pancreatic ductal, acinar and islet cells (62). SARS-CoV-2 is also able to cause diffuse severe endotheilitis of the submucosal vessels in several anatomical sites, and these changes, in turn, cause diffuse microischemic disease (63). Similar ischemic damage could occur in the pancreas due to expression of ACE2 isoform in pancreatic microvasculature (64). Infected pancreatic islets demonstrated reduced glucose-stimulated insulin secretion, fewer insulin granules (65, 66) and characterized with increased islet-cell apoptosis that may be due to the viral spike

protein (60). Müller et al. also suggested that infected cells may lose their hormone content via de-differentiation (65). Data from current studies at least partly could give the background for more aggressive presentation of T2D obtained by our results.

Limitations

The study was based on questionnaire results that can impact the accuracy of the data and details concerning treatment regimens. When recording the COVID-19 history, there were no data documenting the test systems used for the diagnostics, viral load and vaccination against SARS-CoV-2.

Conclusion

This study revealed several risk factors facilitating PCS development in T2D patients in Ukraine. We found that patients who were newly diagnosed with T2D, had an HbA1c above 9.2%, had previous cardiovascular or cerebrovascular events, and had severe COVID-19 associated with mechanical lung ventilation were at high risk for PCS development. The developed predictive PNN model allows us to assess the probability of PCS in T2D patients and identify high-risk groups for tailoring their treatment during viral infection.

New-onset T2D which occur during or after acute COVID-19 phase more frequently observed in normal/overweight persons and characterized with more aggressive presentation as compared to matched patient with onset of T2D before COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Bogomolets National Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AM: Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft. VY: Investigation, Methodology, Writing – original draft. SZ: Formal analysis, Methodology, Writing – review & editing. YI: Investigation, Methodology, Writing – original draft. VG: Data curation, Formal analysis, Methodology, Writing –

review & editing. ZS: Investigation, Methodology, Writing – review & editing. TF: Formal analysis, Methodology, Writing – review & editing. OS: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – original draft. NK: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The work resulting in this publication was funded by the National Research Foundation of Ukraine under grant agreement No. 2022.01/0089 “The optimization of medical care to patients with type 2 diabetes during the war and postwar periods”.

References

- Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet (London England)*. (2023) 402:203–34. doi: 10.1016/S0140-6736(23)01301-6
- Yousri NA, Suhre K, Yassin E, Al-Shakaki A, Robay A, Elshafei M, et al. Metabolic and metabo-clinical signatures of type 2 diabetes, obesity, retinopathy, and dyslipidemia. *Diabetes*. (2022) 71:184–205. doi: 10.2337/db21-0490
- Marushchak M, Kozak K, Krynytska I. Comorbid overweight/obesity and chronic pancreatitis exacerbate the dyslipidemia progression in type 2 diabetic patients. *Endocrine Regulations*. (2022) 56:168–77. doi: 10.2478/enr-2022-0018
- Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. *Int J antimicrobial Agents*. (2020) 56:106054. doi: 10.1016/j.ijantimicag.2020.106054
- Sulaieva O, Dudin O, Botsun P, Pischanska S, Karpachova V, Omelianenko I, et al. The detrimental consequences of two consecutive disasters impacting cytopathology in Ukraine: COVID followed by the war. *Cytopathology: Off J Br Soc Clin Cytology*. (2023) 34:442–9. doi: 10.1111/CYT.13236
- Buchynskyi M, Kamyshna I, Lyubomirskaya K, Moshynets O, Kobylak N, Oksenysh V, et al. Efficacy of interferon alpha for the treatment of hospitalized patients with COVID-19: A meta-analysis. *Front Immunol*. (2023) 14:1069894. doi: 10.3389/FIMMU.2023.1069894
- Abumayyaleh M, Núñez Gil JJ, Viana-LLamas MC, Raposeiras Roubin S, Romero R, Alfonso-Rodríguez E, et al. Post-COVID-19 syndrome and diabetes mellitus: a propensity-matched analysis of the International HOPE-II COVID-19 Registry. *Front Endocrinol*. (2023) 14:1167087. doi: 10.3389/FENDO.2023.1167087
- Petakh P, Kobylak N, Kamyshnyi A. Gut microbiota in patients with COVID-19 and type 2 diabetes: A culture-based method. *Front Cell Infection Microbiol*. (2023) 13:1142578. doi: 10.3389/FCIMB.2023.1142578
- Cao H, Baranova A, Wei X, Wang C, Zhang F. Bidirectional causal associations between type 2 diabetes and COVID-19. *J Med Virol*. (2023) 95:e28100. doi: 10.1002/JMV.28100
- Pranata R, Henrina J, Raffaello WM, Lawrensia S, Huang I. Diabetes and COVID-19: The past, the present, and the future. *Metabolism: Clin Exp*. (2021) 121:154814. doi: 10.1016/J.METABOL.2021.154814
- Nazari P, Pozzilli P. Type 2 diabetes and Covid-19: Lessons learnt, unanswered questions and hints for the future. *Diabetes Res Clin Pract*. (2023) 204:110896. doi: 10.1016/J.DIABRES.2023.110896
- Rajpal A, Rahimi L, Ismail-Beigi F. Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *J Diabetes*. (2020) 12:895–908. doi: 10.1111/1753-0407.13085
- Yin Y, Rohli KE, Shen P, Lu H, Liu Y, Dou Q, et al. The epidemiology, pathophysiological mechanisms, and management toward COVID-19 patients with Type 2 diabetes: A systematic review. *Primary Care Diabetes*. (2021) 15:899–909. doi: 10.1016/J.PCD.2021.08.014
- Wu KCH, He Q, Bennett AN, Li J, Chan KHK. Shared genetic mechanism between type 2 diabetes and COVID-19 using pathway-based association analysis. *Front Genet*. (2022) 13:1063519. doi: 10.3389/FGENE.2022.1063519

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- Khunti K, Prato SD, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. *Diabetes Care*. (2021) 44:2645–55. doi: 10.2337/DC21-1318
- Kim SH, Arora I, Hsia DS, Knowler WC, LeBlanc E, Mylonakis E, et al. New-onset diabetes after COVID-19. *J Clin Endocrinol Metab*. (2023) 108:E1164–74. doi: 10.1210/CLINEM/DGAD284
- Mittal J, Ghosh A, Bhatt SP, Anoop S, Ansari IA, Misra A. High prevalence of post COVID-19 fatigue in patients with type 2 diabetes: A case-control study. *Diabetes Metab syndrome*. (2021) 15:102302. doi: 10.1016/j.dsx.2021.102302
- Raveendran AV, Misra A. Post COVID-19 syndrome (“Long COVID”) and diabetes: challenges in diagnosis and management. *Diabetes Metab syndrome*. (2021) 15:102235. doi: 10.1016/J.DSX.2021.102235
- Matviichuk A, Yerokhovych V, Ilkiv Y, Krasniykov D, Korcheva V, Gurbych O, et al. HbA1c and leukocyte mtDNA levels as major factors associated with post-COVID-19 syndrome in type 2 diabetes patients. *Sci Rep*. (2024) 14:25533. doi: 10.1038/S41598-024-77496-2
- Post COVID-19 condition . Available online at: <https://www.who.int/teams/health-care-readiness/post-covid-19-condition> (Accessed November 13, 2024).
- Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol*. (2022) 10:311–21. doi: 10.1016/S2213-8587(22)00044-4
- Harding JL, Oviedo SA, Ali MK, Ofotokun I, Gander JC, Patel SA, et al. The bidirectional association between diabetes and long-COVID-19 - A systematic review. *Diabetes Res Clin Pract*. (2023) 195:110202. doi: 10.1016/J.DIABRES.2022.110202
- Kirbiš S, Sobotkiewicz N, Schaubach BA, Završnik J, Kokol P, Završnik M, et al. The effects of diabetes and being overweight on patients with post-COVID-19 syndrome. *Infect Dis Rep*. (2023) 15:747–57. doi: 10.3390/IDR15060067
- Lai H, Yang M, Sun M, Pan B, Wang Q, Wang J, et al. Risk of incident diabetes after COVID-19 infection: A systematic review and meta-analysis. *Metabolism: Clin Exp*. (2022) 137:155330. doi: 10.1016/J.METABOL.2022.155330
- Clinical management of COVID-19 . Available online at: <https://www.who.int/teams/health-care-readiness/covid-19> (Accessed March 27, 2024).
- Hegazy MA, Lithy RM, Abdel-Hamid HM, Wahba M, Ashoush OA, Hegazy MT, et al. COVID-19 disease outcomes: does gastrointestinal burden play a role? *Clin Exp Gastroenterol*. (2021) 14:199–207. doi: 10.2147/CEG.S297428
- Nance SA, Muir L, Lumeng C. Adipose tissue macrophages: Regulators of adipose tissue immunometabolism during obesity. *Mol Metab*. (2022) 66:101642. doi: 10.1016/J.MOLMET.2022.101642
- El-Sayed Moustafa JS, Jackson AU, Brotman SM, Guan L, Villicaña S, Roberts AL, et al. ACE2 expression in adipose tissue is associated with cardio-metabolic risk factors and cell type composition-implications for COVID-19. *Int J Obes (2005)*. (2022) 46:1478–86. doi: 10.1038/S41366-022-01136-W
- Mykhalchyshyn G, Kobylak N, Bodnar P. Diagnostic accuracy of acyl-ghrelin and its association with non-alcoholic fatty liver disease in type 2 diabetic patients. *J Diabetes Metab Disord*. (2015) 14:44. doi: 10.1186/s40200-015-0170-1

30. D'Souza F, Buzzetti R, Pozzilli P. Diabetes, COVID-19, and questions unsolved. *Diabetes/metabolism Res Rev.* (2023) 39:e3666. doi: 10.1002/DMRR.3666
31. Maglietta G, Diodati F, Funtoni M, Lazzarelli S, Marcomini B, Patrizi L, et al. Prognostic factors for post-COVID-19 syndrome: A systematic review and meta-analysis. *J Clin Med.* (2022) 11:1541. doi: 10.3390/JCM11061541
32. Lemhöfer C, Bahmer T, Baumbach P, Besteher B, Boekel A, Finke K, et al. Variations and predictors of post-COVID syndrome severity in patients attending a post-COVID outpatient clinic. *J Clin Med.* (2023) 12:4013. doi: 10.3390/JCM12124013
33. Zemni I, Gara A, Bennisrallah C, Ezzar S, Kacem M, Chokri R, et al. Incidence and risk factors of post COVID-19 syndrome: a Tunisian cohort study. *BMC Infect Dis.* (2024) 24:461. doi: 10.1186/S12879-023-08949-8
34. Fernóandez-De-las-Penas C, Guijarro C, Torres-Macho J, Velasco-Arribas M, Plaza-Canteli S, Hernóandez-Barrera V, et al. Diabetes and the risk of long-term post-COVID symptoms. *Diabetes.* (2021) 70:2917–21. doi: 10.2337/DB21-0329
35. Nassar M, Abosheishaa H, Singh AK, Misra A, Bloomgarden Z. Noninsulin-based antihyperglycemic medications in patients with diabetes and COVID-19: A systematic review and meta-analysis. *J Diabetes.* (2023) 15:86–96. doi: 10.1111/1753-0407.13359
36. Nguyen NN, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, et al. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. *Metabolism: Clin Exp.* (2022) 131:155196. doi: 10.1016/J.METABOL.2022.155196
37. Dimnjaković J, Buble T, Ivanko P, Pristaš I, Brborović O, Brborović H. Association of anti-diabetic drugs and COVID-19 outcomes in patients with diabetes mellitus type 2 and cardiomyopathy. *Sci Rep.* (2024) 14:7227. doi: 10.1038/S41598-024-57871-9
38. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, et al. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. *BMC Med.* (2020) 18:359. doi: 10.1186/S12916-020-01832-2
39. McCarthy MW. Metformin as a potential treatment for COVID-19. *Expert Opin pharmacotherapy.* (2023) 24:1199–203. doi: 10.1080/14656566.2023.2215385
40. Wise J. Covid-19: Metformin reduces the risk of developing long term symptoms by 40%, study finds. *BMJ (Clinical Res ed).* (2023) 381:p1306. doi: 10.1136/BMJ.P1306
41. COVID-19 update: Metformin to prevent long COVID? *Med letter Drugs Ther.* (2023) 65:87–8. doi: 10.58347/TML.2023.1677E
42. Bramante CT, Buse JB, Liebovitz DM, Nicklas JM, Puskarich MA, Cohen K, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *Lancet Infect Dis.* (2023) 23:1119–29. doi: 10.1016/S1473-3099(23)00299-2
43. Lima-Martínez MM, Carrera Boada C, Madera-Silva MD, Marín W, Contreras M. COVID-19 and diabetes: A bidirectional relationship. *Clinica e investigación en arteriosclerosis: publicación oficial la Sociedad Española Arterioscler.* (2021) 33:151–7. doi: 10.1016/J.ARTERI.2020.10.001
44. Heald AH, Williams R, Jenkins DA, Stewart S, Bakerly ND, Mccay K, et al. The prevalence of long COVID in people with diabetes mellitus-evidence from a UK cohort. *EclinicalMedicine.* (2024) 71:102607. doi: 10.1016/J.ECLINM.2024.102607
45. Wu J, Zhang J, Sun X, Wang L, Xu Y, Zhang Y, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. *Diabetes Obes Metab.* (2020) 22:1907–14. doi: 10.1111/DOM.14105
46. Steenblock C, Hassanein M, Khan EG, Yaman M, Kamel M, Barbir M, et al. Diabetes and COVID-19: short- and long-term consequences. *Hormone Metab Res = Hormon- und Stoffwechselforschung = Hormones métabolisme.* (2022) 54:503–9. doi: 10.1055/A-1878-9566
47. Primorac D, Vrdoljak K, Brlek P, Pavelić E, Molnar V, Matišić V, et al. Adaptive immune responses and immunity to SARS-coV-2. *Front Immunol.* (2022) 13:848582. doi: 10.3389/FIMMU.2022.848582
48. Fleming N, Sacks LJ, Pham CT, Neoh SL, Ekinci EI. An overview of COVID-19 in people with diabetes: Pathophysiology and considerations in the inpatient setting. *Diabetic medicine: J Br Diabetic Assoc.* (2021) 38:e14509. doi: 10.1111/DME.14509
49. Fedotkina O, Sulaieva O, Ozgumus T, Cherviakova L, Khalimon N, Svetleisha T, et al. Novel reclassification of adult diabetes is useful to distinguish stages of β -cell function linked to the risk of vascular complications: the DOLCE study from northern Ukraine. *Front Genet.* (2021) 12:637945. doi: 10.3389/FGENE.2021.637945
50. Feldman EL, Savelieff MG, Hayek SS, Pennathur S, Kretzler M, Pop-Busui R. COVID-19 and diabetes: A collision and collusion of two diseases. *Diabetes.* (2020) 69:2549–65. doi: 10.2337/DBI20-0032
51. Turk Wensveen T, Gašparini D, Rahelić D, Wensveen FM. Type 2 diabetes and viral infection; cause and effect of disease. *Diabetes Res Clin Pract.* (2021) 172:108637. doi: 10.1016/J.DIABRES.2020.108637
52. Tsai S, Clemente-Casares X, Zhou AC, Lei H, Ahn JJ, Chan YT, et al. Insulin receptor-mediated stimulation boosts T cell immunity during inflammation and infection. *Cell Metab.* (2018) 28:922–934.e4. doi: 10.1016/J.CMET.2018.08.003
53. Šestan M, Marinović S, Kavazović I, Cekinović Đ, Wueest S, Turk Wensveen T, et al. Virus-induced interferon- γ Causes insulin resistance in skeletal muscle and derails glycemic control in obesity. *Immunity.* (2018) 49:164–177.e6. doi: 10.1016/J.IMMUNI.2018.05.005
54. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol.* (1999) 26:259–65. doi: 10.1111/J.1574-695X.1999.TB01397.X
55. Kumar NP, Sridhar R, Nair D, Banurekha VV, Nutman TB, Babu S. Type 2 diabetes mellitus is associated with altered CD8(+) T and natural killer cell function in pulmonary tuberculosis. *Immunology.* (2015) 144:677–86. doi: 10.1111/IMM.12421
56. Vigili de Kreutzenberg S. Long COVID-19 and diabetes mellitus: a short review. *Metab Target Organ Damage.* (2023) 3:4. doi: 10.20517/MTOD.2022.30
57. Li J, Zhou Y, Ma J, Zhang Q, Shao J, Liang S, et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. *Signal transduction targeted Ther.* (2023) 8:416. doi: 10.1038/S41392-023-01640-Z
58. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol.* (2022) 23:194–202. doi: 10.1038/S41590-021-01104-Y
59. Sherif ZA, Gomez CR, Connors TJ, Henrich TJ, Reeves WB. Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *eLife.* (2023) 12:e86002. doi: 10.7554/ELIFE.86002
60. Wu CT, Lidsky PV, Xiao Y, Lee IT, Cheng R, Nakayama T, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab.* (2021) 33:1565–1576.e5. doi: 10.1016/J.CMET.2021.05.013
61. de-Madaria E, Capurso G. COVID-19 and acute pancreatitis: examining the causality. *Nat Rev Gastroenterol Hepatol.* (2021) 18:3–4. doi: 10.1038/S41575-020-00389-Y
62. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* (2004) 203:631–7. doi: 10.1002/PATH.1570
63. Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care (London England).* (2020) 24:353. doi: 10.1186/S13054-020-03062-7
64. Fignani D, Licata G, Brusco N, Nigi L, Grieco GE, Marselli L, et al. SARS-coV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β -cells and in the human pancreas microvasculature. *Front Endocrinol.* (2020) 11:596898. doi: 10.3389/FENDO.2020.596898
65. Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab.* (2021) 3:149–65. doi: 10.1038/S42255-021-00347-1
66. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, et al. A human pluripotent stem cell-based platform to study SARS-coV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell.* (2020) 27:125–136.e7. doi: 10.1016/J.STEM.2020.06.015



OPEN ACCESS

EDITED BY

Jeff M. P. Holly,
University of Bristol, United Kingdom

REVIEWED BY

Peter Toth-Heyn,
Semmelweis University, Hungary
Arpana Parihar,
Advanced Materials and Processes Research
Institute (CSIR), India

*CORRESPONDENCE

Dimitris Grammatopoulos
✉ d.grammatopoulos@warwick.ac.uk

RECEIVED 07 August 2024

ACCEPTED 24 December 2024

PUBLISHED 04 February 2025

CITATION

Panesar A, Gharanei P, Khovanova N, Young L
and Grammatopoulos D (2025) Thyroid
function during COVID-19 and post-COVID
complications in adults: a systematic review.
Front. Endocrinol. 15:1477389.
doi: 10.3389/fendo.2024.1477389

COPYRIGHT

© 2025 Panesar, Gharanei, Khovanova, Young
and Grammatopoulos. This is an open-access
article distributed under the terms of the
[Creative Commons Attribution License \(CC BY\)](#).
The use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Thyroid function during COVID-19 and post-COVID complications in adults: a systematic review

Anisha Panesar¹, Palma Gharanei¹, Natasha Khovanova²,
Lawrence Young¹ and Dimitris Grammatopoulos^{1,3*}

¹Warwick Medical School, University of Warwick, Coventry, United Kingdom, ²School of Engineering, University of Warwick, Coventry, United Kingdom, ³Institute of Precision Diagnostics and Translational Medicine, University Hospitals Coventry and Warwickshire National Health Service (NHS) Trust, Coventry, United Kingdom

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has presented multifaceted health challenges. COVID-19 primarily targets the respiratory system but also affects multiple organ systems, including the endocrine system. Emerging evidence suggests interactions between thyroid function, the acute phase of COVID-19, and the prolonged symptoms known as post-COVID sequelae or long COVID. Several studies have reported that COVID-19 can induce thyroid dysfunction, leading to conditions such as thyroiditis and alterations in thyroid hormone levels. The mechanisms through which SARS-CoV-2 affects the thyroid include direct viral infection of thyroid cells, leading to viral thyroiditis, which causes inflammation and transient or sustained thyroid dysfunction, as well as an excessive systemic immune response (cytokine storm). This is associated with elevated levels of cytokines, such as IL-6, that disrupt thyroid function and lead to nonthyroidal illness syndrome (NTIS). Medications administered during the acute illness phase, such as corticosteroids and antiviral drugs, can also impact thyroid hormone actions. The involvement of the thyroid gland in long COVID, or postacute sequelae of SARS-CoV-2 infection, is an area not well defined, with potential implications for understanding and managing this condition. Persistent low-grade inflammation affecting thyroid function over time can lead to ongoing thyroiditis or exacerbate pre-existing thyroid conditions. Viral infections, including SARS-CoV-2, can trigger or worsen autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease. Long COVID may disrupt the hypothalamic-pituitary-adrenal (HPA) axis, which can, in turn, affect the hypothalamic-pituitary-thyroid (HPT) axis, leading to abnormal thyroid function. This review was designed to systematically capture recent literature on COVID-19-related thyroid dysfunction in the adult population, the prognostic consequences of thyroid dysfunction during COVID-19, and the effects of thyroid dysfunction on patients with long COVID. A comprehensive search of PubMed and EMBASE databases was conducted. The systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Study quality was

assessed using the Critical Appraisal Skills Programme (CASP). A total of 53 studies met the inclusion criteria. The review summarises recent findings and provides an update of the current understanding of thyroid dysfunction in COVID-19-related spectrum of disorders, underscoring the complex nature of SARS-CoV-2 infection and its far-reaching impacts on human health.

KEYWORDS

cytokines, thyroid, COVID-19, long COVID, inflammation

Introduction

Since the first case of the coronavirus disease 2019 (COVID-19), an extensive volume of literature has been published on its acute phase, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as well as its chronic counterpart, long COVID or postacute COVID syndrome. Although COVID-19 is predominately known for affecting the respiratory system, it also presents nonpulmonary symptoms, such as cardiac abnormalities, liver disease, and endocrine dysfunction (1). Among the endocrine systems affected during COVID-19 infection, thyroid dysfunction is frequently recognised, resulting from both direct and indirect mechanisms that can disrupt thyroid homeostasis.

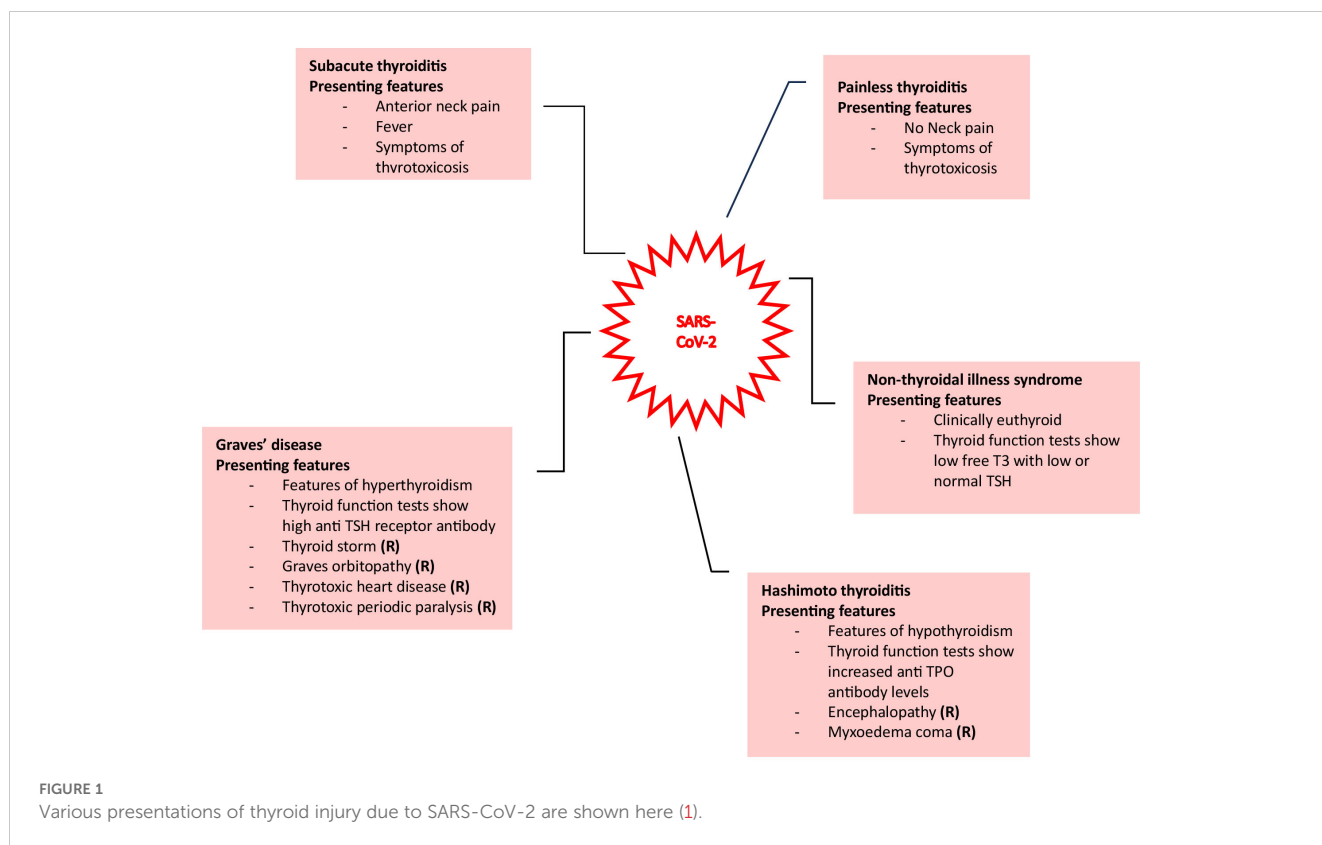
Thyroid function is tightly controlled by the hypothalamic–pituitary–thyroid axis (HPT), which regulates the secretion of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). These hormones induce the synthesis of thyroid hormones (namely 3,3',5,5'-tetraiodo-L-thyroxine (T4) and 3,5,3'-triiodo-L-thyronine (T3) triiodothyronine), which are then released into circulation. A series of negative feedback loops tightly regulate HPT axis activity (2). Moreover, the peripheral availability of T3 is controlled by deiodination of T4 and its conversion into T3 in the liver, kidneys, and muscles by deiodinase (DIO)1 and DIO2 enzymes, whereas DIO3 deiodinates T4 to produce reverse T3 (2).

Immune system regulation by thyroid hormones is well recognised, as they have been shown to influence leucocyte proliferation and migration, antibody production, and the release of cytokines, which can trigger immune responses against microbial or sterile insults. Effects in the opposite direction have also been described where the activation of inflammatory pathways and infection can affect the HPT axis and the downstream activity of thyroid hormones. This can occur indirectly through the action of cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)- α , which act on the hypothalamus, dampening TSH activity and resulting in decreased production of T3 and T4 (2). Additionally, indirect insults are also thought to play a role in autoimmune thyroid disease, as SARS-CoV-2 hyperactivates the immune response, leading to a consequent increase in IL-6 and T-cell helper (Th) lymphocytes, such as interferon (IFN)- γ -secreting Th1 cells and IL-17-secreting Th17 cells. These Th cells are produced in peripheral lymphocytes, and increased levels of these Th cells and

their associated cytokines have been reported in cases of autoimmune thyroid disease, making it plausible that they could be involved the development of autoimmune disease through apoptotic pathways in thyroid follicular cells, leading to thyroid cell destruction (3).

Alternatively, direct viral injury can occur, whereby infections such as SARS-CoV-2 and disorders like acute respiratory distress syndrome can cause destruction of thyrocytes. The manifestations of injury specifically linked to SARS-CoV-2 are displayed in Figure 1. The ability of the virus to exert these multisystem effects is thought to be due to the widespread expression of receptors for SARS-CoV-2, namely angiotensin-converting enzyme 2 (ACE2) and its coreceptor transmembrane protease serine 2 (TMPRSS2) (1). This has been shown in deceased patients due to COVID-19, where viral mRNA was detected in the blood, urine, and stool of these patients. Furthermore, immunohistochemical detection of SARS-CoV-2 viral proteins within thyroid tissue provides further evidence for the interaction of SARS-CoV-2 with ACE2 and TMPRSS2 (4–6). Additionally, multiple studies in patients with COVID-19 employing ultrasound identified markedly hypoechoic focal areas in thyroid tissue consistent with inflammation. These patients were later diagnosed with subacute or atypical thyroiditis. Piecing this evidence together, direct damage to the thyroid gland by SARS-CoV-2 is a plausible explanation for thyroid involvement during COVID-19.

Following the initial wave of disease in early 2020, chronic symptoms have been reported and investigated in survivors. In the disease setting now identified as long COVID, these symptoms are often serious and are thought to affect at least 10% of COVID-19 survivors. Fatigue, joint pain, “brain fog”, chest pain, low mood, cough, shortness of breath, headaches, and muscle pain are some of the symptoms that have been reported to be associated with long COVID (3, 7). The underlying pathogenesis of this syndrome is not completely understood; however, one hypothesis suggests that thyroid involvement, especially the transient phase of thyroid dysfunction in the convalescent period, remains an ongoing issue in some COVID-19 patients. Conversely, it is also thought that the immunological dysfunction from the virus can lead to increased antithyroid antibodies, resulting in autoimmune thyroid disease (8). Such pathological processes involve either autoantibodies to thyroid peroxidase (TPO-Ab) and thyroglobulin (Tg-Ab), leading to hypothyroidism, or TSH receptor autoantibodies (TSH-R Ab) causing hyperthyroidism (9).



A wide range of thyroid dysfunctions have been reported, with their symptoms described in Table 1. Concerns have been raised that thyroid abnormalities might be masked or remain unnoticed, as many symptoms overlap with the symptoms of COVID-19, such as intense fatigue and fever. Furthermore, the complications related to thyroid function can vary and, in extreme cases, can be life-threatening, such as subacute thyroiditis.

The global response to the pandemic is shifting towards disease prevention, with the implementation of widespread vaccination programmes and management of the long-term consequences of the disease. Therefore, a summary of the latest findings regarding thyroid dysfunction in COVID-19 could provide a timely update on the current understanding (1). The objectives of this review were to systematically evaluate recent literature on COVID-19-related thyroid dysfunction, the prognostic consequences of thyroid dysfunction during COVID-19, and the effects of thyroid dysfunction on patients with long COVID.

Methods

Search strategies and study selection

To develop the search strategy and review question, a Population, Intervention, Comparison, and Outcome (PICO) format (Table 2) was used.

A search was then carried out systematically on Medline and EMBASE, and papers in the English language published between January 2020 and April 2024 were included to ensure the results

were accurately interpreted. The search strategy, shown in Table 3, was based on the following keywords/phrases: (COVID-19 OR coronavirus disease OR long COVID OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2) AND (subacute thyroiditis OR painless thyroiditis OR subacute lymphocytic thyroiditis OR silent thyroiditis OR Graves' disease OR Hashimoto's thyroiditis OR Hashimoto's disease OR nonthyroidal illness syndrome OR euthyroid sick syndrome). These terms were used in order to ensure a broad search that covered all relevant literature. On the other hand, terms such as "autoimmune thyroiditis" were excluded to avoid ambiguity, providing more specific results and capture the most relevant studies. Specific quality control papers were also included to ensure the search retrieved appropriate publications. Furthermore, relevant secondary sources and grey literature were searched, as well as reference lists, to identify additional pertinent papers. EndNote was utilised to import and manage abstracts and full texts. Once the searches were completed, duplicates were removed. The title and abstracts, followed by the full texts, were then reviewed independently by two reviewers at separate times.

The full search strategy is shown in Table 3.

Inclusion/Exclusion criteria

Case studies and reports, observational studies, retrospective studies, prospective studies describing the clinical features and outcomes of thyroid disease, including subacute thyroiditis, painless thyroiditis, silent thyroiditis, Graves' disease, Hashimoto's thyroiditis,

TABLE 1 Types of thyroid dysfunction identified in COVID-1 patients.

Thyroid Condition	Common Symptoms	Investigations	Treatment
Subacute thyroiditis	Characteristically, it has three phases: painful swelling of the thyroid gland, hypothyroidism, and euthyroidism. Typical symptoms, such as neck pain and persistent tachycardia, are key indicators (10).	Thyroid dysfunction present as thyrotoxicosis; most cases are antithyroid antibody negative. Ultrasound of the thyroid gland will show focal hypoechoic areas. Typically, thyroid scintigraphy shows less than 2% uptake of radioactive iodine within 24 h (3).	Self-limiting; however, beta-blockers are used for symptom relief. Nonsteroidal anti-inflammatory drugs are given in mild cases to reduce inflammation and pain. Prednisolone is administered to patients with severe pain (3).
Painless thyroiditis	A variation of thyroiditis with the absence of neck pain. Other symptoms are similar to those of subacute thyroiditis (1).	Thyroid dysfunction presents as thyrotoxicosis; most cases are antithyroid antibody negative. Ultrasound of the thyroid gland shows focal hypoechoic areas. Typically, thyroid scintigraphy shows low uptake of radioactive iodine in 24 h (1).	Beta blockers are used for symptom control. Glucocorticoids are administered in severe cases (1).
Graves' disease	An autoimmune condition causes immune cells to attack the thyroid, resulting in hyperthyroidism. It can also lead to thyroid eye disease and pretibial myxoedema. Graves' disease involves increased thyroid hormone synthesis, release, and growth due to thyroid-stimulating hormone receptor antibodies (1).	Thyroid function will show thyrotoxicosis, and high levels of antithyroid-stimulating hormone receptor (TSH-R) antibodies will help confirm the diagnosis. A thyroid ultrasound will show diffuse enlargement of the thyroid gland, as well as increased vascularity. Thyroid scintigraphy will show a diffuse increase in the uptake of radioactive iodine (1).	Thionamides and beta blockers are administered (1).
Hashimoto's thyroiditis	A common autoimmune condition caused by the destruction of the thyroid gland and the presence of either antithyroid peroxidase antibodies and/or antithyroglobulin antibodies. In the short term, it can present with fatigue, weight gain, dry skin, and constipation. It typically presents with neuromuscular symptoms, with or without a goitre (11).	Thyroid function shows primary hypothyroidism with high levels of antithyroid peroxidase antibodies to help confirm the diagnosis (1).	Levothyroxine is given (1).
Non-thyroidal illness syndrome	This syndrome presents with alterations in thyroid hormones and is seen in up to 70% of hospitalised patients with critical illness, e.g., after major surgery, sepsis and SIRS, COVID-19, and other viral illnesses. Clinically, patients are euthyroid (1).	Thyroid profile exhibits low T3, high levels of reverse T3 (rT3), low or normal T4, and low or normal thyroid-stimulating hormone (TSH) (1).	Self-limiting, but close supervision is needed (1).

Thyroid condition is identified in bold.

or nonthyroidal illness syndrome, were included. Papers describing patients who were pregnant, those in the paediatric population (specifically under 18 years of age), or those with a previous history of thyroid disease, as well as letters/comments to the editor, were excluded from this review.

Case definition and diagnostic investigations

Only papers with positive COVID-19 PCR tests, confirming COVID-19 infection, were included in this review; in contrast, cases speculated to be COVID-19 were not considered further.

In terms of thyroid dysfunction investigations, in the studies included in the review, the diagnosis of subacute thyroiditis was made on thyroid function tests suggestive of thyrotoxicosis, thyroid ultrasonography showing focal hypoechoic areas, and thyroid scintigraphy showing low or absent radiotracer uptake. Painless thyroiditis would show the same investigation results as subacute thyroiditis, but in the absence of pain.

The diagnosis of Graves' disease was based on the presence of TSH-R Ab or thyroid-stimulating immunoglobulins (12), as well as the combination of suppressed TSH levels and increased free T4 levels. However, in some cases, the diagnosis of thyrotoxicosis was based on raised levels of T3, but not T4, and undetectable TSH (T3-induced thyrotoxicosis).

Diagnosis of Hashimoto's thyroiditis causing hypothyroidism was based on low or normal serum free T4 and increased serum TSH levels, along with the presence of high levels of thyroid peroxidase (TPO) autoantibodies. Additionally, thyroid

TABLE 2 PICO format.

Population	Patients over the age of 18 years with COVID-19 and no history of thyroid disease
Intervention	Awareness of thyroid abnormalities in COVID-19 patients
Comparison	Patients without COVID-19 and a history of thyroid disease
Outcomes	Whether the presence of thyroid abnormalities in COVID-19 patients affects their outcomes and recovery

Bold: components of the clinical question.

TABLE 3 Search strategy used for the databases Embase and Medline.

Database	Search strategy
Embase	1. COVID 19.mp. or exp coronavirus disease 2019/ 2. limit 1 to (English language and yr='2020 - Current*) 3. exp long COVID/or long covid.mp. 4. limit 3 to (English language and yr='2020 - Current*) 5. SARS-CoV-2.mp. or exp Severe acute respiratory syndrome coronavirus 2/ 6. limit 5 to (English language and yr="2020 -Current*) 7. 2 or 4 or 6 8. subacute thyroiditis.mp. or exp subacute thyroiditis/ 9. limit 8 to (English language and yr=*2020 - Current*) 10. 7 and 9 11. painless thyroiditis.mp. 12. limit 11 to (English language and yr="2020 - Current*) 13. subacute lymphocytic thyroiditis.mp. 14. limit 13 to (English language and yr="2020 - Current') 15. silent thyroiditis.mp. 16. limit 15 to (English language and yr=*2020 - Current") 17. 12 or 14 or 16 18. 7 and 17 19. Graves disease.mp. or exp Graves disease/ 20. limit 19 to (English language and yr="2020 - Current') 21. 7 and 20 22. Hashimoto thyroiditis.mp. or exp Hashimoto disease/ 23. limit 22 to (English language and yr="2020 - Current*) 24. 7 and 23 25. non-thyroidal illness syndrome.mp. or exp euthyroid sick syndrome/ 26. limit 25 to (English language and yr=*2020 - Current') 27. 7 and 26
Medline	1. COVID 19.mp. or exp COVID-19/ 2. limit 1 to (English language and yra"2020 - Current*) 3. long covid.mp. or exp Post-Acute COVID-19 Syndrome/ 4. limit 3 to (English language and yr="2020 -Current") 5. long covid.mp. or exp Post-Acute COVID-19 Syndrome/ 6. SARS-CoV-2.mp. or exp SARS-CoV-2/ 7. limit 6 to (English language and yr="2020 - Current") 8. 2 or 4 or 7 9. subacute thyroiditis.mp. 10. limit 9 to (English language and yr="2020 - Current") 11. 8 and 10 12. painless thyroiditis.mp. 13. limit 12 to (English language and yr="2020 - Current*) 14. subacute lymphocytic thyroiditis.mp. 15. limit 14 to (English language and yra"2020 - Current*) 16. silent thyroiditis.mp. 17. limit 16 to (English language and yr="2020 - Current*) 18. 13 or 15 or 17 19. 8 and 18 20. Graves disease.mp. or exp Graves Disease/ 21. limit 20 to (English language and yr=*2020 - Current*) 22. 8 and 21 23. Hashimoto thyroiditis.mp. or exp Hashimoto Disease/ 24. limit 23 to (English language and yre"2020 - Current*) 25. 8 and 24 26. non-thyroidal illness syndrome.mp. or exp Euthyroid Sick Syndromes/ 27. limit 26 to (English language and yr«2020 - Current') 28. 8 and 272

Database searched is identified in bold.

ultrasonography would show an enlarged thyroid gland with a hypoechoic, diffusely heterogeneous echotexture which hypoechoic micronodules.

Finally, in the studies mentioned, the diagnosis of nonthyroidal illness syndrome was based on normal serum levels of TSH but reduced serum levels of free triiodothyronine (fT3).

Data extraction

Data extraction from the included studies was organised by author, publication year, title, country, study design, number of patients included, patient data (including the age, sex, and severity of COVID-19), and thyroid characteristics. This was analysed independently by two authors and is displayed in [Supplementary Table 1](#).

Study quality assessment

A critical appraisal was completed using the Critical Appraisal Skills Programme (CASP), (<https://casp-uk.net/checklists/casp-systematic-review-checklist-fillable.pdf>). This was used to assess the quality of the studies included, as shown in [Tables 4–6](#).

Risk of bias assessment

A risk of bias assessment was completed using a customised risk of bias tool, due to the nature of each study, as shown in [Table 7](#).

Synthesis of extracted evidence

Narrative synthesis was used to critically review the latest advancements related to thyroid dysfunction and COVID-19.

Results

Search results and studies characteristics

The total number of studies identified from the searches was 53 studies. A PRISMA flow diagram, displayed in [Figure 2](#), shows the included and excluded articles, as well as the reasons for exclusion. The most common study design was case studies, and details of the findings of each study can be found in [Supplementary Table 1](#).

Case reports

The total number of patients reported with thyroid dysfunction from the case studies was 43, from 31 case studies. Subacute thyroiditis was the most commonly reported, with 64% (28 patients) of patients being diagnosed with the condition ([9, 15, 17, 21, 24, 38, 39, 41–44, 59, No. 77; 28, 45–48, 53, 60](#)). Graves' disease was reported in 21% (nine patients) of patients ([20, 23, 24, 26, 28, 32, 57, 58](#)). Hashimoto's thyroiditis was reported in 9% (four patients) of patients ([11, 28, 29](#)), and 5% (two patients) were diagnosed with painless thyroiditis ([30, 31](#)). These cases have been described from multiple countries, including Spain, the USA, Italy, Turkey, Switzerland, Korea, Singapore, and Brazil. From the case reports, most patients were women (66% of patients [29]), and the age range was between 18 and 81.

TABLE 4 Risk of bias assessment.

Studies	Publication bias	Generalisability bias	Self-selection bias	Attrition bias	Reporting bias	Confirmation bias	Confounding bias	Other sources of bias
Baldelli et al. (13)	✓	✓	✓	✓	✓	✓	✗	?
Álvarez Martín et al. (14)	✓	?	✗	✗	✓	?	✓	✓
Mehmood et al. (15)	✓	?	✗	✗	✓	?	✓	✓
Brancatella et al. (16)	✓	?	✗	✗	✓	?	✓	✓
Asfuroglu Kalkan and Ates (17)	✓	?	✗	✗	✓	?	✓	✓
Batman et al. (18)	✓	?	✗	✗	✓	✗	✓	✓
Arora et al. (19)	✓	✓	?	✗	✓	✗	✓	✓
Shermetaro and Bushman (20)	✓	?	✗	✗	✓	✗	✓	✓
Henke et al. (21)	✓	?	✗	✗	✓	?	✓	✓
Lee et al. (11)	✓	✓	?	?	✓	?	✓	✓
Muller et al. (22)	✓	?	✗	✗	✓	?	✓	✓
Franca et al. (23)	✓	?	✗	✗	✓	?	✓	✓
Nham et al. (24)	✓	?	✗	✗	✓	?	✓	✓
Peng et al. (25)	✓	?	✗	✗	✓	✓	✓	✓
Boyle and Mullally (26)	✓	?	✗	✗	✓	?	✓	✓
Lee et al. (11)	✓	?	✗	✗	✓	?	✓	✓
Rossini et al. (27)	✓	?	✗	✗	✓	?	✓	✓
Feghali et al. (28)	✓	?	✗	✗	✓	?	✓	✓
Knack et al. (29)	✓	?	✗	✗	✓	?	✓	✓
Lui et al. (1)	✓	?	✗	✗	✓	?	✗	✓
Millan et al. (30)	✓	?	✗	✗	✓	?	✓	✓
Dolkar et al. (31)	✓	?	✗	✗	✓	?	✓	✓
Sousa et al. (32)	✓	?	✗	✗	✓	?	✓	✓
A.M Urbanovych 2021	✓	?	✗	✗	✓	?	✓	✓
Asaf Harris, MD2020	✓	?	✗	✗	✓	?	✓	✓

(Continued)

TABLE 4 Continued

Studies	Publication bias	Generalisability bias	Self-selection bias	Attrition bias	Reporting bias	Confirmation bias	Confounding bias	Other sources of bias
Vassiliadi et al. (12)	✓	?	✗	✗	✓	?	?	✓
Swistek et al. (33)	✓	✗	✗	✗	✓	?	?	✓
Sparano et al. (34)	✓	✗	✗	✗	✓	✗	?	✓
Okwor et al. (35)	✓	?	✗	✗	✓	?	?	✓
Gong et al. (36)	✓	?	✗	✗	✓	?	?	✓
Schwarz et al. (37)	✓	?	✗	✗	✓	?	?	✓
Campos-Barrera et al. (38)	✓	?	✗	✗	✓	?	✓	✓
Sohrabpour et al. (39)	✓	?	✗	✗	✓	?	✓	✓
Akshay Khatri 2021	✓	?	✗	✗	✓	?	✓	✓
Whiting et al. (40)	✓	?	✗	✗	✓	?	✓	✓
Davoodi et al. (41)	✓	?	✗	✗	✓	?	✓	✓
Ruggeri et al. (42)	✓	?	✗	✗	✓	?	✓	✓
Brancatella et al. (16)	✓	?	✗	✗	✓	?	✓	✓
Hajosi-Kalcakosz et al. (43)	✓	?	✗	✗	✓	?	✓	✓
Elawady et al. (44)	✓	?	✗	✗	✓	?	✓	✓
Tjonnfjord et al. (45)	✓	?	✗	✗	✓	?	✓	✓
Chong et al. (46)	✓	?	✗	✗	✓	?	✓	✓
Sato et al. (47)	✓	?	✗	✗	✓	?	✓	✓
Al-Shammaa and Abdulkadir (48)	✓	?	✗	✗	✓	?	✓	✓
Gezer and Ecin (49)	✓	✗	✗	✗	✓	?	✓	✓
Ahn et al. (50)	✓	✗	✗	✗	✓	?	✓	✓
Edwards and Hussain (51)	✓	?	✗	✗	✓	?	✓	✓
Mondal et al. (52)	✓	✗	✗	✗	✓	?	✓	✓
De Souza et al. (53)	✓	?	✗	✗	✓	?	✓	✓
Lui et al. (1)	✓	✗	✗	✗	✓	?	✓	✓

(Continued)

TABLE 4 Continued

Studies	Publication bias	Generalisability bias	Self-selection bias	Attrition bias	Reporting bias	Confirmation bias	Confounding bias	Other sources of bias
Zou et al. (54)	✓	✗	✗	✗	✓	?	✓	✓
Wang et al. (55)	✓	✗	✗	✗	✓	?	✓	✓
Georgios Tsivgoulis et al. (56)	✓	✓	✗	✗	✓	?	✗	?
Vesselina Yanachkova and Radiana (8)	✓	?	✗	✗	✓	?	✓	✓

Key: ✓ Low risk; ? Not Clear; ✗ High risk.

All patients suspected of having subacute thyroiditis presented with symptoms such as neck pain and tenderness and hypothyroidism-related fatigue. Typical symptoms, investigations, and management are described in Table 1. One patient experienced thyrotoxicosis and was later diagnosed with subacute thyroiditis after further investigation. However, 2 months later, a diagnosis of Graves' disease was made due to fluctuating thyroid function tests (24). Two patients with painless thyroiditis exhibited the same pattern of investigations, showing signs of thyrotoxicosis, but without neck pain or tenderness (30, 31).

Among the patients who developed Graves' disease, one also experienced eye irritation in addition to the typical symptoms outlined in Table 1. Patients with untreated Graves' disease can deteriorate into life-threatening illness, as shown in two patients who experienced a thyroid storm, defined by Burch–Warsofsky point scale (BWPS) scores of 45 and 55, respectively. Two additional patients had BWPS scores of 35 and 40, indicating an impending thyroid storm. All the patients were treated with medication until they became euthyroid. Once they reached this point, they were continued on a maintenance dose (20, 26, 51).

Patients who experienced Hashimoto's thyroiditis following COVID-19 all reported fatigue as one of their symptoms. Other characteristic symptoms, investigative approaches, and management are shown in Table 1.

Retrospective studies

Altogether, the total number of retrospective studies included in this review was 12. Three focused on subacute thyroiditis post-COVID-19 (11, 18, 52), five focused on general thyroid dysfunction post COVID-19 (13, 19, 49, 50, 55), and four focused on nonthyroidal illness syndrome (NTIS) post-COVID-19 (33, 36, 37, 54).

One study focusing on subacute thyroiditis, which included a sample size of 98 patients with subacute thyroiditis after COVID-19 infection, found that the most common symptom was neck pain and tenderness, with the average time from diagnosis of subacute thyroiditis following COVID-19 being 21 days (18). Another study with a sample size of 160 found that the mean onset of subacute thyroiditis following COVID-19 was 23.8 days, whereas painless thyroiditis was reported more frequently soon after COVID-19 recovery, with a mean onset of around 10.6 days following COVID-19 infection (52). The study by Lee et al. (11), with a large sample size of 407,427, found a higher incidence rate of subacute thyroiditis (SAT) in COVID-19 patients compared to non-COVID-19 patients.

Among all five studies focusing on general thyroid dysfunction, all included patients who were diagnosed with or had clinical markers of NTIS (13, 19, 49, 50, 55). One study with a sample size of 119 identified NTIS in 18.5% of all patients, which was the most common abnormality found, followed by subclinical thyrotoxicosis, diagnosed in 14.3% of patients (50). Another study investigated 102 patients and reported similar findings, with NTIS diagnosed in 58.8% of patients (19). This was also demonstrated in the study by Baldelli et al. (13), where 28 out of 46 patients had low serum fT3 levels and were diagnosed with NTIS. The study by Gezer

TABLE 5 Summary of JBL checklist for case reports.

Author and publication year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Critical appraisal score
Álvarez Martín et al. (2021)(14)	?	✓	✓	✓	✓	✓	N/A	✓	6/7
Mehmood et al. (2020)(15)	?	✓	✓	✓	✓	✓	N/A	✓	6/7
Brancatella et al. (2020a)(16)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Asfuroglu Kalkan and Ates (2020)(17)	?	✓	✓	✓	✓	✓	N/A	✓	6/7
Henke et al. (2023)(21)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Franca et al. (2023)(23)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Nham et al. (2023)(24)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Shermetaro and Bushman (2023)(20)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Boyle and Mullally (2023)(26)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Lee et al. (2023)(11)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Feghali et al. (2021)(28)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Knack et al. (2021)(29)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Millan et al. (2020)(30)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Dolkar et al. (2022)(31)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Sousa et al. (2022)(32)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Urbanovych et al. (2021)(57)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Harris and Al Mushref (2021)(58)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Campos-Barrera et al. (2020)(38)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Sohrabpour et al. (2021)(39)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Khatri et al. (2021)(59)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Whiting et al. (2021)(40)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Davoodi et al. (2021)(41)	?	✓	✓	✓	✓	✓	N/A	✓	6/7
Ruggeri et al. (2021)(42)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Brancatella et al. (2020a)(16)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Hajosi-Kalcakosz et al. (2022)(43)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Elawady et al. (2022)(44)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Tjonnfjord et al. (2021)(45)	?	✓	✓	✓	✓	✓	N/A	✓	6/7
Chong et al. (2021)(46)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Sato et al. (2021)(47)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Al-Shammaa and Abdlkadir (2022)(48)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
Edwards and Hussain (2021)(51)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7
De Souza et al. (2022)(53)	✓	✓	✓	✓	✓	✓	N/A	✓	7/7

Key: ✓ Yes; ? Not clear; N/A, Not Applicable.

and Ecin (49) found that a low TSH level was significantly correlated with increased length of hospital stay and clinical severity, with 110 patients diagnosed with subclinical hypothyroidism. Furthermore, 116 patients from this study had low T3 levels, indicating that more than half of the sample size had clinical markers suggestive of NTIS. This was based on a sample size of 201.

The paper by Arora et al. (19) further demonstrated that low fT3 levels, which are common in NTIS, were shown to have a

TABLE 6 Summary of the CASP checklist for quantitative studies; Q7 and 8 omitted, as the results of the studies are provided in [Supplementary Table 1](#).

Author and publica- tion year	Q1	Q2	Q3	Q4	Q5 (A)	Q5 (B)	Q6 (A)	Q6 (B)	Q9	Q10	Q11	Q12	Critical appraisal score
Baldelli et al. (2021)(13)	✓	✓	✓	✓	✓	✗	✗	✗	✓	✓	✓	✓	9/12
Batman et al. (2023)(18)	✓	✓	✓	✓	✓	?	✗	✓	✓	✓	✓	✓	10/12
Arora et al. (2022)(19)	✓	✓	✓	✓	✗	?	?	?	✓	✓	✓	✓	8/12
Lee et al. (2023)(11)	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	11/12
Muller et al. (2023)(22)	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	11/12
Peng et al. (2023)(25)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	12/12
Rossini et al. (2023)(27)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	12/12
Lui et al. (1)	✓	✓	✓	✓	✓	?	?	?	✓	✓	✓	✓	9/12
Vassiliadi et al. (2021)(12)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	12/12
Swistek et al. (2022)(33)	✓	✓	✓	✓	✓	?	?	?	✓	✓	✓	✓	9/12
Sparano et al. (2022)(34)	✓	✓	✓	✓	✓	?	?	?	✓	✓	✓	✓	9/12
Okwor et al. (2021)(35)	✓	✓	✓	✓	?	?	?	?	✓	✓	✓	✓	8/12
Gong et al. (2021)(36)	✓	✓	✓	✓	✓	?	?	?	✓	✓	✓	✓	9/12
Schwarz et al. (2021)(37)	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	10/12
Gezer and Ecin (2022)(49)	✓	?	✓	✓	✓	✓	?	?	✓	✓	✓	✓	9/12
Ahn et al. (2021)(50)	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	10/12
Mondal et al. (2023)(52)	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	10/12
Lui et al. (1)	✓	✓	✓	✓	✓	✗	?	✓	✓	✓	✓	✓	10/12
Zou et al. (2020)(54)	✓	✓	✓	✓	✓	✗	?	?	✓	✓	✓	✓	9/12
Wang et al. (2020)(55)	✓	✓	?	✗	✓	✗	?	?	✓	✓	✓	✓	7/12
Vesselina Yanachkova and Radiana (2023)(8)	✓	✓	✓	✓	✓	?	?	?	✓	✓	✓	✓	9/12

Key: ✓ Low risk; ? Not Clear; ✗ High risk.

significant relationship with increased severity of COVID-19 and mortality. This is reiterated in all four studies focusing specifically on NTIS following COVID-19. For example, the paper by Swistek et al. (33) found that 28 out of 82 patients who developed NTIS died during hospitalisation, compared to 15 out of 133 patients without thyroid dysfunction during hospitalisation for COVID-19. In the paper by Gong et al. (36), the mortality rate was shown to be significantly higher in the low FT4 group of patients, and low TSH levels were shown to be independently related to 90-day mortality. Schwarz et al. (37) similarly found fT3 to be a significant independent predictor of mortality, which was echoed in the study by Zou et al. (54), which reported a significantly higher prevalence of severe events in patients diagnosed with euthyroid sick syndrome, also known as NTIS. Comparably, the study by Wang et al. (55) concluded that abnormal thyroid dysfunction was more common in severe cases of COVID-19 (47 patients out of a total of 52) than in mild or moderate cases of COVID-19 (16 patients out of a total of 52).

TABLE 7 Summary of the CASP checklist for case control studies; Q7 and Q8 omitted, as results of the studies are provided in [Supplementary Table 1](#).

Author and publication year	Q1	Q2	Q3	Q4	Q5	Q6(a)	Q6(b)	Q9	Q10	Q11
Georgios Tsvigoulis et al. (2021)(56)	✓	✓	✗	?	?	✓	✗	✓	?	?

Key: ✓ Low risk; ? Not Clear; ✗ High risk.

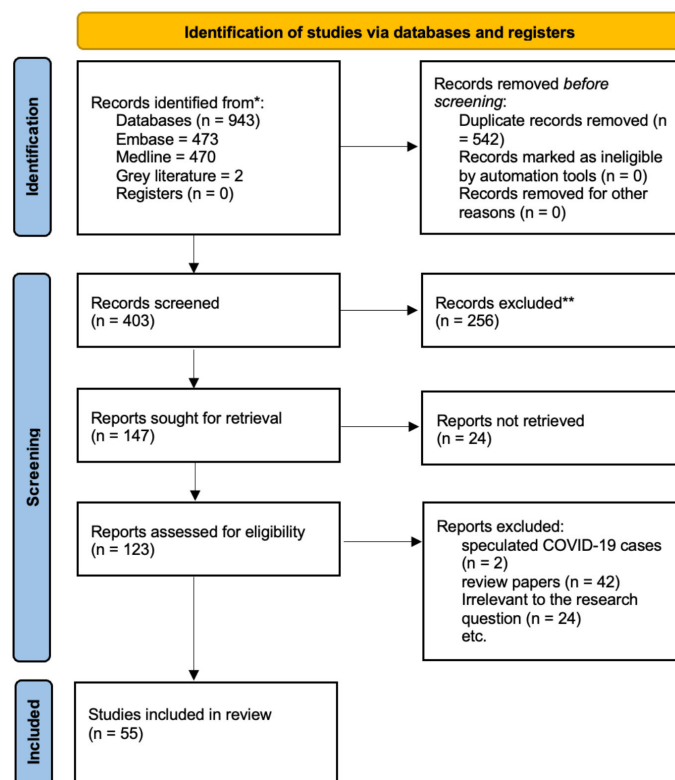


FIGURE 2

The PRISMA flowchart, depicting the searches of registers and databases, is shown here.

Prospective studies

Four of the papers included in this review were prospective studies. One study, exploring the increased prevalence of autoimmune thyroid disease after COVID-19 in a patient cohort of 494, found that the prevalence doubled in COVID-19 survivors compared to controls (27). Another study, with a patient size of 506, focusing on NTIS after COVID-19 and its impact on patient outcomes, demonstrating a 3.5-fold increased risk of diminished survival in patients with lower fT3 levels (34). Lui et al. (1) studied 191 COVID-19 survivors to investigate thyroid disease, finding that 2% had new-onset abnormal thyroid function tests. Follow-up studies from the same group described the most common symptoms experienced by patients with thyroid dysfunction post-COVID-19.

Discussion

Thyroid involvement in COVID-19

The relationship between COVID-19 infection and its impact on thyroid gland function and activity is not yet fully understood. Emerging studies suggest both direct viral injury through pathophysiological mechanisms (3) and indirect systemic and generalised inflammatory responses (5) targeting the thyroid gland.

A significant number of publications focus on the role of the cytokine storm, which causes indirect injury due to an uncontrolled systemic inflammatory response. In many patients, this is associated with NTIS (also known as euthyroid sick syndrome), which is commonly present in up to 70% of hospitalised patients that have critical illnesses, e.g., after major surgery, sepsis, SIRS, COVID-19, and other viral illnesses (61). The main cytokines involved in the COVID-19-driven inflammatory response have been identified as interleukin 6 and interleukin 1b (IL-1b) (62). These cytokines have also been found to act on the hypothalamic–pituitary–thyroid axis, altering TSH responsiveness to circulating low fT3 levels and resulting in inappropriately low/normal levels of serum TSH (Figure 3). Activation of cytokines involves a series of inflammatory signalling pathways, including nuclear factor kappa-light-chain enhancer of activated B cells (NFkB). During inflammation, NFkB has been demonstrated to upregulate deiodinase 2 (DIO2). In contrast DIO1 is downregulated with IL-1b stimulation. DIO1 has been closely linked to the pathogenesis of NTIS/ESS, as it has been shown to be greatly reduced during illness, resulting in low T3 levels. DIO1 and DIO2 mediate the peripheral conversion of circulating T4 into the biologically active hormone T3. Another deiodinase isoform, D3, is known as the key player in inactivating thyroid hormones, as it converts T4 and T3 into the biologically inactive rT3 (63).

The development of autoimmune thyroid diseases post-COVID-19 is not completely understood. A proposed hypothesis

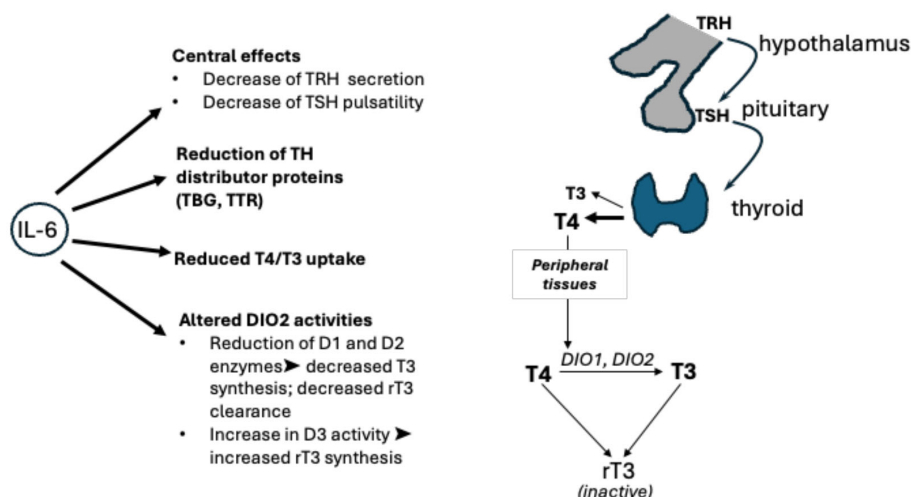


FIGURE 3

Hypothalamic–pituitary–thyroid axis: interactions between TRH, TSH, T3, and T4 along the hypothalamic–pituitary–thyroid axis are shown, alongside conversion by deiodinases 1, 2, and 3. The effects of interleukin (IL)-6 on thyroid hormone levels as shown on the left. The inflammatory cytokine acts on the hypothalamus and pituitary gland of the brain, on levels of free hormones, on transporters (TBG, TTR), and on cellular deiodinases. TBG, thyroxine binding globulin; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; TTR, transthyretin.

suggests that COVID-19 can trigger latent hyperactive reactions or instigate new-onset autoimmune disease. This reaction is thought to be linked to the “cytokine storm”, whereby the “viral infection-mediated hyperinflammatory condition” could activate the immune system, leading to autoimmune thyroid diseases such as Graves’ disease and Hashimoto’s thyroiditis. The “cytokine storm”, which leads to the overproduction of proinflammatory cytokines, is responsible for an overresponsive, uncontrolled reaction of the immune, coagulation, inflammatory, and complement systems, as well as multiorgan failure. This pathological setting can lead to death in severe cases, as the “cytokine storm” causes epithelial and endothelial cell injury, resulting in vascular leakage and increased permeability, ultimately leading to end-organ damage. In autoimmune thyroid disease, there have been reports of an increase in specific Th and cytokines. Imbalances in Th1 and Th2, along with increases in Th1 and Th17 in peripheral lymphocytes, as well as elevated levels of cytokines such as IL-17, IL-21, IL-23, IFN- γ , and TNF- α , have been observed in the serum of COVID-19 patients, further linking autoimmune disease to hyperstimulation of the immune system from COVID-19 (3).

Another potential explanation for the development of autoimmune thyroid disease post-COVID-19 is molecular mimicry. Research has identified several SARS-CoV-2 peptide sequences as homologous to human peptide sequences, resulting in cross-reactions between newly produced antibodies against the virus and the body’s self-antigens. Proteins identified in the SARS-CoV-2 proteome, such as the spike protein, membrane protein, and nucleoprotein, share similar peptide sequences with TPO, leading to this cross-reactions and, subsequently, thyroid autoimmunity. Transcriptional changes within immune genes of the thyroid gland have also been proposed as a plausible hypothesis for the pathogenesis of autoimmune thyroid disease in COVID-19. Studies have demonstrated a stronger innate immune response, which

increases macrophage activity. This response could lead to inflammation and damage to thyroid tissue, resulting in symptoms frequently observed in SAT (7).

Subacute thyroiditis post-COVID-19 illness

SAT, also known as de Quervain thyroiditis, is more commonly triggered by viral infections, specifically those of the upper respiratory tract, such as Coxsackie viruses and coronaviruses (1). Since the start of COVID-19 pandemic, many case reports have described an association between the two conditions, and this review identified 23 papers that focused on COVID-19-related SAT. As outlined in Table 1, the common symptoms described by patients were neck pain and tenderness and symptoms of hyperthyroidism or thyrotoxicosis. More female patients were identified with SAT than male patients, which is not surprising as the incidence has been shown to be 19.1 vs. 4.1 per 100,000/year for women and men, respectively (64). The retrospective study by Batman et al. (18) stated the average age of patients was 41, with a mean onset time of 21 days (range: 5–39) from the time of a positive COVID-19 PCR result to the diagnosis of SAT. Similar findings were described in a recent review paper, where the mean age of patients was 40. However, the mean onset of symptoms was longer, with an average onset time of 4 weeks following SARS-CoV-2 infection (1). As there is an overlap of symptoms in SAT and COVID-19, such as fever, malaise, and lethargy, it can be difficult to distinguish which symptoms are due to SAT or COVID-19. This can lead to uncertainty and prolong the diagnosis of SAT, potentially delaying treatment and having detrimental effects on the prognosis of patients. Some of these symptoms were described in the case study by Henke et al. (21), where the patient experienced weakness and headaches that progressively worsened. However, the distinguishing symptoms were neck pain, palpitations, and hand tremors. These,

coupled with laboratory investigations, allowed for the diagnosis of SAT. Furthermore, treatment of severe COVID-19 with high-dose corticosteroids can mask symptoms such as pyrexia and neck pain, making SAT harder to diagnose. Several studies identified the need for healthcare professionals to be aware of the relationship between SAT and COVID-19 infection.

The diagnosis of SAT is routinely based on laboratory tests and specific imaging. Laboratory results typically show a state of thyrotoxicosis, with negative TPO antibodies, as well as increased C-reactive protein (CRP) and erythrocyte sedimentation rate (65). Thyroid-specific imaging is used to further support the diagnosis of SAT. Thyroid ultrasound reveals a diffuse decrease in vascularity, heterogenous parenchyma, and hypoechoic areas in the thyroid gland, while thyroid scintigraphy demonstrates low or absent uptake of radioactive iodine within 24 h. An immune-mediated response is thought to occur after a viral infection, where cytotoxic T lymphocytes damage the thyroid follicular cells (1).

Over 50 years ago, the possibility of genetic influence increasing the susceptibility of developing SAT was first mentioned in the literature, exploring genotypes for human leukocyte antigen (HLA), which is involved in antigen presentation by T cells and antibody production by B cells in the immune system. Preliminary reports of a higher incidence of SAT in patients with the genotype HLA-B35 or HLA-B-67 have been recorded, with 70% of patients who develop SAT being carriers of HLA-B35 (66, 67). Other HLA haplotypes, such as HLA-B15/62 and HLA-Drw8, have also been implicated. One study suggested that viral insults like COVID-19 can trigger the stimulation of aberrant HLA DR isotype expression, as well as the activation of toll-like receptors (68).

The treatment of COVID-19-related SAT in all patients from studies examined in this systematic review involved NSAIDs and/or glucocorticoids, usually prednisolone, to reduce inflammation and eventually correct thyroid markers. Treatment of patients experiencing symptoms of hyperthyroidism, such as palpitations and tremors, may also involve drugs, such as beta blockers, to help alleviate these symptoms. On follow-up, one patient developed subclinical hypothyroidism, which was treated with levothyroxine (46). One patient also developed SAT alongside Graves' disease (24), and another patient was diagnosed with an inflammatory nodule secondary to SAT but showed no signs of inflammation upon follow-up (53). These further complications highlight the need for long-term follow-up, even after SAT has been successfully treated.

The relationship between COVID-19 and SAT incidence was reported in one study, where the incidence of SAT was compared in patients with and without COVID-19. This was a population-based, retrospective, cross-sectional study that included 407,427 patients and found a positive correlation between COVID-19 patients and SAT diagnosis. Due to the large number of patients, the risk of bias was small, suggesting a possible association between COVID-19 infection and SAT (11).

Graves' disease post-COVID-19 infection

Graves' disease is the most common form of hyperthyroidism, resulting from high levels of thyroid-stimulating immunoglobulins

that activate the TSH-R. It is an autoimmune condition and commonly observed in middle-aged women. Two patients from the studies included in this review experienced thyroid storms, and one experienced Graves' orbitopathy. Other rare symptoms identified include thyrotoxic periodic paralysis. Thyroid storm, in particular, is a life-threatening complication of Graves' disease with a high level of mortality and requires timely detection and treatment in patients with clinical signs of thyrotoxicosis (66).

The population-based cohort study by Peng et al. (25) found a 1.3 hazard ratio (95% confidence interval: 1.10–1.54) between COVID-19 and Graves' disease compared with COVID-19-negative patients, as well as an increased risk of Graves' disease specifically in the 18–40-year-old age group with COVID-19. This suggests a possible link between COVID-19 and the development of Graves' disease; however, more studies are needed to establish whether a correlation between COVID-19 infection and Graves' disease is indeed present.

Hashimoto's thyroiditis after COVID-19

A few reports suggested that viral infections, including COVID-19, are able to trigger Hashimoto's thyroiditis. This condition is a common autoimmune disease resulting from the infiltration of intrathyroidal mononuclear cells, which leads to the production of antithyroglobulin and antithyroid peroxidase antibodies, causing thyroid hormone derangement (29).

From the studies included in this review, only four patients were reported to develop Hashimoto's thyroiditis after COVID-19 infection. These patients had overlapping symptoms at presentation, identical to those of patients with Hashimoto's thyroiditis without COVID-19. Furthermore, treatment of Hashimoto's thyroiditis involved replacement of thyroid hormones in the form of levothyroxine, which normalised the biochemical parameters and resolved clinical presentations of the patients (3).

Painless thyroiditis after COVID-19

A number of reports described cases of COVID-19 patients who developed painless thyroiditis, which exhibits distinct characteristics compared to its counterpart, SAT. Painless thyroiditis, also known as silent thyroiditis, is thought to be a subtype of autoimmune thyroid disease or to a type of destructive thyroiditis (66).

A retrospective-prospective study focusing on patients who presented with SAT following COVID-19 infection described a total of 11 patients with COVID-19-associated thyroiditis, including five patients with painless thyroiditis. In this small series of patients, a comparison of symptoms allowed the following findings: symptoms consistent with painless thyroiditis presented earlier after COVID-19 infection than their comparator, and their levels of serum CRP and IL-6 were significantly higher (52). Patients with silent thyroiditis have also been reported to have a "transient" form of thyrotoxicosis, with high levels of serum thyroid hormones and low levels of TSH. This condition then

spontaneously resolves, with the whole syndrome lasting for several months (66). Thyrotoxicosis is thought to be associated with an excessive inflammatory state that destroys thyroid follicles, thus causing the increase of thyroid hormones in the bloodstream, with elevated ESR (30).

The absence of anterior neck pain is thought to be related to the presence of lymphopenia associated with COVID-19. Within the thyroid gland, there is lower lymphocytic infiltration and giant cell formation, which in turn reduces the tension in the thyroid capsule and therefore does not cause any pain. These findings were also shown in the study by Mondal et al. (52), as patients with painless thyroiditis had low levels of absolute lymphocyte count and a high neutrophil-to-lymphocyte ratio. This study also found a “significant correlation” between IL-6 and free T4, total T4, and total T3, which could imply a role for proinflammatory cytokines in the development of painless thyroiditis (52).

The above studies also emphasised the need for increased awareness due to the “invisible” nature of this type of thyroiditis, especially in higher-risk patients, so that management can be delivered in a timely manner.

Nonthyroidal illness syndrome after COVID-19

NTIS has been extensively reported in patients with COVID-19, although it is not exclusive to coronavirus infection, as it can occur during any type of severe illness, including myocardial infarctions, stroke, as well as during physiological stress and fasting. NTIS is considered an adaptive response to decrease energy expenditure during acute illness and, therefore, at least in the early stages of disease, to play a protective role. However, it has been linked to adverse effects and poor outcomes by prolonging recovery time, as the typical effect it exhibits on thyroid homeostasis lowers T3/ftT3, with a consequential rise in reverse T3, but usually no effect on TSH and T4. The pathophysiology is complex, involving dysregulation of the HPT axis at multiple levels, including decreased peripheral conversion of T4 to T3 and decreased sensitivity of the pituitary TSH responses to decreased thyroid hormone levels (7, 69). In addition, prolonged secretion of cortisol following viral infection might be important, as it is thought to lower the activity of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis can modulate the HPT axis, whereby acute stress can increase levels of TSH, whereas sustained stress can lower TSH release (3). Moreover, the role of inflammatory markers in NTIS has been investigated by numerous studies. Ilera et al. (70) found that thyroid hormone levels and their ratios (T3, T4, T3/T4, and ftT3/FT4) negatively correlated with inflammatory markers such as CRP, LHD, fibrinogen and D-dimer. Inflammatory cytokines impairing the activity of deiodinase could provide a potential explanation (70). The severity of illness has been associated with the decrease in TSH, ftT4, and ftT3 due to the lower secretion levels of TRH. Therefore, the use of these thyroid levels has been investigated in relation to disease severity, with studies reporting a prognostic value for free T3. A number of studies showed that low ftT3 levels had a significant association with disease severity and mortality (19); this was supported by another study, which showed that deceased patients

due to COVID-19 had significantly lower T3 and TSH levels than survivors. The latter study also found that patients with the lowest T3 in their cohort (< 0.77 ng/ml) had higher rates of mechanical ventilation, intensive care unit admissions, and death when compared with patients with higher levels of T3 (> 1.00 ng/ml) (50). Additionally, the study by Baldelli et al. (13) found that hospitalised patients with COVID-19 had a “statistically significant reduction in ftT3 and TSH” levels when compared to euthyroid controls, and patients admitted to the ICU had lower ftT3 and TSH levels.

The frequency of COVID-19 patients developing NTIS was explored in a single-centre retrospective study by Arora et al. (19), where 58.8% of 102 patients exhibited NTIS. This was further supported in the retrospective study by Ahn et al. (50), which reported NTIS as the most common manifestation of thyroid dysfunction in a relatively small sample size of 119 patients. These findings highlight the need to monitor thyroid function and the possible development of NTIS in COVID-19 patients; enhanced surveillance of thyroid function can offer prognostic clues (7). In addition, a key recommendation in the review by Lui et al. (1) was that patients diagnosed with NTIS should be reassessed after 6 weeks of recovery from COVID-19, highlighting the need for monitoring, as around 15% of COVID-19 patients go on to develop thyroid abnormalities, with most cases being identified as NTIS. This, coupled with the potential prognostic implications of NTIS, could allow higher-risk patients to receive more timely intervention and improve their outcomes.

Thyroid dysfunction in long COVID

Usually, patients with COVID-19 recover within up to 12 weeks; however, those who continue exhibiting varying symptoms after recovery have been termed as experiencing post-COVID-19 syndrome, post-acute COVID-19 syndrome, post-acute sequelae of SARS-CoV-2, and long COVID. As SARS-CoV-2 can affect the thyroid during the acute period, it is important to understand the impact on the thyroid during the post-acute infection period, associated with the development of chronic disease. Furthermore, data from reported cases of long COVID suggest that 53% share the symptom of fatigue, making it the most common symptom of the syndrome. This nonspecific symptom has led to the investigation of the relationship between thyroid function and long COVID (3).

A small observational study by Muller et al. (22) followed 75 COVID-19 survivors for 12 months, which included thyroid function assessment, ultrasound scans, and autoantibody assessment. They concluded that long-term thyroid consequences from COVID-19 “seemed unlikely”, as their results found that, at the end of their study period, all patients had normalised thyroid function and inflammatory markers, with no increased prevalence of autoantibodies. The only difference noted was the presence of focal hypoechoic areas in the thyroid gland, indicative of thyroiditis. This was seen for up to 1 year post-COVID-19 but was notably smaller in size when compared to those found during acute COVID-19 (22).

Conversely, a case-control study focusing on anosmia due to SARS-CoV-2 found a significant correlation between

hypothyroidism and the prolongation of smell dysfunction in COVID-19 patients. It was postulated that this continuation of anosmia is due to direct virus-induced injury to the thyroid and olfactory nerve. Thyroid hormones regulate development of nearly all systems in the body, including the neural maturation of olfactory receptor neurons. Therefore, impaired thyroid hormone secretion or action due to SARS-CoV-2 could affect the development of these neurons, ultimately leading to COVID-19-induced anosmia (56). There are few studies focusing on potential thyroid dysfunctions during long COVID, highlighting the need for further research to understand the incidence and complications of long COVID and how the thyroid gland is related to this condition. However, the studies included in this review show an unclear pattern of the long-term effects of COVID-19 on the thyroid gland.

Conclusion

Thyroid dysfunction is an endocrine complication frequently identified in the literature describing symptoms of COVID-19. Following SARS-CoV-2 infection, SAT, NTIS, and new-onset autoimmune thyroid disorders are the most common thyroid abnormalities. A number of studies included in this review also investigated the association between long COVID and thyroid disease, as well as autoimmune thyroid conditions. With the increased awareness of COVID-19-associated thyroid abnormalities, this could lead to improved detection of patient symptoms, especially those considered to be medically unexplained, such as chronic fatigue, by linking them to thyroid abnormalities. Furthermore, increasing evidence will eventually help to prevent complications, particularly in patients with multiple comorbidities, and reduce the risk of developing chronic conditions such as permanent hypothyroidism. Therefore, based on the evidence provided, thyroid function should be considered in patients displaying relevant clinical features so that management of these patients can be tailored and comprehensive care offered in a timely manner.

However, it is important to acknowledge the limitations of our study. Conflicting results identify the need for additional high-quality studies with larger, well-characterised patient groups. Furthermore, the majority of studies were case reports, where causality cannot be inferred due to the lack of control groups. However, the increase in case reports has warranted further research into thyroid dysfunction following COVID-19 infection, as demonstrated through the retrospective and prospective studies included. Nevertheless, as our study is a systematic review, it has inherent strengths, such as transparent and reproducible stages in our methodology, ensuring a low risk of bias, as results are

generated based on the defined PICO criteria, which are clearly stated in Table 2.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

DG: Writing – original draft, Writing – review & editing. PG: Writing – review & editing. AP: Writing – original draft, Writing – review & editing. LY: Writing – original draft, Writing – review & editing. NK: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1477389/full#supplementary-material>

References

1. Lui DTW, Lee CH, Woo YC, Hung IFN, Lam KSL. Thyroid dysfunction in COVID-19. *Nat Rev Endocrinol.* (2024) 20:226–348. doi: 10.1038/s41574-023-00946-w
2. De Luca R, Davis PJ, Lin HY, Gionfra F, Percario ZA, Affabris E, et al. Thyroid hormones interaction with immune response, inflammation and non-thyroidal illness syndrome. *Front Cell Dev Biol.* (2020) 8:614030. doi: 10.3389/fcell.2020.614030
3. Murugan AK, Alzahrani AS. SARS-coV-2: emerging role in the pathogenesis of various thyroid diseases. *J Inflammation Res.* (2021) 14:6191–221. doi: 10.2147/JIR.S332705
4. Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, et al. Early and late endocrine complications of COVID-19. *Endocrine connections.* (2021) 10:R229–39. doi: 10.1530/EC-21-0184

5. Jakovac H, Ferencic A, Stemberger C, Mohar Vitezic B, Cuculic D. Detection of Sars-Cov-2 antigens in thyroid gland showing histopathological features of subacute thyroiditis. *Eur Thyroid J.* (2022) 11. doi: 10.1530/ETJ-22-0005
6. Sofia Macedo AP, Santos L, Neves C, Guimarães S, Duarte-Neto A, Dolnikoff M, et al. Detection of SARS-CoV-2 infection in thyroid follicular cells from a COVID-19 autopsy series. *Eur Thyroid J.* (2022) 11. doi: 10.1530/ETJ-22-0074
7. Fallahi P, Elia G, Ragusa F, Paparo SR, Patrizio A, Balestri E, et al. Thyroid autoimmunity and SARS-coV-2 infection. *J Clin Med.* (2023) 12:6365. doi: 10.3390/jcm12196365
8. Vesselina Yanachkova TS, Radiana S. Thyroid dysfunction as a long-term post-COVID-19 complication in mild-to-moderate COVID-19. *Biotechnol Biotechnol Equip.* (2023) 37:194–202. doi: 10.1080/13102818.2023.2170829
9. Brancatella A, Viola N, Santini F, Latrofa F. COVID-induced thyroid autoimmunity. *Best Pract Res Clin Endocrinol Metab.* (2023) 37:101742. doi: 10.1016/j.beem.2023.101742
10. Cabuk SA, Cevher AZ, Kucukardali Y. Thyroid function during and after COVID-19 infection: A review. *TouchREVIEWS Endocrinol.* (2022) 18:58–62. doi: 10.17925/EE.2022.18.1.58
11. Lee ZC, Wong YJE, Ti LL, Shrikant DP, Tay TL, Santosa A. Hashimoto's thyroiditis-related myopathy in a patient with SARS-CoV-2 infection: A case report and systematic literature review. *Medicine.* (2023) 102:e35720. doi: 10.1097/MD.00000000000035720
12. Vassiliadi DA, Ilias I, Pratikaki M, Jahaj E, Vassiliou AG, Detsika M, et al. Thyroid hormone alterations in critically and non-critically ill patients with SARS-CoV-2 infection. *Endocrine connections.* (2021) 10:646–55. doi: 10.1530/EC-21-0029
13. Baldelli R, Nicastrì E, Petrosillo N, Marchioni L, Gubbio A, Sperduti I, et al. Thyroid dysfunction in COVID-19 patients. *J endocrinological Invest.* (2021) 44:2735–9. doi: 10.1007/s40618-021-01599-0
14. Alvarez Martin MC, Del Peso Gilsanz C, Hernandez Lopez A. Subacute De Quervain thyroiditis after SARS-CoV-2 infection. *Endocrinologia Diabetes y nutricion.* (2021) 68:754–5. doi: 10.1016/j.endien.2020.10.010
15. Mehmood MA, Bapna M, Arshad M. A case of post-COVID-19 subacute thyroiditis. *Cureus.* (2020) 12:e12301. doi: 10.7759/cureus.12301
16. Brancatella A, Ricci D, Cappellani D, Viola N, Sgro D, Santini F, et al. Is subacute thyroiditis an underestimated manifestation of SARS-coV-2 infection? Insights from a case series. *J Clin Endocrinol Metab.* (2020) 105. doi: 10.1210/clinem/dgaa537
17. Asfuroglu Kalkan E, Ates I. A case of subacute thyroiditis associated with Covid-19 infection. *J endocrinological Invest.* (2020) 43:1173–4. doi: 10.1007/s40618-020-01316-3
18. Batman A, Yazici D, Dikbas O, Agbaht K, Saygili ES, Demirci I, et al. Subacute THYROIDitis related to SARS-coV-2 VAccine and covid-19 (THYROVAC study): A multicenter nationwide study. *J Clin Endocrinol Metab.* (2023) 108:e1013–26. doi: 10.1210/clinem/dgad235
19. Arora S, Singh A, Kumar V, Mohan B, Mahajan R, Singh N, et al. Endocrine and metabolic manifestations of COVID-19 patients admitted to an intensive care unit. *Cureus.* (2022) 14:e24702. doi: 10.7759/cureus.24702
20. Shermetaro A, Bushman J. New-onset graves' Disease with thyroid storm after COVID-19 infection. *Cureus.* (2023) 15:e47995. doi: 10.7759/cureus.47995
21. Henke K, Odermatt J, Ziaka M, Rudovich N. Subacute thyroiditis complicating COVID-19 infection. *Clin Med Insights Case Rep.* (2023) 16:11795476231181560. doi: 10.1177/11795476231181560
22. Muller I, Daturi A, Varallo M, Re TE, Dazzi D, Maioli S, et al. Long-term outcome of thyroid abnormalities in patients with severe Covid-19. *Eur Thyroid J.* (2023) 12. doi: 10.1530/ETJ-22-0200
23. Franca AS, Pinto SM, Vieira DC, Silva MT, Pinho PL. Graves disease: A new association with COVID-19? *Semergen.* (2023) 49:101834. doi: 10.1016/j.semerg.2022.101834
24. Nham E, Song E, Hyun H, Seong H, Yoon JG, Noh JY, et al. Concurrent subacute thyroiditis and graves' Disease after COVID-19: A case report. *J Korean Med Sci.* (2023) 38:e134. doi: 10.3346/jkms.2023.38.e134
25. Peng K, Li X, Yang D, Chan SCW, Zhou J, Wan EYF, et al. Risk of autoimmune diseases following COVID-19 and the potential protective effect from vaccination: a population-based cohort study. *EClinicalMedicine.* (2023) 63:102154. doi: 10.1016/j.eclinm.2023.102154
26. Boyle DC, Mullally JA. Thyrotoxicosis after COVID-19 infection with a delay in graves' Disease antibody positivity. *Case Rep Endocrinol.* (2023) 2023:8402725. doi: 10.1155/2023/8402725
27. Rossini A, Cassibba S, Perticone F, Benatti SV, Venturelli S, Carioli G, et al. Increased prevalence of autoimmune thyroid disease after COVID-19: A single-center, prospective study. *Front Endocrinol.* (2023) 14:1126683. doi: 10.3389/fendo.2023.1126683
28. Feghali K, Atallah J, Norman C. Manifestations of thyroid disease post COVID-19 illness: Report of Hashimoto thyroiditis, Graves' disease, and subacute thyroiditis. *J Clin Trans Endocrinol Case Rep.* (2021) 22:100094. doi: 10.1016/j.jecr.2021.100094
29. Knack RS, Hanada T, Knack RS, Mayr K. Hashimoto's thyroiditis following SARS-CoV-2 infection. *BMJ Case Rep.* (2021) 14. doi: 10.1136/bcr-2021-244909
30. Barahona San Millan R, Tantinya Daura M, Hurtado Ganoza A, Recasens Sala M. Painless thyroiditis in SARS-CoV-2 infection. *Tiroiditis indolora en infeccion por SARS-CoV-2. Endocrinologia, Diabetes y Nutricion (English ed.)* (2020) 10:757–8. doi: 10.1016/j.endien.2021
31. Dolkar T, Jitidhar F, Patel MJ, Hamad AM, Salauddin F, Shiferaw-Deribe Z, et al. Painless subacute thyroiditis in a patient with acute COVID-19 infection: A transient event. *Cureus.* (2022) 14:e26924. doi: 10.7759/cureus.26924
32. Sousa B, Pestana Santos C, Goncalves Ferreira A, Judas T. Graves' Disease caused by SARS-coV-2 infection. *Eur J Case Rep Internal Med.* (2022) 9:003470. doi: 10.12890/2022_003470
33. Swistek M, Broncel M, Gorzelak-Pabis P, Morawski P, Fabis M, Wozniak E. Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality. *Endocrine Pract.* (2022) 28:494–501. doi: 10.1016/j.eprac.2022.02.006
34. Sparano C, Zago E, Morettini A, Nozzoli C, Yannas D, Adornato V, et al. Euthyroid sick syndrome as an early surrogate marker of poor outcome in mild SARS-CoV-2 disease. *J endocrinological Invest.* (2022) 45:837–47. doi: 10.1007/s40618-021-01714-1
35. Okwor CJ, Meka IA, Akinwande KS, Edem VF, Okwor VC. Assessment of thyroid function of newly diagnosed SARS-CoV-2 infected patients in Nigeria. *Pan Afr Med J.* (2021) 40:9. doi: 10.11604/pamj.2021.40.9.26358
36. Gong J, Wang D-K, Dong H, Xia Q-S, Huang Z-Y, Zhao Y, et al. Prognostic significance of low TSH concentration in patients with COVID-19 presenting with non-thyroidal illness syndrome. *BMC endocrine Disord.* (2021) 21:111. doi: 10.1186/s12902-021-00766-x
37. Schwarz Y, Percik R, Oberman B, Yaffe D, Zimlichman E, Tirosh A. Sick euthyroid syndrome on presentation of patients with COVID-19: A potential marker for disease severity. *Endocrine Pract.* (2021) 27:101–9. doi: 10.1016/j.eprac.2021.01.001
38. Campos-Barrera E, Alvarez-Cisneros T, Davalos-Fuentes M. Subacute thyroiditis associated with COVID-19. *Case Rep Endocrinol.* (2020) 2020:8891539. doi: 10.1155/2020/8891539
39. Sohrabpour S, Heidari F, Karimi E, Ansari R, Tajdini A, Heidari F. Subacute thyroiditis in COVID-19 patients. *Eur Thyroid J.* (2021) 9:321–3. doi: 10.1159/000511707
40. Whiting A, Reyes JVM, Ahmad S, Lieber J. Post-COVID-19 fatigue: A case of infectious hypothyroidism. *Cureus.* (2021) 13:e14815. doi: 10.7759/cureus.14815
41. Davoodi L, Oladi Z, Jafarpour H, Zakariaei Z, Soleymani E, Razavi A. A 33-year-old man with COVID-19 presented with subacute thyroiditis: A rare case report and literature review. *New Microbes New infections.* (2021) 41:100871. doi: 10.1016/j.nmni.2021.100871
42. Ruggeri RM, Campenni A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones (Athens Greece).* (2021) 20:219–21. doi: 10.1007/s42000-020-00230-w
43. Hajosi-Kalkaczos S, Denes J, Goth M. Subacute thyroiditis associated with COVID-19 infection: a report of an increasing entity. *Arch Endocrinol Metab.* (2022) 66:118–28. doi: 10.20945/2359-3997000000446
44. Elawady SS, Phuyal D, Shah RK, Mirza L. A case of subacute thyroiditis following COVID-19 infection. *Case Rep Endocrinol.* (2022) 2022:2211061. doi: 10.1155/2022/2211061
45. Tjonnfjord E, Moe RB, Ghanima W, Aballi S. Subacute thyroiditis after COVID-19. *Tidsskrift for Den norske legeforening* (2021), 141.
46. Chong WH, Shkolnik B, Saha B, Beegle S. Subacute thyroiditis in the setting of coronavirus disease 2019. *Am J Med Sci.* (2021) 361:400–2. doi: 10.1016/j.amjms.2020.09.011
47. Sato D, Nishiguchi S, Tanaka E. Successful management of subacute thyroiditis following SARS-coV-2 infection. *Internal Med (Tokyo Japan).* (2021) 60:3573–6. doi: 10.2169/internalmedicine.7913-21
48. Al-Shammaa MS, Abdulkadir AS. A case of post COVID-19 subacute thyroiditis. *Clin Case Rep.* (2022) 10:e6092. doi: 10.1002/ccr3.6092
49. Gezer D, Ecin MS. Effects of covid-19 infection on thyroid functions. *J Med Biochem.* (2022) 41:491–6. doi: 10.5937/jomb0-34934
50. Ahn J, Lee MK, Lee JH, Sohn SY. Thyroid hormone profile and its prognostic impact on the coronavirus disease 2019 in Korean patients. *Endocrinol Metab (Seoul Korea).* (2021) 36:769–77. doi: 10.3803/EnM.2021.1109
51. Edwards K, Hussain I. Two cases of severe autoimmune thyrotoxicosis following SARS-coV-2 infection. *J Invest Med High impact Case Rep.* (2021) 9:23247096211056497. doi: 10.1177/23247096211056497
52. Mondal S, Dasgupta R, Lodh M, Ganguly A. Subacute thyroiditis following recovery from COVID-19 infection: novel clinical findings from an Eastern Indian cohort. *Postgraduate Med J.* (2023) 99:558–65. doi: 10.1136/postgradmedj-2021-141429
53. De Souza CV, Motta PCC, Nestor AB, Coifman R, Demarzo MMP. Subacute thyroiditis and thyroid inflammatory nodule secondary to COVID-19: a primary care case report. *Family practice.* (2022). doi: 10.1093/fampra/cmabc136
54. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. *Front Endocrinol.* (2020) 11:566439. doi: 10.3389/fendo.2020.566439
55. Wang W, Su X, Ding Y, Fan W, Zhou W, Su J, et al. Thyroid function abnormalities in COVID-19 patients. *Front Endocrinol.* (2020) 11:623792. doi: 10.3389/fendo.2020.623792

56. Georgios Tsivgoulis PCF, Karofylakis E, Paneta M, Papathanasiou K, Palaodimou L, Psarros C, et al. Hypothyroidism is associated with prolonged COVID-19- induced anosmia: a case- control study. *J Neurol Neurosurg Psychiatry*. (2021) 92:911–2. doi: 10.1136/jnnp-2021-326587
57. Urbanovych AM, Laniush F, Borovets M, Kozlovska K. Coronavirus as a trigger of graves' Disease. *Acta endocrinologica (Bucharest Romania: 2005)*. (2021) 17:413–5. doi: 10.4183/aeb.2021.413
58. Harris A, Al Mushref M. Graves' Thyrotoxicosis following SARS-coV-2 infection. *AACE Clin Case Rep*. (2021) 7:14–6. doi: 10.1016/j.aace.2020.12.005
59. Khatri A, Charlap E, Kim A. Subacute thyroiditis from COVID-19 infection: A case report and review of literature. *Eur Thyroid J*. (2021) 9:324–8. doi: 10.1159/000511872
60. Brancatella A, Ricci D, Viola N, Sgro D, Santini F, Latrofa F. Subacute thyroiditis after sars-COV-2 infection. *J Clin Endocrinol Metab*. (2020) 105:2367–70. doi: 10.1210/clinem/dgaa276
61. Sciacchitano S, Capalbo C, Napoli C, Anibaldi P, Salvati V, De Vitis C, et al. Nonthyroidal illness syndrome: to treat or not to treat? Have we answered the question? A review of metanalyses. *Front Endocrinol (Lausanne)*. (2022) 13:850328. doi: 10.3389/fendo.2022.850328
62. Rossetti CL, Cazarin J, Hecht F, Beltrao FEDL, Ferreira ACF, Fortunato RS, et al. COVID-19 and thyroid function: What do we know so far? *Front Endocrinol*. (2022) 13:1041676. doi: 10.3389/fendo.2022.1041676
63. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol*. (2015) 3:816–25. doi: 10.1016/S2213-8587(15)00225-9
64. Christensen J, O'callaghan K, Sinclair H, Hawke K, Love A, Hajkowicz K, et al. Risk factors, treatment and outcomes of subacute thyroiditis secondary to COVID-19: a systematic review. *Internal Med J*. (2022) 52:522–9. doi: 10.1111/imj.15432
65. Tatal E, Ozaras R, Leblebicioglu H. Systematic review of COVID-19 and autoimmune thyroiditis. *Travel Med Infect Dis*. (2022) 47:102314. doi: 10.1016/j.tmaid.2022.102314
66. Inaba H, Aizawa T. Coronavirus disease 2019 and the thyroid - progress and perspectives. *Front Endocrinol*. (2021) 12:708333. doi: 10.3389/fendo.2021.708333
67. Ziaka M, Exadaktylos A. Insights into SARS-CoV-2-associated subacute thyroiditis: from infection to vaccine. *Virology*. (2023) 20:132. doi: 10.1186/s12985-023-02103-1
68. Naguib R. Potential relationships between COVID-19 and the thyroid gland: an update. *J Int Med Res*. (2022) 50:50. doi: 10.1177/03000605221082898
69. Gorini F, Vassalle C. A literature review on SARS-coV-2 and other viruses in thyroid disorders: environmental triggers or no-guilty bystanders? *Int J Environ Res Public Health*. (2023) 20:2389. doi: 10.3390/ijerph20032389
70. Ilera V, Delfino LC, Zunino A, Glikman P, Drnovsek M, Reyes A, et al. Correlation between inflammatory parameters and pituitary-thyroid axis in patients with COVID-19. *Endocrine*. (2021) 74:455–60. doi: 10.1007/s12020-021-02863-2



OPEN ACCESS

EDITED BY

Kamyar Asadipooya,
University of Kentucky, United States

REVIEWED BY

Khadijeh Irandoust,
Imam Khomeini International University, Iran
Warda Abdullah,
Hawler Medical University, Iraq

*CORRESPONDENCE

Yuan Zhu
✉ zhuyuan0528@aliyun.com
Hongying Xu
✉ jxxuhongying@163.com
Shaoping Zhong
✉ zhong_hua86@163.com

[†]These authors have contributed
equally to this work and share
first authorship

RECEIVED 19 March 2024

ACCEPTED 01 May 2025

PUBLISHED 04 June 2025

CITATION

Bao M, Xia L, Ling Y, Wen Q, Shen X, Wang T,
Qian S, Wang L, Wang C, Peng S, Zhang Y,
Zhong S, Xu H and Zhu Y (2025) Effect of
COVID-19 inactivated vaccine on anti-
Müllerian hormone in Chinese women:
a retrospective cohort study.
Front. Endocrinol. 16:1403722.
doi: 10.3389/fendo.2025.1403722

COPYRIGHT

© 2025 Bao, Xia, Ling, Wen, Shen, Wang, Qian,
Wang, Wang, Peng, Zhang, Zhong, Xu and Zhu.
This is an open-access article distributed under
the terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

Effect of COVID-19 inactivated vaccine on anti-Müllerian hormone in Chinese women: a retrospective cohort study

Mingjie Bao^{1†}, Leizhen Xia^{2†}, Yan Ling^{1†}, Quan Wen¹, Xin Shen¹,
Ting Wang³, Si Qian^{3,4}, Liqun Wang^{3,4}, Changhua Wang³,
Shiwei Peng¹, Yongping Zhang¹, Shaoping Zhong^{1*},
Hongying Xu^{3*} and Yuan Zhu^{1*}

¹Department of Obstetrics and Gynecology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, China, ²Department of Reproductive Medicine, Jiangxi Maternal and Child Health Hospital, Nanchang, China, ³Department of Gynecology, Jiangxi Maternal and Child Health Hospital, Nanchang, China, ⁴Department of Clinical Medicine, Nanchang University, Nanchang, China

Introduction: This study aimed to assess the impact of inactivated COVID-19 vaccine on Anti-Müllerian hormone (AMH) levels in Chinese women.

Methods: A retrospective analysis was conducted on women aged 18–45 who had undergone two AMH tests between March 2020 and September 2021. Participants were grouped based on vaccine doses (two- and three-dose), time intervals since vaccination, and manufacturers. The difference in AMH levels and the percentage changes in AMH were measured.

Results: The results revealed no significant differences in AMH levels between the vaccinated groups (two- and three-dose) and the control group, both in unadjusted and adjusted analyses. Subgroup analysis showed no statistical difference in either absolute or percentage changes of AMH levels among different time-interval groups and manufacturer groups.

Discussion: In conclusion, the number of doses, time interval, and manufacturer of the inactivated COVID-19 vaccine did not affect AMH levels in Chinese women.

KEYWORDS

COVID-19 vaccine, COVID-19 inactivated vaccine, anti-Müllerian hormone, ovarian reserve, reproductive health

1 Introduction

Coronavirus disease 2019 (COVID-19), or the “new coronavirus pneumonia,” is a respiratory infectious disease that has been spreading rapidly worldwide since December 2019. The COVID-19 epidemic is the most severe global public health outbreak since World War II, and it seriously threatens human health. As the first country to be hit by the COVID-19 epidemic (1), China is the best place for the research on the novel coronavirus and its vaccines. The Chinese government announced the lifting of epidemic control on December 7, 2022, implying that the focus of epidemic prevention and control has shifted from controlling the source of infection and blocking transmission routes to the direction of protecting susceptible populations, representing a need for more people to participate in vaccination in the face of a raging epidemic, resulting in a surge in demand for vaccines. Driven by policy support and media coverage, the vast majority of Chinese residents choose to be vaccinated against the COVID-19 epidemic. However, young people who are planning to become pregnant are hesitant to receive vaccination because of the concern about the safety of the vaccination. A survey in 2023 showed that the COVID-19 vaccination rate of men and women preparing for pregnancy was significantly lower than the average vaccination rate in China (2). On the other hand, some people who have been vaccinated also worry about the harm to their physical health. Among these concerns, apprehensions regarding reproductive health are notably prevalent.

First, some evidence supports that coronaviruses may have an impact on human reproductive health. COVID-19 is caused by SARS-CoV-2 pathogen infection (3–6), a single positive-stranded RNA coronavirus with regularly arranged spines on the envelope. The virus binds to angiotensin-converting enzyme 2 (ACE2), mediated by the viral surface spine glycoprotein (S protein), to enter cells (6, 7). ACE2 has been detected in human tissues of different organs, including the heart, kidney, intestine, and blood vessels. ACE2 has also been detected in organs related to reproduction, such as ovaries, uterus, vagina, placenta, and testes (8, 9). Based on the considerable regulatory role of ACE2 on reproduction (10, 11), SARS-CoV-2 may affect female reproductive function by affecting ACE2. Studies have shown that SARS-CoV-2 affects ovarian reserve in women. A study by Ding et al. in March 2021 showed that women infected with COVID-19 had lower Anti-Müllerian hormone (AMH) levels, higher FSH levels, and higher levels of testosterone and prolactin than healthy women (12).

Secondly, a vaccine is a biological agent derived from a virus. If a virus exerts a specific effect on the body, it is plausible that the vaccine may elicit similar effects. Since the outbreak of COVID-19, many types of vaccines, such as mRNA vaccines, DNA vaccines, inactivated vaccines, recombinant protein subunit vaccines, virus vector vaccines, and virus-like particle vaccines, have been used. Studies have shown that other new crown vaccines, such as mRNA vaccines, impact women’s ovarian reserve (13–15). Inactivated vaccines, widely administered in China, are known to retain the intact structure of the virus, so inactivated vaccines may be more

likely to cause damage to reproductive health than other types of vaccines. However, current research on the impact of inactivated vaccines on female reproductive health in China is rather limited.

Therefore, the purpose of this study was to investigate whether the COVID-19 vaccination of inactivated vaccines in China would affect AMH in Chinese women, and thus indirectly assess whether it would affect ovarian function in Chinese women.

2 Methods

2.1 Subjects

This study was a retrospective study of patients admitted to a provincial tertiary hospital in China from March 2020 to September 2021. Informed consent was obtained from all subjects. Inclusion criteria are as follows: female, aged between 18 and 45; received two or more AMH tests between March 2020 and September 2022; the first AMH was within the normal range (16). The exclusion criteria were as follows: postmenopausal women, those with polycystic ovarian syndrome, those who were pregnant, and those who had ovarian surgery during this period. The cases with incomplete information were excluded in our analysis. The cases with incomplete information were excluded in our analysis. This study was approved by the Ethics Committee of Jiangxi Provincial Maternal and Child Health Hospital (approval number: EC-KT-202309). We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments.

2.2 Vaccination strategy

The vaccination strategy in China is as follows: voluntary principle, available to people ≥ 18 years, with two doses routinely administered by intramuscular injection into the deltoid muscle of the upper arm, and the interval between the two doses should be ≥ 3 weeks but ≤ 8 weeks. The third dose (booster) should not be given until 6 months after the second dose. If the vaccination is not completed in accordance with the procedure, making up the vaccination as soon as possible is recommended. Patients who received Sinopharm vaccine or Sinovac vaccine were included in this study, and some patients who received both vaccines were also included in this study. Vaccination information from official immunization records was collected in a personal mobile application (app).

2.3 Research grouping criteria

In this study, the subjects were divided into three groups in accordance with the number of doses received and whether they received the vaccine: a two-dose group (two doses received), a three-dose group (three doses received), and control group (no vaccination due to voluntary principle). From March 2020 to September 2022, women who received two or 3 doses of the

vaccine and were tested for AMH before the first dose and after the last dose were included in the two- or three-dose vaccine group. During the same period, women who underwent two AMH tests at the research hospital and had never been vaccinated were included in the control group. In current studies focusing on the effects of inactivated vaccines on AMH, participants who received two doses of the vaccine were included as subjects (17). In addition to investigating the effects of two doses of vaccination, this study also incorporated individuals who received booster shots (three-dose groups). Due to the novelty of designing two vaccine regimens and the uncertainty surrounding the effect of vaccination on AMH levels, the sample size could not be predetermined.

In the end, 526, 79, and 389 women were included in the two-dose, three-dose, and control groups, respectively (Figure 1).

2.4 Study indicators

AMH was measured by Elecsys® AMH Plus immunoassay in this provincial tertiary hospital in China. After taking venous blood at the blood sampling window, the serum was obtained by centrifugation by experienced laboratory staff, and the serum was obtained by Cobas e 801 analyzer 127 (Roche Diagnostics, Switzerland) for testing. The study metrics were as follows: the difference in AMH (last AMH – first AMH) and the percentage change in AMH [(last AMH – first AMH)/first AMH].

2.5 Statistical methods

SAS 9.4 software was applied for statistical analysis. Count data were described by frequencies or percentages, and the chi-square test was

applied for comparisons. The measurement data were tested for normality by the Shapiro–Wilk test. The data conforming to a normal distribution were compared by t-test and expressed as mean ± standard deviation ($\bar{x} \pm s$), whereas those not conforming to a normal distribution were expressed as median P50 (25th percentile, P25; 75th percentile, P75) and compared by Kruskal–Wallis rank sum test. The AMH change values were used in the Wilcoxon signed-rank test. A generalized linear model was applied for multivariate analysis of AMH change values. $p < 0.05$ was considered a statistically significant difference.

3 Results

3.1 The baseline characteristics of the study participants

Table 1 shows the baseline characteristics of the study participants. The data were presented in the form of median after normality test. Among the 994 women included in the study, significant differences were observed in terms of median age, first AMH level, and the time interval between AMH (days) in the two-dose ($n = 526$) and three-dose ($n = 79$) groups compared with the control group ($n = 389$). Due to the differences in the underlying information, multifactorial analysis was applied to adjust the data for the following statistical analysis to increase the credibility of the study results.

3.2 Difference and percentage change in AMH among the three groups

As illustrated in Table 2, compared with the control group, the two-dose (-0.14 vs. -0.07 , $P = 0.332$; -8% vs. -5% , $P = 0.322$) and three-dose groups (-0.17 vs. -0.07 , $P = 0.303$; -14% vs. -5% , $P = 0.073$) showed non-statistically significant difference in the difference and percentage change in AMH, respectively.

Table 3 also shows no significant difference in the difference in AMH between the two/three-dose groups and the control group after adjusting for the first AMH, age, and time interval between AMH examinations by using a generalized linear model for the analysis ($P = 0.630$; $P = 0.416$). In addition, the percentage change in AMH ($P = 0.515$; $P = 0.651$) was not statistically significant.

3.3 Effect of time interval on the difference and percentage change in AMH

Table 4a and Table 4b shows the influence of the time interval from the last vaccine injection to the last AMH examination over the difference in AMH and the percentage change in AMH. All patients in the two-dose group were grouped by the time interval from the last vaccine injection to the last AMH examination received, and they were divided into four groups of up to 0–60 days ($n = 135$), 61–120 days ($n = 154$), 121–180 days ($n = 146$), and more than 180 days ($n = 91$). The median age of patients and the first-time AMH median values were not significantly different

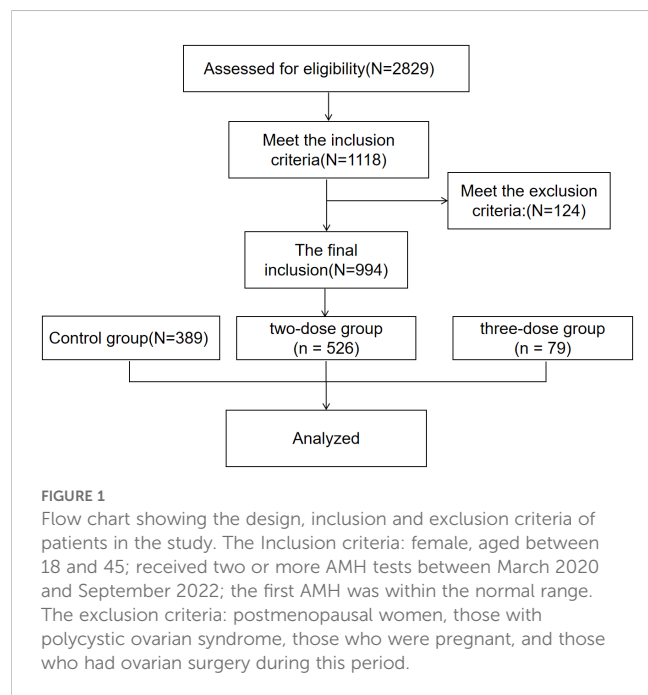


TABLE 1 Demographic characteristics of the study population.

Variables	Two-dose (n = 526)	Three-dose (n = 79)	Control group (n = 389)	P-value 1*	P-value 2 [#]
Age (years)	32.67 (28.78,37.3)	33.76 (29.04,39.44)	31.33 (28.1,35.18)	0.002	0.002
Classification				0.023	0.009
<30 years (%)	169 (32.1)	21 (26.6)	149 (38.3)		
30–34 years (%)	176 (33.5)	24 (30.4)	138 (35.5)		
≥35 years (%)	181 (34.4)	34 (43)	102 (26.2)		
First AMH (ng/mL)	2.44 (1.12,4.21)	1.89 (0.82,3.71)	2.63 (1.35,4.8)	0.043	0.001
Last AMH (ng/mL)	2.16 (0.97,4.09)	1.32 (0.66,3.03)	2.52 (1.14,4.58)	0.020	0.000
Time interval between AMH examinations (days)	335 (238,432)	429 (355,556)	221 (132,329)	<.001	<.001
Classification				<.001	<.001
Within 6 months	70 (13.3)	0 (0)	147 (37.8)		
7 to 12 months	239 (45.4)	22 (27.9)	175 (45)		
13 to 18 months	183 (34.8)	36 (45.6)	58 (14.9)		
More than 18 months	34 (6.5)	21 (26.6)	9 (2.3)		

*Two-dose vs. Control group; # Three-dose vs. Control group. Shapiro-Wilk test and Kruskal-Wallis rank sum test were used for statistical analysis.

among the four groups. The results of the statistical analysis found no significant change in the difference and percentage change in AMH among the four groups. By using data within 0–60 days as a reference, the difference in AMH adjusted β values (95% CI) of the other groups were -0.01 ($-0.26, 0.24$), -0.16 ($-0.42, 0.09$), and -0.25 ($-0.55, 0.06$), respectively, and the adjusted β values (95% CI) for the percentage change in AMH were 0.1 ($-0.13, 0.32$), -0.03 ($-0.26, 0.2$), and -0.02 ($-0.29, 0.25$), there was no statistical difference.

3.4 Effect of vaccine manufacturers on the difference in AMH and the percentage change in AMH

Table 5a and Table 5b shows the effect of vaccine manufacturers on AMH. In this study, the vaccine manufacturers in the two-dose group were analyzed, which included China National Pharmaceutical Group Co. Ltd. (Sinopharm vaccine) and Sinovac Life Sciences Co., Ltd. (Sinovac vaccine). The participants were further divided in accordance with the vaccine manufacturer: Sinopharm group (Sinopharm Vaccine only, $n = 129$), Sinovac group (Sinovac vaccine only, $n = 153$), and a mixed group (inoculated against Sinopharm and Sinovac vaccines, $n = 244$). The results found no significant difference in the AMH difference and the percentage change in AMH among these three groups. As shown in Table 5b, with Sinopharm as the reference, the adjusted β values (95% CI) for the difference in AMH were -0.05 ($-0.3, 0.2$) and 0.01 ($-0.21, 0.24$), and those for the percentage change in AMH were -0.11 ($-0.34, 0.11$) and -0.07 ($-0.27, 0.14$), there was no statistical difference.

For requirements for a specific article type please refer to the Article Types on any Frontiers journal page. Please also refer to Author Guidelines for further information on how to organize your manuscript in the required sections or their equivalents for your field¹.

4 Discussion

Indicators reflecting ovarian reserve include inhibin B, estradiol (E2), FSH, etc. However, these indicators are affected by the menstrual cycle (18). AMH is produced by stratum granulosum cells of small ovarian follicles and is not affected by the dominant follicle. Therefore, the circulating level of AMH is unaffected by the menstrual cycle and can be used to measure ovarian follicular reserve. So, they are now considered the preferred measure for ovarian reserve assessment (19–22). As AMH testing is not typically included in routine gynecological examinations, it is generally conducted in most hospitals only when female patients present with symptoms indicative of abnormal ovarian function, such as insomnia, hyperhidrosis, or infertility related to ovulation. Consequently, in numerous retrospective studies, establishing a control group with normal AMH levels poses a significant challenge. However, this research relies on a sizeable Grade 3A provincial obstetrics and gynecology hospital, where the reproductive center is the main specialty. In order to screen for the causes of infertility, women visiting the reproductive center at this hospital undergo routine AMH

¹ For Original Research articles, please note that the Material and Methods section can be placed in any of the following ways: before Results, before Discussion or after Discussion.

TABLE 2 Comparison of the difference in AMH and the percentage change in AMH among the 3 groups.

Outcome Measures	Two-dose group (n = 526)	Three-dose group (n = 79)	Control group (n = 389)	P-value 1*	P-value 2 [#]
The difference in AMH (ng/mL)	−0.14 (−0.64, 0.33)	−0.17 (−0.58, 0.17)	−0.07 (−0.66, 0.51)	0.332	0.303
The percentage change in AMH (%)	−8 (−30, 18)	−14 (−37, 12)	−5 (−28, 25)	0.322	0.073

*two-dose group versus control group; [#]three-dose group versus control group. The difference in AMH: last AMH – first AMH; The percentage change in AMH: (last AMH – first AMH)/first AMH. Shapiro-Wilk test and Wilcoxon signed-rank test were used for statistical analysis.

testing, resulting in a substantial collection of samples with normal AMH levels. This includes women with other fertility issues, such as uterine adhesions and blocked fallopian tubes, who also seek treatment at the reproductive center. Consequently, this pool of patients provides the source of the research samples included in this study. Therefore, in this study, AMH was chosen as the indicator of ovarian reserve. Retrospective analysis from different angles was applied to investigate the effect of the inactivated COVID-19 vaccine on AMH levels among women. The results showed that the inactivated vaccine in China did not affect the AMH levels in women.

As a member of the TGF- β superfamily (23–25), AMH follows the classical SMAD signal transduction pathway to transmit its biological information. In the case of COVID-19 virus infection, the

lungs and other affected organs trigger an inflammatory response, and in this inflammatory microenvironment, the expression of transforming growth factor β (TGF- β) is significantly increased. In theory, when the TGF- β signaling pathway is overactive, the activity or effective concentration of the Smad protein may encounter some threshold or saturation state, which prevents the Smad protein from receiving more upstream signal input or efficiently transmitting the signal further to the nucleus. If this hypothesis is true, then during COVID-19 infection, AMH may be affected by a receptor shared with the inflammatory mediator TGF- β , and interestingly, studies have shown that AMH does change significantly during COVID-19 infection (26, 27). In addition, it is worth noting that the severity of COVID-19 disease is generally

TABLE 3 Generalized linear models of AMH change.

Parameter	B (95% CI)	SE	Wald Chi-square	P-value
The difference in AMH (ng/mL) between two-dose group and control group				
Two-dose group versus control group	−0.04 (−0.2, 0.12)	0.0826	0.231	0.630
First AMH	−0.13 (−0.16, −0.09)	0.0179	48.632	< 0.001
Age (years)	−0.04 (−0.06, −0.03)	0.0077	27.024	< 0.001
Time interval between AMH examinations (days)	0 (0, 0)	0.0003	0.391	0.532
The percentage change in AMH (%) between two-dose group and control group				
Two-dose group versus control group	−9 (−34, 17)	0.1311	0.424	0.515
First AMH	−0.09 (−0.14, −0.03)	0.0283	9.25	0.002
Age (years)	−0.01 (−0.03, 0.02)	0.0121	0.346	0.556
Time interval between AMH examinations (days)	0 (0, 0)	0.0005	3.126	0.077
The difference in AMH (ng/mL) between three-dose group and control group				
Three-dose group versus control group	−0.14 (−0.49, 0.2)	0.1754	0.66	0.416
First AMH	−0.13 (−0.19, −0.08)	0.0263	25.878	0.000
Age (years)	−0.05 (−0.07, −0.03)	0.0113	19.902	0.000
Time interval between AMH examinations (days)	0 (0, 0)	0.0004	0	0.991
The percentage change in AMH (%) between three-dose group and control group				
Three-dose group versus control group	−16 (−83, 52)	0.3434	0.205	0.651
First AMH	−0.12 (−0.22, −0.02)	0.0515	5.094	0.024
Age (years)	−0.01 (−0.05, 0.04)	0.0222	0.161	0.688
Time interval between AMH examinations (days)	0 (0, 0)	0.0008	1.167	0.280

Generalized linear model was used for statistical analysis.

TABLE 4A Statistical characteristics of different AMH time intervals in the 2-dose group.

Variables	0–60 days (n = 135)	61–120 days (n = 154)	121–180 days (n = 146)	≥181 days (n = 91)	P-value
Age (years)	32.68 (28.32, 36.52)	32.74 (29.3, 38.69)	32.9 (29.3, 37.43)	31.53 (27.72, 35.88)	0.143
First AMH (ng/mL)	2.58 (1.32, 4.28)	2.13 (0.93, 3.86)	2.62 (0.99, 4.55)	2.49 (1.09, 4.18)	0.465
Last AMH (ng/mL)	2.26 (1.28, 4.12)	1.86 (0.91, 3.89)	2.27 (0.83, 4.23)	1.94 (0.86, 4.03)	0.662
Time interval between AMH examinations (days)	276 (166, 369)	324 (212, 409)	348.5 (257, 451)	406 (314, 507)	< 0.001

*adjusted factors: Age, First AMH, Time interval between AMH examinations. Shapiro-Wilk test and Kruskal-Wallis rank sum test were used for statistical analysis.

TABLE 4B Effect of the time interval on the difference in AMH and the percentage change in AMH in the two-dose group.

Parameters	0–60 days (n = 135)	61–120 days (n = 154)	121–180 days (n = 146)	≥181 days (n = 91)	P-value
The difference in AMH (ng/mL)	–0.03 (–0.63, 0.44)	–0.12 (–0.61, 0.34)	–0.21 (–0.63, 0.23)	–0.1 (–0.75, 0.39)	0.403
Crude B (95% CI)	–	0.01 (–0.25, 0.26)	–0.17 (–0.43, 0.09)	–0.22 (–0.51, 0.07)	
Adjust B (95% CI)*	–	–0.01 (–0.26, 0.24)	–0.16 (–0.42, 0.09)	–0.25 (–0.55, 0.06)	
The percentage change in AMH (%)	0 (–28, 30)	–7 (–30, 20)	–9 (–30, 12)	–10 (–32, 15)	0.202
Crude B (95% CI)	–	0.08 (–0.14, 0.31)	–0.09 (–0.31, 0.14)	–0.1 (–0.36, 0.16)	
Adjust B (95% CI)*	–	0.1 (–0.13, 0.32)	–0.03 (–0.26, 0.2)	–0.02 (–0.29, 0.25)	

The difference in AMH:last AMH – first AMH; The percentage change in AMH:(last AMH – first AMH)/first AMH. Rank sum test and regression analysis were used for statistical analysis.

thought to be related to sex (28); After COVID-19 infection, women produce fewer inflammatory factors than men (28). And mortality rates are observed to be higher in males compared to females, which suggests that premenopausal status may confer some protection against COVID-19 infection (29). This protective effect may be attributed to AMH competitively occupying a greater number of Smad receptors, and consequently, AMH may be less able to exert its effects because of this competitive binding. This may be explained from the perspective of alleviating the inflammatory response, which in turn demonstrates the association of AMH with COVID-19 infection. However, there is no conclusive evidence to confirm this saturation property of Smad protein, and more rigorous experimental studies are needed to verify this hypothesis.

Whether vaccines have the same effect on AMH levels as viruses is equally essential. This study used univariate and multivariate analyses to investigate whether the vaccine affected AMH. First, compared with the control group, the two- and three-dose groups showed no statistically significant difference in the difference and percentage change in AMH. Next, after adjusting for the first AMH, age, and time interval between AMH examinations by using a generalized linear model, no statistically significant difference in the difference and percentage change in AMH was observed among the three groups. These results suggested that different inactivated vaccine doses did not affect AMH.

A prospective study has been conducted to determine whether mRNA vaccines affect AMH. Statistical analysis of AMH levels in subjects before and after the first vaccination and three months after

that study showed that AMH levels did not change significantly before and after mRNA vaccination (12). In particular, the authors mentioned that AMH changes may occur after three months or longer and require further long-term follow-up. Therefore, this study was also designed to investigate the effect of time interval after vaccination on AMH. In the two-dThe author(s) declare that fose group with the largest sample size, the patients were divided into four groups (0–60 days, 61–120 days, 121–180 days, and more than 180 days) according to the time interval from the last vaccine dose injection to the last AMH examination. The results of multivariate analysis showed no significant difference in AMH difference and percentage change of AMH in each group when the data within 0–60 days were used as a reference. This suggests that AMH levels did not change significantly after vaccination, at least during the time interval of this study. As the novel coronavirus is a recently emerged virus, it is currently unfeasible to collect samples at longer intervals to study the effect of time intervals post-vaccination on AMH levels. Our findings indicate that AMH levels remained relatively stable beyond a six-month period following vaccination. Our future research will track AMH fluctuations over a more extended duration.

The inactivated vaccines commonly administered to the Chinese population are those manufactured by Sinopharm and Kexing. The vaccination authorities do not have strict regulations on whether the manufacturer of the second dose of vaccine should be the same as the first dose, resulting in some of the population receiving vaccines from different manufacturers. Therefore, information on vaccine manufacturers was collected, and

TABLE 5A Statistical characteristics of different vaccine manufacturers in the 2-dose group. Effect of vaccine dose manufacturer on the difference in AMH and the percentage change in AMH in the two-dose group.

Variables	Sinopharm (n = 129)	Sinovac (n = 153)	Sinopharm + Sinovac (n = 244)	P-value 1
Age (years)	32.36 (28.89,36.92)	33 (29.33, 37.33)	32.42 (28.5, 37.17)	0.472
First AMH (ng/mL)	2.72 (1.1, 4.21)	2.39 (1.18, 3.45)	2.39 (1.04, 4.75)	0.771
Last AMH (ng/mL)	2.52 (0.88, 4.03)	1.95 (1.05, 3.57)	2.14 (0.92, 4.29)	0.697
Time interval between AMH examinations (days)	342 (238, 426)	333 (229, 436)	335 (239.5, 435.5)	0.935

*adjusted factors: Age, First AMH, Time interval between AMH examinations. Shapiro-Wilk test and Kruskal-Wallis rank sum test were used for statistical analysis.

TABLE 5B Effect of vaccine dose manufacturer on the difference in AMH and the percentage change in AMH in the two-dose group(before and after adjustment).

Parameters	Sinopharm (n = 129)	Sinovac (n = 153)	Sinopharm + Sinovac (n = 244)	P-value 1
The difference in AMH (ng/mL)	−0.16 (−0.55, 0.39)	−0.1 (−0.61, 0.24)	−0.15 (−0.74, 0.36)	0.906
Crude B (95% CI)	–	−0.06 (−0.32, 0.2)	−0.01 (−0.24, 0.22)	
Adjust B (95% CI)	–	−0.05 (−0.3, 0.2)	0.01 (−0.21, 0.24)	
The percentage change in AMH (%)	−8 (−27, 23)	−7 (−29, 15)	−9 (−32, 18)	0.798
Crude B (95% CI)	–	−0.11 (−0.34, 0.11)	−0.08 (−0.28, 0.13)	
Adjust B (95% CI)	–	−0.11 (−0.34, 0.11)	−0.07 (−0.27, 0.14)	

The difference in AMH:last AMH – first AMH; The percentage change in AMH:(last AMH – first AMH)/first AMH. Rank sum test, regression analysis, Shapiro-Wilk test and Kruskal-Wallis rank sum test were used for statistical analysis.

subgroup analysis was performed. The results suggested that the vaccine manufacturers did not affect the AMH level.

In conclusion, the inactivated COVID-19 vaccine, including the different vaccine doses, the time interval after vaccination, and the different vaccine manufacturers, did not affect AMH. This is consistent with the results of previous studies on the effects of other types of COVID-19 vaccines on human reproduction and female fertility. In 2022, Mohr-Sasson et al. found that ovarian reserve, as assessed by serum AMH levels, was not altered 3 months after SARS-CoV-2 mRNA vaccination (12). In 2023, Another prospective study found that although menstruation in adolescent girls may be affected by the COVID-19 mRNA vaccine, ovarian reserve did not appear to be impaired, as estimated by AMH (13). In a prospective cross-sectional study in Turkey, vaccination with COVID-19 mRNA was found to have no effect on AMH levels (30). The present study was a retrospective study to examine whether inactivated vaccines produce changes in female AMH levels in Chinese inactivated vaccine recipients. In some existing prospective analyses, due to the effect of ethics and policies actively promoting vaccination, a blank control group without vaccination was not set up (12). In the present study, a large number of samples that did not receive vaccine due to social or health factors were collected for blank control analysis, which significantly increased the credibility of the results. In addition, for the first time, this study provides a separate analysis of populations who were offered inactivated vaccines of different doses and different manufacturers.

As a result, our study provides richer and more credible data on the effects of vaccines on AMH level in women.

Although AMH is widely used as a representative marker of ovarian function, studies on AMH alone to reflect the impact of COVID-19 vaccines on female reproductive capacity are far from sufficient. In fact, researchers have conducted different studies to understand the impact of various COVID-19 vaccines on female reproduction. First of all, menstruation is an essential physiological phenomenon in women of reproductive age, and the results of a study from the United States on the relationship between menstrual cycle length and COVID-19 vaccination show that the change in menstrual cycle after vaccination is less than 1 day (31). Another study examining the relationship between multiple types of COVID-19 vaccines worldwide and menstrual cycle length further found that multiple types of COVID-19 vaccination (such as mRNA vaccine, inactivated vaccine, etc.) are not associated with menstrual cycle length (32). Second, pregnancy is the most direct manifestation of average female reproductive capacity. An Internet-based pre-pregnancy cohort study in the United States found that COVID-19 vaccination had no significant correlation with the pregnancy rate of either party, and COVID-19 vaccination did not harm the fertility of either party (33). Researchers are also concerned about whether the vaccination of the COVID-19 vaccine will have an impact on assisted reproduction. A study examining women undergoing *in vitro* fertilization revealed that administration of China's novel coronavirus inactivated vaccine did not impact key parameters in the *in vitro* fertilization process, including the

number of oocytes retrieved, the implantation rate, and the sustained pregnancy rate (34). These studies, together with this and other studies on the effects of COVID-19 vaccines on AMH, provide evidence that vaccination does not have an impact on women's reproductive health.

By analyzing a substantial amount of data, this study conclusively demonstrates that there is no basis for concern regarding reproductive health safety following administration of China's inactivated COVID-19 vaccine. The study's findings hold significant clinical relevance. Firstly, it dispels prevalent societal apprehensions and misconceptions about the safety of COVID-19 vaccines, thereby alleviating the need for women planning pregnancies to postpone their family planning due to vaccination concerns. Secondly, it offers a valuable perspective for women experiencing long-term infertility, suggesting that their infertility may stem from factors unrelated to vaccination.

However, this study has some limitations. Compared with those prospective studies, the age distribution of the samples in each group, the time interval between vaccinations, and the time interval between AMH examinations could not be strictly controlled. In particular, AMH is greatly affected by time factors, and AMH was measured over a long time span in this study, which may bring some errors to the results of the study. This study might benefit from additional sensitivity analyses to account for potential confounding variables or different age groups. So, a multicenter study with a larger sample size is recommended. In addition, a study by Rasa Khodavirdilou in 2022 found that AMH fluctuates significantly with the change in the menstrual cycle and that AMH at the stage of ovulation is recommended as a research indicator in clinical research on AMH (35), which may bring particular information bias to the results of this study.

5 Conclusion

This study demonstrated that the COVID-19 inactivated vaccine did not affect AMH levels in Chinese women from the number of doses, the manufacturer and the time interval after vaccination. The findings of this study present compelling clinical proof in support of the safety of COVID-19 vaccination, with particular emphasis on the reproductive health safety of Chinese women. These findings effectively address the concerns that vaccines might adversely affect AMH levels. Consequently, healthcare professionals can confidently recommend the COVID-19 vaccine to female patients without hesitation regarding its potential negative impact on fertility. This not only boosts public trust in vaccination and increases vaccination rates but also serves as a crucial measure to safeguard public health and promote women's health and well-being.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

This retrospective study utilized anonymized medical records without additional patient intervention. The protocol was approved by the Ethics Committee of Jiangxi Provincial Maternal and Child Health Hospital (Approval No. EC-KT-202309). All procedures complied with the Declaration of Helsinki and relevant Chinese ethical regulations to protect patient privacy and data security.

Author contributions

MB: Investigation, Writing – original draft. LX: Visualization, Writing – original draft. YL: Data curation, Writing – review & editing. QW: Writing – review & editing. XS: Writing – review & editing. TW: Writing – review & editing. SQ: Writing – review & editing. LW: Writing – review & editing. CW: Writing – review & editing. SP: Writing – review & editing. YPZ: Writing – review & editing. SZ: Supervision, Writing – review & editing. HX: Supervision, Writing – review & editing. YZ: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China (grant numbers 82360299 and 81660265), the Key project of Jiangxi Provincial Natural Science Foundation (grant number 20232ACB206011), the Applied Research and Cultivation Program of Jiangxi Province (grant number 20212BAG70049), the Key Research and Development Program of Jiangxi Province (grant number 20202BBGL73065), the Natural Science Foundation of Jiangxi Province (grant numbers 20224BAB206026 and 20181BAB205015); the Science and Technology Plan of Jiangxi Provincial Health Commission (grant numbers 202130758 and 202210060); the Science and Technology Program of Health Commission of Jiangxi Province (grant number 202310061).

Acknowledgments

We would like to acknowledge EnPapers editorial team for editing this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Ashouri M, Nehzat Norozi Tehrani S, Govindasamy K, Zouhal H. Effect of covid-19 on the lifestyles of vaccinated and unvaccinated elite athletes: A cross-country analysis. *Health Nexus*. (2023) 1:1–6. doi: 10.61838/kman.hn.1.2.1
2. Lei A, Xi C, Luo X, Pu Y, You H. COVID-19 vaccine uptake and hesitation among men and women preparing for pregnancy: a cross-section survey based on the theory of planned behavior. *BMC Public Health*. (2023) 23:227. doi: 10.1186/s12889-023-15171-3
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
4. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. (2020) 5:536–44. doi: 10.1038/s41564-020-0695-z
5. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiol Mol Biol Rev*. (2005) 69:635–64. doi: 10.1128/MMBR.69.4.635-664.2005
6. Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Virol*. (2020) 127:104371. doi: 10.1016/j.jcv.2020.104371
7. Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J*. (2020) 39:e105114. doi: 10.15252/embj.20105114
8. Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, Santos RA. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. *Fertil Steril*. (2011) 95:176–81. doi: 10.1016/j.fertnstert.2010.06.060
9. la Pena Sol D, Isela SR, Zandy OV, Monica NM, Irene XR, Omar AH. Changes in trophoblasts gene expression in response to perchlorate exposition. *Toxicol In Vitro*. (2018) 50:328–35. doi: 10.1016/j.tiv.2018.04.006
10. Li R, Yin T, Fang F, Li Q, Chen J, Wang Y, et al. Potential risks of SARS-CoV-2 infection on reproductive health. *Reprod BioMed Online*. (2020) 41:89–95. doi: 10.1016/j.rbmo.2020.04.018
11. Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Mol Hum Reprod*. (2020) 26:367–73. doi: 10.1093/molehr/gaaa030
12. Hu Y, Tao R, Chen L, Xiong Y, Xue H, Hu L, et al. Exosomes derived from pioglitazone-pretreated MSCs accelerate diabetic wound healing through enhancing angiogenesis. *J Nanobiotechnol*. (2021) 19:150. doi: 10.1186/s12951-021-00894-5
13. Bentov Y, Beharier O, Moav-Zafir A, Kabessa M, Godin M, Greenfield CS, et al. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. *Hum Reprod*. (2021) 36:2506–13. doi: 10.1093/humrep/deab182
14. Mohr-Sasson A, Haas J, Abuhassira S, Sivan M, Doitch Amdurski H, Dadon T, et al. The effect of Covid-19 mRNA vaccine on serum anti-Mullerian hormone levels. *Hum Reprod*. (2022) 37:534–41. doi: 10.1093/humrep/deab282
15. Mohr-Sasson A, Haas J, Sivan M, Zehori Y, Hemi R, Orvieto R, et al. The effects of Covid-19 mRNA vaccine on adolescence gynecological well-being. *Arch Gynecol Obstet*. (2023) 307:1625–31. doi: 10.1007/s00404-023-06981-2
16. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria. *Hum Reprod*. (2011) 26:1616–24. doi: 10.1093/humrep/der092
17. Huang J, Guan T, Tian L, Xia L, Xu D, Wu X, et al. Impact of inactivated COVID-19 vaccination on female ovarian reserve: a propensity score-matched retrospective cohort study. *Front Immunol*. (2023) 14:1198051. doi: 10.3389/fimmu.2023.1198051
18. Shrikhande L, Shrikhande B, Shrikhande A. AMH and its clinical implications. *J Obstet Gynaecol India*. (2020) 70:337–41. doi: 10.1007/s13224-020-01362-0
19. Russell N, Gilmore A, Roudabush WE. Clinical utilities of anti-mullerian hormone. *J Clin Med*. (2022) 11(23):7209. doi: 10.3390/jcm11237209
20. Tal R, Seifer DB. Ovarian reserve testing: a user's guide. *Am J Obstet Gynecol*. (2017) 217:129–40. doi: 10.1016/j.ajog.2017.02.027
21. Gat I, Kedem A, Dvir M, Umanski A, Levi M, Hourvitz A, et al. Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. *Andrology*. (2022) 10:1016–22. doi: 10.1111/andr.13209
22. Carlsen E, Andersson AM, Petersen JH, Skakkebaek NE. History of febrile illness and variation in semen quality. *Hum Reprod*. (2003) 18:2089–92. doi: 10.1093/humrep/deg412
23. Josso N. Anti-mullerian hormone: hormone or growth factor? *Prog Growth Factor Res*. (1990) 2:169–79. doi: 10.1016/0955-2235(90)90003-3
24. Arai H, Minami Y, Chi S, Utsu Y, Masuda S, Aotsuka N. Molecular-targeted therapy for tumor-agnostic mutations in acute myeloid leukemia. *Biomedicines*. (2022) 10(12):3008. doi: 10.3390/biomedicines10123008
25. Josso N, Picard JY. Genetics of anti-Mullerian hormone and its signaling pathway. *Best Pract Res Clin Endocrinol Metab*. (2022) 36:101634. doi: 10.1016/j.beem.2022.101634
26. Ding T, Wang T, Zhang J, Cui P, Chen Z, Zhou S, et al. Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in wuhan, China: an observational study. *Front Med (Lausanne)*. (2021) 8:635255. doi: 10.3389/fmed.2021.635255
27. Gullo G, Lopez A, Loreto C, Cucinella G, La Verde M, Andrisani A, et al. COVID-19 and female fertility: an observational prospective multicenter cohort study: upholding reproductive rights in emergency circumstances. *Diagnostics (Basel)*. (2024) 14(19):2118. doi: 10.3390/diagnostics14192118
28. Yalcin AD, Yalcin AN. Future perspective: biologic agents in patients with severe COVID-19. *Immunopharmacol Immunotoxicol*. (2021) 43:1–7. doi: 10.1080/08923973.2020.1818770
29. Fidicicchi T, Fruzzetti F, Lete Lasa LI, Calaf J. COVID-19, gender and estroprogestins, what do we know? *Eur J Contracept Reprod Health Care*. (2022) 27:67–74. doi: 10.1080/13625187.2021.2000959
30. Soysal C, Yilmaz E. The effect of COVID-19 vaccine on ovarian reserve. *Saudi Med J*. (2022) 43:486–90. doi: 10.15537/smj.2022.43.5.20220007
31. Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: A U.S. Cohort. *Obstet Gynecol*. (2022) 139:481–9. doi: 10.1097/AOG.0000000000004695
32. Edelman A, Boniface ER, Male V, Cameron ST, Benhar E, Han L, et al. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. *BMJ Med*. (2022) 1(1):e000297. doi: 10.1136/bmjmed-2022-000297
33. Wesselink AK, Hatch EE, Rothman KJ, Wang TR, Willis MD, Yland J, et al. A prospective cohort study of COVID-19 vaccination, SARS-coV-2 infection, and fertility. *Am J Epidemiol*. (2022) 191:1383–95. doi: 10.1093/aje/kwac011
34. Wu Y, Cao M, Lin Y, Xu Z, Liang Z, Huang Q, et al. Inactivated COVID-19 vaccination does not affect *in vitro* fertilization outcomes in women. *Hum Reprod*. (2022) 37:2054–62. doi: 10.1093/humrep/deac160
35. Khodavirdilou R, Pournaghi M, Rastgar Rezaei Y, Hajizadeh K, Khodavirdilou L, Javid F, et al. Does Anti-Mullerian hormone vary during a menstrual cycle? A systematic review and meta-analysis. *J Ovarian Res*. (2022) 15:78. doi: 10.1186/s13048-022-01006-z

Frontiers in Endocrinology

Explores the endocrine system to find new therapies for key health issues

The second most-cited endocrinology and metabolism journal, which advances our understanding of the endocrine system. It uncovers new therapies for prevalent health issues such as obesity, diabetes, reproduction, and aging.

Discover the latest Research Topics

[See more →](#)

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact

