Sleep Medicine:X 6 (2023) 100089

Contents lists available at ScienceDirect

Sleep Medicine: X

journal homepage: www.sciencedirect.com/journal/sleep-medicine-x

COVID-19 breakthrough infections and sleep disorders: A population-based propensity matched analysis

Mantavya Punj [a,*], Aakash Desai [b], Jana G. Hashash [b], Francis A. Farraye [b], Pablo R. Castillo [c]

[a] Kadlec Regional Medical Center, USA
[b] Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA
[c] Department of Allergy, Pulmonary, and Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

ARTICLE INFO

Keywords:
COVID-19
Long-COVID
Breakthrough infections
Sleep disorders
Insomnia
Sleep deprivation
Vaccination

ABSTRACT

Objectives: Examine risks for breakthrough COVID-19 infections in vaccinated patients with selected sleep disorders.
Methods: Real-time search and analysis using the TriNetX platform to evaluate risk of COVID-19 breakthrough infections (BTI) for patients having ICD-10 diagnoses relating to insomnia, circadian rhythm disorders, and inadequate sleep. The sleep disorder and control cohorts underwent propensity matching including factors for age, gender, race, ethnicity, and multiple co-morbid conditions.
Results: Of 24,720 patients identified as having a sleep disturbance relating to insomnia, circadian rhythm disorder, or inadequate sleep, 815 (3.2 %) were found to have a developed a BTI. There was a significant increased risk of BTI noted between the sleep disorder and control cohorts (adjusted odds ratio (aOR) of 1.40, 95 % confidence interval (CI) of 1.23–1.58). Subgroup analysis showed an elevated risk for BTI receiving two doses (aOR 1.53, 95 % CI 1.24–1.89) versus three doses (aOR 1.45, 95 % CI 1.24–1.69). Patients with the sleep disturbance were not found to be at an increased risk of hospitalization, intubation, death, or composite outcome of death and intubation.
Conclusion: The presence of having a diagnosis of insomnia, circadian rhythm disorder, or inadequate sleep was associated with increased risk of COVID-19 breakthrough infection.

1. Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to significant morbidity and mortality on a global scale. As of May 2023, there have been over 767 million confirmed causes and over 6.9 million deaths [1]. Vaccination efforts against COVID-19 played an important role in lowering morbidity and mortality associated with COVID-19 [2]. There has also been emerging evidence of waning immunity and breakthrough infections (BTI) despite vaccination efforts [3–5]. Higher rates of BTI have been shown to be present in immunosuppressed patients including those with HIV, rheumatoid arthritis, and solid organ transplant [6]. There has been an increased focus on identifying and addressing additional factors which have an impact on the effectiveness of vaccines, especially as new variants have emerged.

Sleep has not been at the forefront when thinking of factors that affect vaccine efficacy despite there being a growing body of evidence examining the relationship between the immune system and sleep. Early evidence noted sleep restriction at the time of Influenza vaccination led to decreased antibody titers post inoculation [7]. Another study showed that subjects with adequate sleep who received Hepatitis A virus (HAV) vaccine had almost a twofold higher HAV antibody titers at 4 weeks compared to a sleep deprived group [8]. A recent meta-analysis examining insufficient sleep and antibody response to vaccination noted that insufficient sleep decreases the response to anti-viral vaccination; however, findings were more robust in men versus women [9]. One limiting factor of these studies has been the relatively small number of patients involved in the studies themselves [9]. The presence of chronic insomnia has shown to be associated with a lower antibody titer after Influenza vaccination versus in subjects without insomnia [10]. Shorter sleep duration, confirmed with actigraphy and sleep diaries, was noted to have lower secondary antibody response at the six-month mark for patients receiving Hepatitis B vaccination series [11].

Our study aims to further the level of evidence demonstrating the

* Corresponding author. 888 Swift Blvd, Richland, WA 99352, USA
E-mail address: mantavya.punj@kadlec.org (M. Punj).

https://doi.org/10.1016/j.sleepx.2023.100089
Received 30 June 2023; Received in revised form 30 September 2023; Accepted 11 October 2023
Available online 12 October 2023

relationship between sleep and vaccination efficacy. In this effort, we used data from a large national database to examine the relationship between the risk of breakthrough COVID-19 infections in patients with certain sleep related disturbances.

2. Material and methods

2.1. Database

A retrospective cohort study utilizing the multi-Institutional research network TriNetX (Cambridge, USA) was performed. TriNetX is a global federated research network which provides real-time access to de-identified electronic health records (EMRs) of more than 85 million patients within 52 health care organizations (HCOs) in the United States of America. The de-identification process is determined and done at a network-level and attested to through a formal determination by a qualified expert as defined in the Health Insurance Portability and Accountability Act Privacy Rule (HIPAA). TriNetX obfuscates patient counts which are less than 10 to ensure patient anonymity. Clinical variables are derived directly from EMRs of included HCOs as well as retrieved through a built-in natural language processing system that extracts variables from clinical documents. Robust quality assurance is achieved at the time of extraction from EHRs before inclusion in the database, in a systemic and standardized format. The interface only provides aggregate counts and statistical summaries to protect patient health information and ensures that the data remain de-identified at all levels of data retrieval and dissemination.

2.2. Study participants and cohorts

2.2.1. Study participants and cohorts

A real-time search and analysis of US Collaborative Network in the TriNetX platform was conducted and updated through February 11, 2022. The sleep disorder cohort included adults aged 18 years and older who had International Classification of Disease, Ninth Revision and Tenth Revision, Clinical Modification (ICD-10-CM) code in their EHR for circadian rhythm disorders and insomnia. A complete list of ICD-10-CM codes can be found in Supplementary Table 1. For the purposes of this study, the diagnoses which were included in the sleep disorder cohort did not include obstructive sleep apnea (OSA) since evidence has not been definitive between COVID-19 outcomes and OSA. One meta-analysis noted that OSA was associated with progressing to severe COVID-19, ICU admission, and the need of mechanical ventilation [12]. However, this analysis mainly consisted of reviewing retrospective cohort studies. Furthermore, a cross sectional web-based survey across multiple countries noted that participants who were at high risk of OSA were also at increased odds of having COVID-19 [13]. However, a major limitation of this study was the use of subjective web-based data with self-reported answers about COVID-19, hospitalization, and only screening questionnaires regarding the risk of obstructive sleep apnea. In comparison, the only study to date which utilized objective sleep data with polysomnography and SARS-CoV-2 serology demonstrated a lack of relationship between OSA and SARS-CoV-2 seropositivity and symptomatology [14]. Of note, the same study also noted further studies with objective measures are needed to confirm their findings. Thus, based on these contrasting findings at the time of our analysis, we elected to exclude OSA in our analysis.

Patients in the sleep disorder cohort that had received at least one dose of COVID-19 vaccine were identified using Current Procedural Terminology (CPT) relevant codes for BNT162b2 (0002A), mRNA-1273 (0012A) or 26 CE. COV2 (0031A) vaccine. Patients were required to have an ICD-10-CM code related to a sleep disorder within 3 months prior to vaccine administration. Control cohort included patients without ICD-10-CM codes for a sleep disorder who had received a COVID-19 vaccine.

2.3. Study outcomes

The primary outcome of the study was to compare the risk of COVID-19 breakthrough infection (BTI) within 6 months of vaccination and its adverse outcomes between the sleep disorder cohort and control cohort. Patients diagnosed with COVID-19 in their respective cohorts were identified using either ICD-10-CM code in their EHR: U07.1 COVID-19; or a positive test result identified with COVID-19 specific laboratory Logical Observation Identifiers Names and Codes (LOINCs), SARS coronavirus 2 and related RNA (TNX:LAB:9088). TriNetX allows defining index events and excluding patients with outcomes prior to the index event. This functionality allowed us to find patients who had SARS-CoV-2 infection after the COVID vaccine. Subgroup analysis was performed based on the number of vaccine doses (2 or 3 doses). We only included patients who had CPT codes for BNT162b2 (0002A) or mRNA-1273 (0012A) as only these vaccines have distinctions available for one, two or three doses in the TriNetX platform. Adverse events after COVID-19 included hospitalization, intensive care unit (ICU) care, endotracheal intubation, mortality and composite outcome of intubation and mortality within 30 days. Status of hospitalization and ICU care was based on CPT code “Hospital Inpatient Services” (1013659) and “Critical Care Services” (1013729) respectively. Status of death was based on vital status code “Deceased” that TriNetX regularly imports from the Social Security Death index. Endotracheal intubation was identified based on CPT code 31500 “Intubation, endotracheal, emergency procedure” or mechanical ventilation CPT code 5A09.

2.4. Statistical analysis

All statistical analysis were conducted using the TriNetX software using the browser-based real-time analytics feature, TriNetx Live (TriNetX LLC, Cambridge, MA). Baseline characteristics of cohorts were described using means, standard deviations, and proportions. One-to-one (1:1) propensity score matching was performed for age, gender, race, ethnicity, hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, heart failure, chronic kidney disease, chronic lower respiratory disease, cirrhosis, malignancy, autoimmune diseases, BMI and nicotine dependence between the sleep disorder cohort and control cohort. TriNetX platform utilizes input matrices of the user-identified covariates to conduct logistic regression analysis to obtain propensity scores for all individual subjects. The propensity scores generated are used to match patients using greedy nearest-neighbor algorithms with a caliper width of 0.1 pooled standard deviations. TriNetX randomizes the order of rows to eliminate bias resulting from nearest-neighbor algorithms. After propensity matching, the risk of each outcome was calculated and expressed as adjusted odds ratios (aOR) with 95 % confidence intervals (CIs). Two-sided p-values <0.05 was considered as statistically significant. Statistical analysis was performed using the TriNetX Analytics function in the online research platform.

3. Results

We identified 24,720 patients with a sleep disorder that had received a COVID-19 vaccine (mean age 59.2+/-16.5, female 64.5 %). In this cohort, 19,107 patients (77 %) had received BNT162b2 (0002A), 5110 (20 %) had received mRNA-1273 (0012A) and 801 (3 %) had received 26 CE. COV2 (0031A) vaccine. 11,503 (46.5 %) patients had received two doses and 7938 (32.1 %) patients had received three doses of either BNT162b2 (0002A) or mRNA-1273 (0012A) vaccines. 24,226 (98 %) patients had insomnia, 1052 (4.5 %) had circadian rhythm sleep disorder and 809 (3.2 %) had sleep deprivation. Demographics and co-morbid diseases before and after propensity score matching in the sleep disorder and control cohort can be found in Table 1.

815 patients (3.2 %) developed breakthrough COVID-19 in the sleep disorder cohort (mean age 59+/-16, female 64 %). After propensity score matching, patients in the sleep disorder cohort were at an

Table 1
Clinical and demographic factors.

	Before Matching			After Matching		
	Sleep Disorder	No Sleep Disorder	*P* Value	Sleep Disorder	No Sleep Disorder	*P* Value
Total Number of Patients, n	24,720	1,630,721		24,717	24,717	
Demographic Factors:						
Age	59.2+/-16.5	52.2+/-19.1	<0.0001	59.2+/-16.5	59.5+/-16.7	0.0405
Mean Body Mass Index (BMI)	29.6+/-6.93	28.9+/-6.59	<0.0001	29.6+/-6.93	29.9+/-6.97	0.0001
Female	15,562	899,969	<0.0001	15,559	15,459	0.3522
Male	9156	729,368	<0.0001	9156	9252	0.3718
White	18,667	1,081,608	<0.0001	18,664	18,675	0.9084
Black	3753	231,178	<0.0001	3753	3853	0.2126
Comorbid Conditions:						
Essential Hypertension	15,486	392,519	<0.0001	15,483	15,687	0.0573
Hyperlipidemia	15,313	379,789	<0.0001	15,310	15,694	0.0004
Neoplasms	13,221	324,741	<0.0001	13,218	13,336	0.2872
Chronic lower respiratory disorders	8990	170,553	<0.0001	8987	8837	0.1600
Diabetes	6902	168,660	<0.0001	6899	6816	0.4044
Ischemic Heart Disease	5760	115,958	<0.0001	5759	5494	0.0045
Nicotine Dependence	5178	93,964	<0.0001	5175	5070	0.2440
Chronic Kidney Disease	3716	69,024	<0.0001	3713	3575	0.0800
Heart Failure	3148	51,197	<0.0001	3146	2943	0.0055
Rheumatoid Arthritis	1209	18,688	<0.0001	1207	1028	0.0001
Psoriasis	876	17,804	<0.0001	873	796	0.0552
Cirrhosis	767	9798	<0.0001	766	599	<0.0001
Ulcerative Colitis	413	7976	<0.0001	411	332	0.0035
Systemic Lupus Erythematous	394	5762	<0.0001	392	306	0.0010
Crohn's Disease	323	6741	<0.0001	322	253	0.0038
Ankylosing Spondylitis	115	1855	<0.0001	115	86	0.0404

N: Number of patients.

increased risk for breakthrough COVID-19 (aOR 1.40, 95 % CI 1.23–1.58). Sub-group analysis based on number of vaccine doses showed patients with two doses (aOR 1.53, 95 % CI 1.24–1.89) and three doses (aOR 1.45, 95 % CI 1.24–1.69) were also at an increased risk for breakthrough COVID-19 compared to control cohort after propensity score matching.

Patients in the sleep disorder cohort that developed breakthrough COVID-19 were not at an increased risk for hospitalization (aOR 1.23, 95 % CI 0.93–1.63), ICU care (aOR 0.9, 95 % CI 0.54–1.50), intubation (aOR 0.86, 95 % CI 0.47–1.59), mortality (aOR 1.47, 95 % CI 0.72–3.00) and composite outcome (aOR 0.62, 95 % CI 0.33–1.17) after propensity score matching. These trends were consistent with further subgroup analysis for 2 dose series versus the 3-dose subgroups (Table 2). See Supplementary Table 2 for clinical and demographic factors for the set of patients used in evaluation of these clinical outcomes.

Table 2
Clinical outcomes of breakthrough infections.

	Sleep Disorder, *N*	Control, *N*	Adjusted Odds Ratio (95 % Confidence Interval)
Hospitalization	127	106	1.23 (0.93–1.63)
Critical Care	29	32	0.9 (0.54–1.50)
Intubation	20	23	0.86 (0.47–1.59)
Death	19	13	1.47 (0.72–3.00)
Composite (Intubation + Death)	16	26	0.62 (0.33–1.17)
2 Dose Subgroup			
Hospitalization	99	97	1.02 (0.75–1.38)
Critical Care	–	–	–
Intubation	17	18	0.94 (0.48–1.84)
Death	15	14	1.07 (0.51–2.23)
Composite (Intubation + Death)	17	21	0.83 (0.43–1.58)
3 Dose Subgroup			
Hospitalization	61	43	1.47 (0.97–2.2)
Critical Care	13	11	1.1 (0.52–2.67)
Intubation	10	10	1.0 (0.41–2.42)
Death	10	10	1.0 (0.41–2.42)
Composite (Intubation + Death)	10	10	1.03 (0.42–2.51)

N: Number of patients.

4. Discussion

Our study shows that there is a higher risk of breakthrough COVID -19 infections (BTIs) in vaccinated patients with sleep disorders in comparison to patients without any sleep disorders (aOR 1.40, 95 % CI 1.23–1.58). This trend was also consistent across subgroups of patients receiving two doses (aOR 1.53, 95 % CI 1.24–1.89) and three doses (aOR 1.45, 95 % CI 1.24–1.69). Our findings of increased BTIs in patients with sleep disturbances is consistent with prior studies which have shown that clinical protection post vaccination is decreased in patients with disturbed sleep [7–11]. Sleep after Hepatitis A vaccination doubled virus-specific T helper cells that are known to play a crucial role in adaptive immunity [15]. Furthermore, nocturnal sleep also has been shown to facilitate the cytokine environment which promotes the adaptive immune response [16]. These prior studies provide support for sleep having an impact on vaccine efficacy and are consistent with our results. However, specific mechanisms of sleep affecting vaccine efficacy through clearly outlined cellular mechanisms remain undetermined.

Another implication to consider with an increased risk of COVID-19 BTI is the clinical burden associated with the post-acute sequelae of SARS-CoV-2 (PASC), or commonly known as Long Covid. Literature is continuing to expand on this new syndrome however a consensus is emerging regarding symptoms including pulmonary manifestations like persistent shortness of breath, and extrapulmonary manifestations like chronic fatigue, sleep disturbances, and gastrointestinal difficulties [17]. An examination of a national database involving the US Department of Veterans Affairs (VA) found that patients with COVID-19 had higher risk of death and health care utilization beyond the first 30 days of the illness and this finding was present in the cohort of patients who did not require any hospitalization [18]. A subsequent analysis by the same authors found similar trends for patients with BTI who survived the first 30 days of the illness when compared to contemporary controls with no record of a positive SARS-CoV-2 test [19]. These findings suggest that post-acute sequelae, even in patients with BTI, has clinical and

societal implications. Thus, optimizing risk factors like sleep related disorders should be part of the management of PASC patients.

Our study did not find any significant differences between rates of hospitalization, intubation, and mortality between sleep disorder and control cohorts (Table 2). In contrast, diseases like chronic obstructive pulmonary disease (COPD), primary lung diseases, hypertension, underlying immunocompromised status, diabetes, and obesity have shown to have higher risk for severe outcomes due to COVID-19 [20]. The lack of significant difference between adverse outcomes between patients with sleep disorders and controls is likely due to the fact both cohorts were vaccinated and in turn have clinical protection against severe disease.

There are limitations in our study given the nature of our analysis and study design. Our analysis was completed using a large multi-institutional EMR database and therefore did not involve the use of objective measures of sleep duration like actigraphy or subjective measures like sleep diaries or patient reported questionnaires. Furthermore, our study design does not capture the lack of uniformity in exposure and response to BTIs that is likely present across the various participating institutions along with not capturing patients who did not report for clinical evaluation. Additionally, there was no component of quantitative vaccination data, like immunoglobulin titers, that was used in our analysis. This option was not available for search based on our study design. Despite these limitations, the strength of our study centers on leveraging the breadth and depth of the TriNetX database and complimenting the findings of prior work which has examined vaccine responsiveness in a much smaller number of patients. Our results are novel due to utilization of a large, propensity matched US-based multi-institutional cohorts along with the fact that cohorts were not only matched for basic demographic factors but also multiple comorbidities which can affect vaccination efficacy.

5. Conclusion

Our retrospective cohort study provides real world evidence that patients with sleep disorders have a higher risk of getting COVID-19 breakthrough infections, but this did not result in higher rates of hospitalization, intubation, and mortality. Our analysis did not incorporate OSA as part of the sleep disorders cohort. As COVID-19 management shifts from centering on acute care to managing it chronically, or even seasonally, the findings in our study point to expanding clinical assessments to include sleep associated disorders like insomnia and circadian rhythm disorders, especially in the context of ever-increasing supplies of therapeutics and vaccines.

CRediT authorship contribution statement

Mantavya Punj: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Aakash Desai:** Conceptualization, Methodology, Writing – original draft, Formal analysis. **Jana G. Hashash:** Writing – original draft. **Francis A. Farraye:** Conceptualization, Writing – original draft. **Pablo R. Castillo:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleepx.2023.100089.

References

[1] World Health Organization. Novel Coronavirus (2019-nCoV) situation reports. 2020. Published, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. 6/1/23.

[2] Mohammed I, Nauman A, Paul P, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. Hum Vaccines Immunother 2022;18(1):2027160. https://doi.org/10.1080/21645515.2022.2027160.

[3] Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of covid-19 vaccines against the B.1.617.2 (delta) variant [published correction appears in N engl J med. 2023 feb 16;388(7):672]. N Engl J Med 2021;385(7):585–94. https://doi.org/10.1056/NEJMoa2108891.

[4] Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med 2021;27(12):2136–43. https://doi.org/10.1038/s41591-021-01583-4.

[5] Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. Preprint. medRxiv 2021:2021. https://doi.org/10.1101/2021.08.06.21261707. 08.06.21261707. Published 2021 Aug 21.

[6] Sun J, Zheng Q, Madhira V, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. JAMA Intern Med 2022;182(2):153–62. https://doi.org/10.1001/jamainternmed.2021.7024.

[7] Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. JAMA 2002;288(12):1471–2. https://doi.org/10.1001/jama.288.12.1471-a.

[8] Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. Psychosom Med 2003;65(5):831–5. https://doi.org/10.1097/01.psy.0000091382.61178.f1.

[9] Spiegel K, Rey AE, Cheylus A, et al. A meta-analysis of the associations between insufficient sleep duration and antibody response to vaccination. Curr Biol 2023;33(5):998–1005.e2. https://doi.org/10.1016/j.cub.2023.02.017.

[10] Taylor DJ, Kelly K, Kohut ML, Song KS. Is insomnia a risk factor for decreased Influenza vaccine response? Behav Sleep Med 2017 Jul-Aug;15(4):270–87. https://doi.org/10.1080/15402002.2015.1126596. Epub 2016 Apr 14. PMID: 27077395; PMCID: PMC5554442.

[11] Prather AA, Hall M, Fury JM, et al. Sleep and antibody response to hepatitis B vaccination. Sleep 2012;35(8):1063–9. https://doi.org/10.5665/sleep.1990. 2012 Aug 1.

[12] Hariyanto TI, Kurniawan A. Obstructive sleep apnea (OSA) and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: a systematic review and meta-analysis. Sleep Med 2021;82:47–53. https://doi.org/10.1016/j.sleep.2021.03.029.

[13] Chung F, Waseem R, Pham C, et al. The association between high risk of sleep apnea, comorbidities, and risk of COVID-19: a population-based international harmonized study. Sleep Breath 2021;25(2):849–60. https://doi.org/10.1007/s11325-021-02373-5.

[14] Del Brutto OH, Mera RM, Castillo PR, Recalde BY, Costa AF. Previously diagnosed obstructive sleep apnea is not associated with increased risk of SARS-CoV-2 infection in community-dwelling older adults living in a highly endemic setting [published online ahead of print, 2021 Apr 12]. Clin Neurol Neurosurg 2021;205:106639. https://doi.org/10.1016/j.clineuro.2021.106639.

[15] Lange T, Dimitrov S, Bollinger T, Diekelmann S, Born J. Sleep after vaccination boosts immunological memory. J Immunol 2011;187(1):283–90. https://doi.org/10.4049/jimmunol.1100015.

[16] Lange T, Dimitrov S, Fehm HL, Westermann J, Born J. Shift of monocyte function toward cellular immunity during sleep. Arch Intern Med 2006;166(16):1695–700. https://doi.org/10.1001/archinte.166.16.1695.

[17] Raveendran AV, Jayadevan R, Sashidharan S. 5. Long COVID: an overview [published correction appears in Diabetes Metab Syndr, vol. 16; 2022 May, 102504. https://doi.org/10.1016/j.dsx.2021.04.007 [published correction appears in Diabetes Metab Syndr. 2022 Dec;16(12):102660]. Diabetes Metab Syndr. 2021;15(3):869-875.

[18] Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594(7862):259–64. https://doi.org/10.1038/s41586-021-03553-9.

[19] Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med 2022;28(7):1461–7. https://doi.org/10.1038/s41591-022-01840-0.

[20] Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: deleterious impact on infected patients. J Infect Public Health 2020;13(12):1833–9. https://doi.org/10.1016/j.jiph.2020.07.014.