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Review Article

Risk Factors Associated with Long COVID-19: A Narrative Review

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Abstract

Studying the consequences of coronavirus infections caused by the SARS-CoV-2 virus has become crucial in light of its widespread occurrence in society, and the frequent observation of persistent symptoms and health impairments following recovery from the acute phase of the illness. The pandemic has brought about a new chronic, debilitating condition known as long COVID, which deserves serious attention from scientific and medical communities. Currently, we have conflicting knowledge about the factors that may increase the risk of developing such a debilitating condition. The aim of this review was to assess prognostic risk factors for the development of post-COVID-19 conditions. We conducted a systematic search in the databases PubMed, Web of Science, Scopus, CyberLeninka, and the eLibrary electronic library for reports on post-COVID-19 conditions up to April 2024. A total of 52 full-text studies meeting the inclusion criteria were analyzed from both Russian and international sources. The resulting review paper presents a comprehensive overview of recent studies aimed at examining factors preceding COVID-19 infection (gender, age, comorbidities, and others), factors related to COVID-19 infection (severity of acute phase, influence of biomarkers), and the impact of vaccinations on long-term consequences. Much remains unclear regarding long COVID and its risk factors due to conflicting data, possibly caused by the variety of symptoms and complex pathophysiology, including long-term organ damage and unresolved inflammatory processes. This review underscores the high prevalence of post-COVID conditions and the ambiguity in identifying risk factors, necessitating further research for effective management of these conditions.

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1. Introduction

Studying the consequences of the coronavirus infection caused by the SARS-CoV-2 virus has become highly relevant due to its widespread prevalence and the frequent observation of persistent symptoms and health impairments after recovery from the acute phase of the illness. Post-COVID-19 condition refers to a state where patients experience symptoms following an acute SARS-CoV-2 infection. According to the World Health Organization, these symptoms persist for at least two months after the onset of initial illness signs and cannot be attributed to other causes. Due to its prevalence and clinical significance, this syndrome has been officially recognized as a disease and included in the International Classification of Diseases, 10th Revision, under code U09.9, also known as post-COVID syndrome [1].

In the Republic of Kazakhstan, the importance of addressing post-COVID-19 Condition (post-COVID syndrome) has been recognized at the highest levels of the healthcare system. On September 16, 2021, the Unified Commission for the Quality of Medical Services of the Ministry of Health developed and approved the first clinical protocol regulating the diagnosis and treatment of post-COVID syndrome in adults, designated as Protocol No. 147. This protocol has undergone periodic revisions, with the latest being Protocol No. 178 on January 30, 2023, underscoring the continued relevance of post-COVID syndrome in Kazakhstan's medical practice. Additionally, on April 20, 2022, the Ministry of Health issued Order No. 302, which provided detailed instructions for organizing medical care and rehabilitation for individuals suffering from post-COVID syndrome.

In a broader regional context, the Eurasian Association of Therapists launched the "ACTIV SARS-CoV-2" registry in June 2020. This registry included over 4600 patients with comorbid conditions who had experienced COVID-19, covering countries such as Russia, Armenia, Kazakhstan, Kyrgyzstan, Uzbekistan, Belarus, and Moldova. The data collected from this registry has provided unique insights, allowing for prognostic assessments of the impact of SARS-CoV-2 on the progression of comorbid conditions. Analysis of a cohort of 1,003 individuals revealed that conditions such as diabetes mellitus, obesity, arterial hypertension, chronic kidney disease, and advanced age (over 60 years) significantly worsened the prognosis and increased the risk of fatal outcomes in COVID-19 patients. Furthermore, clusters of diseases typical among deceased patients were identified, with the most unfavorable cluster comprising of arterial hypertension, ischemic heart disease, chronic heart failure, and diabetes mellitus. This ongoing research and the evolving clinical protocols highlight the critical need to understand and manage post-COVID syndrome effectively, reflecting its significant impact on public health in Kazakhstan and the broader Eurasian region.

Recent meta-analyses indicate that a significant number of individuals recovering from COVID-19 experience symptoms for an extended period. According to research findings, between 30% to 50% of patients report persistent symptoms that may last up to one year after infection [4,5]. The latest data

reveals that two years after the initial COVID-19 infection, 42% of recovered patients still experience long-term consequences of the disease [6].

Post-COVID-19 condition can manifest in approximately 200 different and overlapping symptoms, such as fatigue, as well as sensory, neurological, musculoskeletal, dermatological, respiratory, and cardiovascular symptoms [7], adversely affecting daily functioning and quality of life, which could have serious economic implications for society [8]. The new chronic, disabling condition known as long COVID brought about by the pandemic, thus, deserves serious attention from scientific and medical communities.

Currently, we have conflicting knowledge regarding the factors that may increase the risk of developing such debilitating conditions. Current research is focused on identifying risk factors associated with post-COVID-19 conditions, which can be divided into two categories: factors existing before infection (e.g., age, gender, pre-existing health conditions, and comorbidities) and factors related to the infectious process itself (e.g. disease severity, initial symptoms, viral load, hospitalization, and intensive care unit admission).

This review aims to examine the risk factors influencing the onset of post-COVID-19 conditions, since identifying predictors of long COVID-19 is crucial for healthcare planning and management strategies for these patients. The aim of this review article is to evaluate the prognostic risk factors for the development of post-COVID-19 conditions based on literature data.

2. Materials and Methods

We conducted a search in the databases PubMed, Web of Science, Scopus, CyberLeninka, and the eLibrary electronic library for reports on post-COVID-19 conditions up to April 2024. The search used the following keywords: "long COVID," "post-acute," "Post-COVID conditions," "risk factors," "comorbidity," "age," "sex," and others. In planning and conducting the study, we adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The inclusion criteria for the review included cohort studies, cross-sectional studies, systematic reviews, and meta-analyses that investigate risk factors associated with developing symptoms following acute SARS-CoV-2 infection. Exclusion criteria for the literature review by article types included: case reports, case studies, expert opinions, literature reviews, editorials. Studies reporting on risk factors for post-COVID-19 conditions were considered for inclusion based on title, keywords, and abstract. For each study, the following information was extracted: author, year of publication, sample size, patient diagnosis, and key findings. A total of 52 full-text studies meeting the inclusion criteria were selected from Russian and international search systems for analysis. Figure **1** summarizes these steps.
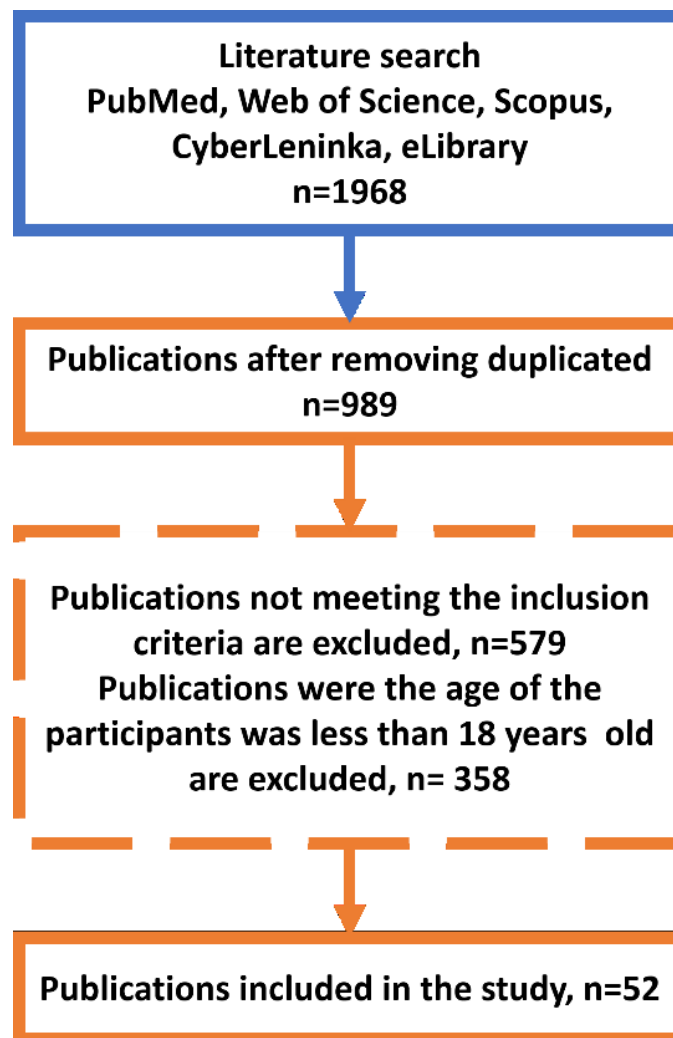
Figure 1: Research flowchart to evaluate the risk factors associated with long COVID-19.

3. Results

We reviewed an extensive meta-analysis encompassing data from 211 studies involving over 13 million individuals and identified key risk factors for developing post-COVID-19 syndrome. These include female gender, older age, severe disease during the acute phase of COVID-19, presence of multiple comorbidities, prolonged hospital stay, and high body mass index (BMI) [9]. For a deeper understanding, we divided the risk factors into two sections in the article: the first part focuses on analyzing factors existing before infection, while the second part explores factors emerging during and after the illness, aiding in determining preventive measures and management strategies for post-COVID conditions. Additionally, we separately examine the impact of vaccination on the occurrence of post-COVID-19 conditions (see Figure **2**).
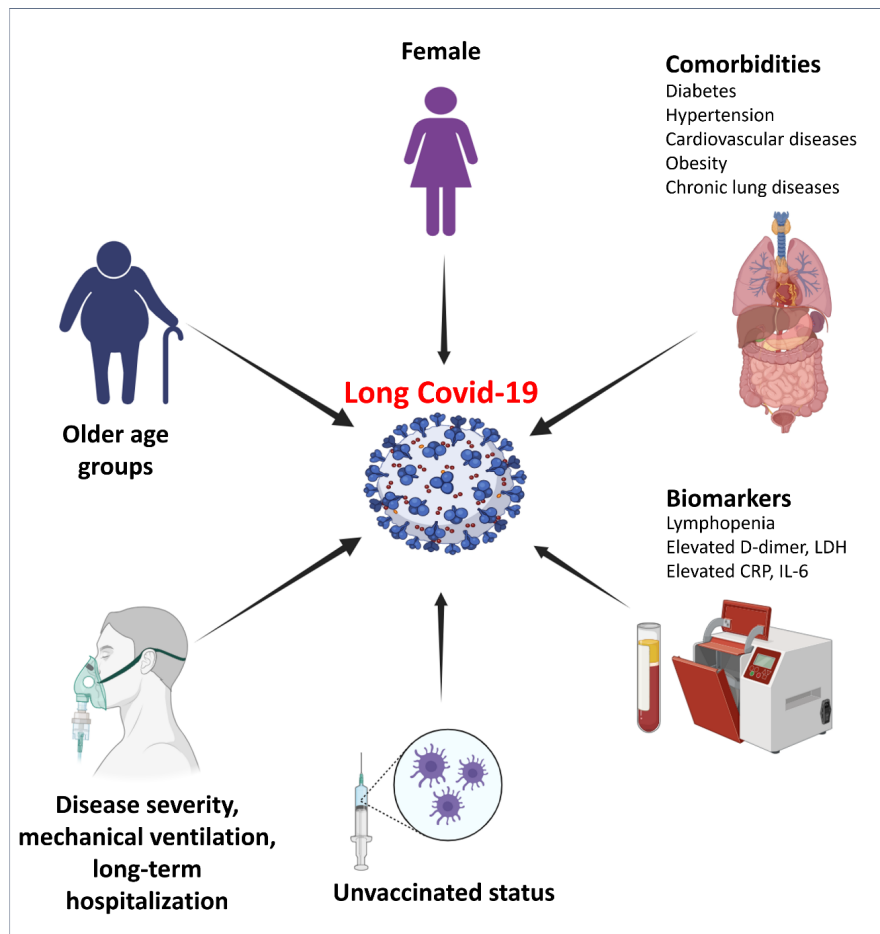
Figure 2: A pictorial demonstration of the various risk factors which when present, make the patients of COVID-19 more susceptible to develop long-COVID-19.

3.1. Factors existing before infection

Post-COVID-19 conditions, which have long-term consequences for a significant number of survivors following the coronavirus pandemic, have become a subject of active scientific research. Special attention has been paid to studying the influence of gender, age, and the presence of comorbidities, which may affect the likelihood of developing such conditions.

3.1.1. Gender

Most articles indicate that being female is associated with a higher risk of developing long COVID-19 [10–26], though two studies reported that female gender was not associated with an increased risk of prolonged COVID-19 [27,28]. Another finding from the review aligns with previous research showing that women are more likely to develop long COVID-19 compared to men [29]. Therefore, it can be inferred that women have an increased risk of developing specific long-term consequences of COVID-19, for which further research is required for clarification.

3.1.2. Age

Old age is a significant risk factor for developing long COVID-19. Some studies indicate an increased risk in individuals over 60 years old [11,15,16,18,19], while others associate it with those over 50 years old ($p < 0.05$) [20]. However, not all studies confirm this relationship: Martínez-Ayala et al. found no statistically significant association between age and prolonged COVID-19 (OR 0.999 [95% CI 0.996–1.002]) [25]. Meanwhile, Subramanian et al. stated that adults aged >70 years have a lower risk of developing prolonged COVID-19 symptoms [30]. This inconsistency highlights the need for additional research to accurately determine age groups at increased risk.

3.1.3. Comorbidities

The literature indicates that the presence of comorbidities can contribute to the development of long COVID-19. Long COVID-19 has been associated with comorbidities such as diabetes mellitus [13, 19], obesity, chronic lung diseases [10, 14], hypertension, and cardiovascular diseases [19, 24].

In a Chinese study, the risk factor of having comorbidities (≥3 chronic diseases) was a significant predictor of severe COVID-19 outcomes. The odds ratio (OR) was 2.71 (95% confidence interval [CI] 1.54-4.79), indicating a statistically significant association between the presence of chronic diseases and severe COVID-19 outcomes [17]. Similarly, another study involving 504 patients found that the development of post-COVID syndrome (PCS) was associated with having ≥3 comorbidities (OR = 2.37, 95% CI 1.19–4.75, p = 0.014), steroid use (OR = 2.13, 95% CI 1.16–3.98, p = 0.016), as well as the presence of congestive phenomena (OR = 1.68, 95% CI 1.05–2.71, p = 0.032) [26]. These findings underscore the importance of controlling and treating comorbidities to reduce the risk of complications following COVID-19 infection.

Emecen et al., in their comprehensive analysis, identified several risk factors associated with reporting symptoms of post-COVID-19 including older age, female gender (OR 1.74, 95% CI 1.57–1.93), poor economic status (OR 1.37, 95% CI 1.14–1.65), current smoking (OR 1.15, 95% CI 1.02–1.29), presence of multiple comorbidities (≥3 conditions, OR 1.78, 95% CI 1.33–2.37), presence of numerous symptoms (>5 symptoms, OR 2.47, 95% CI 2.19–2.78), and hospitalization (intensive care unit admission, OR 2.18, 95% CI 1.51–3.14). These findings underscore the importance of targeted healthcare interventions for individuals who may benefit from post-COVID rehabilitation efforts [25].

3.2. Factors associated with COVID-19 infection

Despite the variety of clinical manifestations and risk factors, the need for further research is underscored by studies on aspects such as the severity of the initial illness, the use of mechanical ventilation, and the pathophysiological processes leading to long-term consequences of SARS-CoV-2 infection.

3.2.1. The severity of COVID-19 and the risk of developing long COVID syndrome

Most studies have not found any association between the long-term course of COVID-19 and the initial severity of the disease during acute COVID-19 [31-34]. However, a review indicated that moderate to severe COVID-19 and having more than four acute symptoms of COVID-19 are risk factors for developing long COVID. Moderate and severe forms of COVID-19 trigger a more pronounced immune response and cytokine storm, leading to greater organ damage and consequently a prolonged course of COVID. Additionally, mechanical ventilation, which can have long-term consequences and cause iatrogenic harm, is often used in the aggressive treatment of severe COVID-19 [35].

The use of mechanical ventilation (MV) and extensive lung involvement areas on chest CT are decisive factors in assessing outcomes in patients after severe COVID-19. A study conducted by Benedetto and colleagues in 2023 identified an association between the need for intensive care and the development of restrictive frontal defects in survivors of mild COVID-19 without pre-existing respiratory diseases [36]. Another study reported that the severity of COVID-19 significantly influenced the risk of developing subsequent conditions. Hospitalized COVID-19 patients had a 26-fold higher risk (OR 25.9) of developing post-COVID syndrome compared to those who only tested positive for PCR [37].

Moreover, another study found that hospitalization related to COVID-19 (OR 3.8, 95% CI 3.05–4.73), prolonged (8–30 days, OR 1.69, 95% CI 1.31–2.17) or extended hospital stay (30+ days, OR 3.38, 95% CI 2.45–4.67), and receiving mechanical ventilation (OR 1.44, 95% CI 1.18–1.74) were associated with an increased likelihood of developing post-COVID-19 conditions [14]. The type of hospitalization—general ward admission (OR 1.247, 95% CI 1.090–1.427) and intensive care unit admission (OR 1.490, 95% CI 1.221–1.818)—was significantly associated with persistent symptoms over a six-month observation period [25]. Indeed, patients experiencing critical conditions often encounter Post-Intensive Care Syndrome (PICS), which involves long-term cognitive, psychological, and physical consequences due to tissue damage [38]. The potential additive impact of COVID-19 on PICS also warrants further investigation.

Asfandiyarova and colleagues note that moderate to severe COVID-19 during the acute phase of infection is a significant risk factor, while mild COVID-19 does not increase the risk of developing long COVID regardless of age or comorbidities [20]. However, another study reported that post-COVID-19 conditions can occur independently of the severity of the initial infection, hospitalization status, age, or pre-existing comorbidities [39]. Similar findings were observed in a study where the patient cohort did not significantly differ based on the severity of COVID-19 during the acute phase [21].

Scientists from the UK demonstrated in one study that nearly two-thirds of hospitalized COVID-19 patients continued to experience long-term symptoms for up to 3 months after discharge from the hospital. The primary predictor of these conditions was COVID-19-induced pneumonia, especially among patients of European descent [40]. In Southeastern Italy, corticosteroid therapy administered during the acute phase was also associated with an increased risk of long COVID. While corticosteroid therapy was

indicated in cases of pneumonia complicated by respiratory failure, there was an excessive prescription of corticosteroid therapy in real-world settings: 64% of patients experienced respiratory failure, and 81% received corticosteroid therapy [12].

3.2.2. Pathophysiological mechanisms and biomarkers

Multivariate regression analysis conducted to identify risk factors associated with long COVID-19 revealed that an increased likelihood was associated with chronic obstructive pulmonary disease (OR 14.35, 95% CI 1.89–109.09; p = 0.010) and higher levels of lactate dehydrogenase (LDH) (OR 3.23, 95% CI 1.34–7.52; p = 0.006), and lower levels of D-dimer (OR 0.164, 95% CI 0.04–0.678; p = 0.012) [41].

Elevated levels of blood urea nitrogen (BUN) and D-dimer have been identified as risk factors for the development of pulmonary dysfunction among survivors of COVID-19 within three months post-discharge from the hospital [42]. Other studies have shown that two months after hospitalization, COVID-19-induced lung injuries are associated with elevated systemic inflammatory biomarkers such as D-dimer, interleukin-6 (IL-6), and C-reactive protein (CRP) [43,44]. Systemic inflammatory biomarkers like CRP, procalcitonin, and neutrophil counts also correlate with radiological changes in the heart, liver, and kidneys in a two to three-month follow-up study of discharged COVID-19 patients [45]. Another study found that elevated levels of D-dimer and CRP, as well as reduced lymphocyte counts, are more common among survivors of COVID-19 with persistent symptoms compared to those who have fully recovered [46]. In another report, lymphopenia was noted to correlate with feelings of chest tightness and increased heart rate, while elevated troponin-1 was associated with recurrence among those suffering from long-term COVID-19 [47]. Thus, fluctuations in the levels of D-dimer, CRP, and lymphocytes are mentioned in several studies and may serve as powerful biomarkers over the long term of COVID-19.

However, some studies have not found significant differences in pro-inflammatory biomarkers (such as CRP, D-dimer, IL-6, CD25, neutrophil count, and lymphocyte count) between COVID-19 patients with persistent symptoms and those without symptoms [33, 34, 48]. These discrepancies may stem from differences in study methods, including selection criteria, measured endpoints, and data collection and analysis processes. Another possible explanation could be the heterogeneous nature of long COVID with diverse symptomatic manifestations, including recurring and remitting periods [49].

In a study by Selvakumar et al., low physical activity (OR 0.96; 95% CI 0.92–1.00) and loneliness (OR 1.01; 95% CI 1.00–1.02) were associated with conditions post-COVID-19, while biological markers did not show a significant association [50]. It is known that levels of inflammatory biomarkers in autoimmune and other chronic inflammatory diseases vary depending on disease activity and duration.

3.3. The impact of vaccination on long-term consequences

According to recent studies, full vaccination against COVID-19 significantly reduces the risk of developing long COVID. Two studies indicated that being unvaccinated is a risk factor for developing long COVID (OR = 0.18) [11] and (OR = 1.21). Similarly, several studies from different countries have shown that full vaccination [16] and vaccination with more than two doses of COVID-19 vaccines (OR = 0.35-0.22, 95% CI 0.08-0.90) [17] are protective factors against long COVID. Such patients had a significantly lower likelihood of developing long-term illness.

The results of a systematic review and meta-analysis demonstrated that patients vaccinated against COVID-19 with two doses had a significantly lower risk of developing long COVID compared to those who were unvaccinated (OR: 0.57; 95% CI: 0.43-0.76) [51]. Farah et al. found that vaccination was associated with lower COVID-19-related mortality (OR = 0.03, 95% CI: 0.0–0.3) and risk of lung fibrosis after COVID-19 (OR: 0.3; 95% CI: 0.1–0.9) [52]. These findings underscore the importance of immunization in preventing not only the acute phase of the disease but also long-term complications.

4. Final Remarks and Future Perspectives

According to recent studies, some key risk factors for developing long COVID include female gender, older age, severity of acute illness, and unvaccinated status. The findings of this review highlight that women are at an increased risk of developing post-COVID syndrome, consistent with previous research [9, 29]. However, there is ambiguity regarding age factors: while older age is often associated with increased risk, some data indicate no significant statistical association [30]. Another significant risk factor is the presence of chronic conditions such as diabetes, obesity, respiratory, and cardiovascular diseases, emphasizing the need for active management and control of these conditions to reduce the risk of complications following infection. Severe illness requiring hospitalization and the use of mechanical ventilation are significant risk factors for subsequent development of post-COVID syndrome. This is associated with a more serious immune response and potential organ damage. Recent studies demonstrate that full vaccination against COVID-19 substantially reduces the risk of developing post-COVID syndrome. Biomarker studies show variability in their association with long-term COVID-19, suggesting diverse pathophysiological mechanisms and supporting hypotheses about the heterogeneity of this condition.

Finally, despite the aforementioned risk factors, some studies have not identified significant predictors of post-COVID syndrome, except possibly the impact of prolonged bedridden states during illness [53]. Reasons for ambiguity in the risk factors of long COVID may include differences in reporting, study design, as well as clinical (e.g., illness severity and treatment received) and demographic (e.g., comorbidities, socio-economic status) characteristics of the participants. It is also possible that long COVID is driven by multifaceted pathophysiology specific to different population groups [54].

5. Limitations

While our study aims to provide valuable insights into the risk factors associated with post-COVID-19 conditions, several limitations should be considered:

5.1. Selection bias

The studies included in our review may themselves have biases, such as selective reporting or publication bias, which could influence the overall conclusions drawn from the literature.

5.2. Heterogeneity of studies

The included studies may vary widely in terms of study design, patient populations, and methodologies used. This heterogeneity can introduce variability and limit the ability to generalize findings across different settings and populations.

5.3. Quality of evidence

The quality of evidence in the studies included in our review may vary. Some studies may have small sample sizes, lack control groups, or have other methodological limitations that could affect the reliability and robustness of the findings.

5.4. Temporal factors

COVID-19 is a rapidly evolving disease, and the understanding of post-COVID-19 conditions is still developing. Some of the included studies may not reflect the most current knowledge or may not have accounted for emerging variants or changes in treatment practices over time.

5.5. Generalizability

The findings of our review may not be universally applicable to all populations or settings. Factors such as regional variations in healthcare practices, socioeconomic conditions, and genetic predispositions may influence the relevance and applicability of our findings.

Despite these limitations, our study provides valuable insights into the current state of knowledge regarding risk factors for post-COVID-19 conditions. Addressing these limitations can guide future research efforts aimed at improving the prevention, management, and outcomes of individuals affected by these conditions.

6. Applications

The findings from this review have several important applications:

6.1. Clinical practice

By identifying key risk factors for developing post-COVID-19 conditions, healthcare providers can more effectively monitor and manage patients who are at higher risk. This can lead to earlier intervention and tailored treatment plans, ultimately improving patient outcomes.

6.2. Healthcare planning and policy

Understanding the predictors of long COVID-19 can inform healthcare planning and resource allocation. Policymakers can develop targeted health policies and allocate resources more efficiently to support the management and rehabilitation of individuals with post-COVID-19 conditions.

6.3. Public health strategies

The insights gained from this review can aid in the development of public health strategies aimed at mitigating the long-term impacts of COVID-19. Public health campaigns can focus on educating the public about risk factors and promoting behaviors that reduce the risk of severe COVID-19 and subsequent long-term symptoms.

6.4. Rehabilitation programs

The study highlights the need for comprehensive rehabilitation programs for individuals affected by post-COVID-19 conditions. These programs can be designed to address the specific symptoms and needs identified in the review, enhancing the quality of life for these patients.

6.5. Economic impact assessment

By quantifying the prevalence and severity of long COVID-19, the study provides a basis for assessing the economic impact of this condition. This information can be used to advocate for funding and support for ongoing research, healthcare services, and patient support programs.

6.6. Further research

The study identifies gaps in current knowledge and areas where further research is needed. This can guide future studies aimed at better understanding the mechanisms underlying post-COVID-19 conditions and developing effective prevention and treatment strategies.

6.7. Patient education and support

The findings can be used to develop educational materials and support programs for patients and their families. By raising awareness about the risk factors and potential long-term effects of COVID-19, patients can be better prepared and more proactive in managing their health.

In summary, the application of this study extends across clinical practice, healthcare policy, public health, rehabilitation, economic impact assessment, research, and patient education. By leveraging these insights, stakeholders can improve the management and support of individuals affected by post-COVID-19 conditions, ultimately reducing the burden of this emerging chronic condition on society.

7. Conclusion

This review highlights the prevalence and complexity of conditions arising after COVID-19. Our findings indicate a variety of factors influencing long-term outcomes, with substantial variability in patient experiences and responses. The heterogeneity of post-COVID syndrome suggests that its pathophysiology may involve multiple mechanisms, reflecting the diverse clinical manifestations observed, and necessitating further research.

Understanding the long-term consequences of COVID-19 remains a crucial global and national priority, especially for Kazakhstan. The aim of this review is to inform healthcare strategies and improve patient outcomes by expanding our knowledge of post-COVID conditions. Future research should focus on detailed studies aimed at identifying the underlying mechanisms and developing tailored interventions to support recovery and effectively treat symptoms. By addressing these gaps, we can better prepare healthcare systems to provide personalized care and improve the quality of life for individuals affected by conditions arising after COVID-19.

Funding

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