

**UNIVERSITY OF MEDICINE AND PHARMACY
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ROXANA MANUELA FERICEAN



DOCTORAL THESIS

**CLINICAL AND PARACLINICAL FEATURES OF PATIENTS
INFECTED WITH SARS-COV-2**

Scientific Coordinator

PROF. UNIV. DR. OANCEA CRISTIAN

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CHAPTER 1: CHARACTERIZATION AND OUTCOMES OF SARS-COV-2 INFECTION IN OVERWEIGHT AND OBESE PATIENTS: A DYNAMIC COMPARISON OF COVID-19 PANDEMIC WAVES.

CONTEXT

Several comorbidities have been studied in relationship with severe COVID-19, and it was observed that 25% of hospitalized patients and approximately three quarters of ICU patients with SARS-CoV-2 had at least one comorbid condition. Comorbidities such as hypertension, cardiovascular disease, and diabetes mellitus were the most common and often mentioned in reports around the world, all of which are known to be connected with obesity, and indeed, obesity is increasingly recognized as both a comorbidity and a risk factor. Obesity prevalence rises with age in both men and women, having a significant consequence for global health, since excess weight, as measured by an elevated body mass index (BMI), affects a large proportion of the world's population; almost 40% being overweight, and more than 10% obese. Western nations have far higher rates of obesity. For example, in the United States more than 40% of the total population is obese and another 32% are overweight, whereas in the United Kingdom, almost 30% of adults are obese and more than 30% who are overweight.

Along with viral replication and antiviral treatment, obesity plays a critical role in COVID-19 development. Obesity was shown to be an independent risk factor for death in a major study and meta-analysis, as well as overweight patients being at higher risk of having severe COVID-19. One possibility is that human ACE2 expression is greater in adipose tissue than in lung tissue. Obese patients may have impaired lung function, a poor response to artificial ventilation, and a variety of other problems. The growing body of research has concentrated on obesity and the adverse consequences associated with severe COVID-19.

Comprehensive investigations indicated that up to fifty percent of COVID-19 victims had metabolic and vascular abnormalities, establishing a clear relationship between COVID-19 and the metabolic and endocrine systems. Thus, not only are individuals with metabolic dysfunction at a higher risk of having severe COVID-19, but infection with SARS-CoV-2 may also result in the establishment of diabetes or a worsening of preexisting metabolic diseases. At molecular level these effects can be explained by effects of metabolic syndrome on mitochondria and inflammation. There are several pathways involving mitochondria and their functions in inflammation that may provide light on why SARS-CoV-2 affects the overweight and obese patients. Several pathways connect aged mitochondria with decreased immunity, including over-stimulated or persistent inflammatory responses with interferon and cytokine production, mitochondrial biogenesis, and interference with apoptosis and mitophagy.

The principal purpose of this research is to examine and elaborate on the intricate dynamics of SARS-CoV-2 viral manifestations in overweight and obese individuals throughout the five waves of the pandemic that have transpired in Romania over the past two years. This research aims to provide a comprehensive description of the variation in case-severity in the target population. It will meticulously analyze the differences in severity among patients based on factors such as age, gender, comorbidities, and the presence of specific symptoms. Additionally, the study sets out to assess the symptomatology of the disease in the subject population. Lastly, the research aims to study the rates of ICU admissions and mortality among overweight and obese patients infected with SARS-CoV-2.

RESULTS

The study consisted of a total of 250 overweight patients, with 50 individuals infected with SARS-CoV-2 during each of the five waves of the COVID-19 pandemic in Romania. To establish a comparative analysis, a control group of 113 patients with a normal body mass index (BMI) was included, carefully matched for age, gender, and cardiovascular comorbidities. The baseline characteristics of both the normal weight and overweight patients with COVID-19 who were admitted to the hospital were assessed. The analysis did not reveal

any significant differences in terms of age, gender, area of residence, occupation, or alcohol use disorder between the patients with a BMI of 18.5-24.9 and those with a BMI greater than 24.9. However, it was observed that smoking behavior was more prevalent among the overweight patients, with 51.6% of them being smokers compared to 38.1% in the normal weight group (p-value = 0.016).

Furthermore, the study examined the prevalence of comorbidities among the participants. It was found that overweight patients had higher proportions of diabetes mellitus (22.4% vs. 12.4%, p-value = 0.025) and digestive diseases (20.4% vs. 9.7%, p-value = 0.012) compared to the normal weight group. These findings highlight the potential association between excess weight and the presence of certain underlying health conditions, which could contribute to the severity of COVID-19 outcomes in overweight individuals.

In terms of the COVID-19 treatment received during hospital admission, there were no significant differences in the proportions between overweight and normal weight patients, except for the administration of antibiotics. Obese patients received antibiotics at a higher frequency (85.6% vs. 77.0%, p-value = 0.043) compared to their overweight counterparts. This observation suggests that healthcare providers may have considered obesity as a potential risk factor for secondary infections or complications, leading to a more cautious approach in prescribing antibiotics to obese patients.

The levels of red blood cells and hematocrit were found to be significantly outside the normal range in the overweight and obese group, with proportions of 65.6% and 49.2% respectively, as opposed to 54.0% and 27.4% in the normal weight group (p-value = 0.034 and p-value < 0.001, respectively). These findings suggest a potential association between excess weight and the development of anemia in patients with COVID-19.

Besides anemia, alterations were also observed in the white blood cell count of overweight and obese patients compared to the normal weight group. The study revealed that 71.6% of overweight and obese patients had significantly altered white blood cell counts, in contrast to 60.2% of patients in the normal weight group (p-value = 0.030). This variation in white blood cell count indicates a potential impact of excess weight on the immune response of individuals infected with SARS-CoV-2. Further investigations are warranted to explore the underlying mechanisms and potential implications of these alterations in the context of COVID-19.

In addition to the differences in ICU admissions and mortality rates, the study also examined the duration of viral clearance among the patients. It was found that during the fourth wave, the median duration of viral clearance was significantly longer, with a median of 17 days, compared to 8 days during the first wave (p-value < 0.001). This observation suggests that the Delta variant may be associated with a prolonged viral shedding period, which could contribute to increased transmission and potentially higher disease burden among overweight and obese patients.

Regarding the medications administered to the patients during the five waves of the pandemic, there were no significant differences, except for the use of antibiotics (p-value = 0.007). This suggests that the treatment approach remained relatively consistent across the waves, except for the increased utilization of immune modulators starting from the third wave. The use of immune modulators reflects the evolving understanding of COVID-19 management and the adoption of therapeutic strategies aimed at modulating the immune response in severe cases.

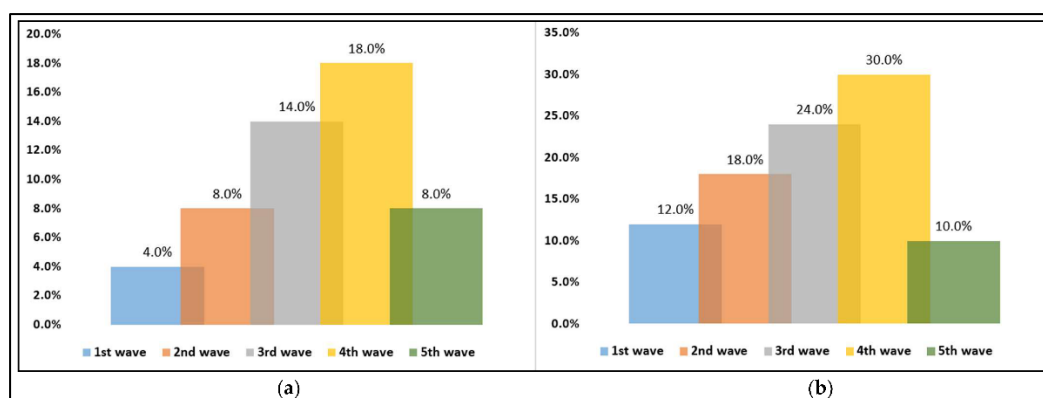


Figure 1 – Dynamic comparison of ICU admissions and mortality in overweight and obese patients with COVID-19.

In the analysis of mortality risk factors, COVID-19 severity, long viral clearance, severe complications, and a heart rate higher than 100 beats per minute were identified as independent risk factors for mortality in overweight and obese patients infected with SARS-CoV-2. These factors signify a greater susceptibility to adverse outcomes and highlight the importance of monitoring and managing these patients with heightened vigilance. The identification of these risk factors can assist healthcare providers in recognizing high-risk individuals and implementing appropriate interventions to mitigate the risks and improve patient outcomes.

The results of the multivariate risk factor analysis emphasize the complex interplay between weight status, clinical parameters, and COVID-19 outcomes in overweight and obese patients. By identifying specific risk factors associated with ICU admission and mortality, healthcare professionals can tailor their approach to effectively manage and monitor these individuals. This knowledge is crucial for implementing preventive measures, providing early interventions, and optimizing care pathways for overweight and obese patients to reduce the burden on healthcare systems and improve patient survival rates. Further research is needed to explore the underlying mechanisms linking these risk factors to disease severity and mortality in overweight and obese patients with COVID-19.

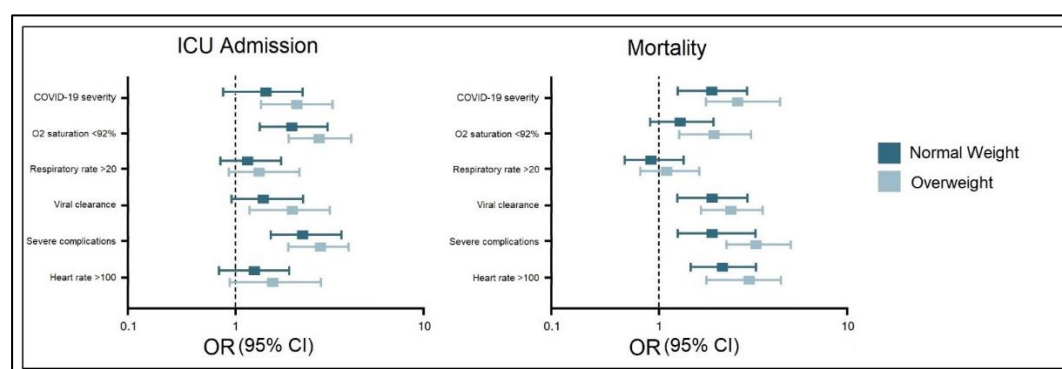


Figure 2 – Multivariate risk factor analysis for ICU admission and mortality in normal weight and over-weight/obese patients with COVID-19.

CONCLUSIONS

Being overweight or obese has been found to increase the likelihood of hospitalization, severe complications, or death from COVID-19. This particular demographic, due to their weight-related factors, is at a higher risk of experiencing more severe disease outcomes. The risk is further exacerbated by the prevalence of obesity-associated comorbidities within this

group. These comorbidities can significantly contribute to the negative health outcomes observed in overweight and obese individuals infected with COVID-19. Therefore, understanding the unique needs of this population is crucial for effective disease management.

However, the current healthcare strategies may not adequately address the specific requirements of this high-risk group. Hence, we advocate for the creation of new guiding principles tailored towards the needs of overweight and obese individuals. These principles should take into account the unique vulnerabilities and challenges faced by this population, such as the higher risk of severe disease outcomes and the prevalence of obesity-associated comorbidities. A more targeted approach to healthcare strategies for this population can potentially lead to improved patient outcomes.

Additionally, these guiding principles should not only focus on the treatment and management of COVID-19 in this group but also on the containment of the pandemic. This includes preventive measures like vaccination and public health guidelines aimed at reducing the risk of infection within this population. By doing so, we can potentially mitigate the impact of future pandemic waves on this high-risk group.

Finally, it's worth noting that these new guiding principles should aim to avoid the recurrence of past mistakes. Previous pandemic waves have resulted in significant economic and human life losses, partly due to the inadequacy of existing guidelines to address the needs of special populations. Therefore, it's crucial that future healthcare strategies learn from these experiences and strive to create a more inclusive and effective approach to managing the pandemic.

CHAPTER 2: COVID-19 CLINICAL FEATURES AND OUTCOMES IN ELDERLY PATIENTS DURING SIX PANDEMIC WAVES

CONTEXT

Despite the worldwide COVID-19 vaccination campaign that gained momentum by early 2021 and resulted in a significant number of vaccinated individuals by 2022, the efficacy of two or even three vaccine doses has shown some decline over time. This decrease in effectiveness can be attributed to the continuous mutations undergone by the SARS-CoV-2 virus. Consequently, it has been observed that during various spikes of the pandemic, the spread of the infection and its severity have fluctuated, leading to varying numbers of hospitalizations and severely ill COVID-19 patients. However, there is a lack of comprehensive data regarding the dynamics of SARS-CoV-2 viral symptoms in elderly patients hospitalized in Romania throughout the last six waves of the pandemic. Thus, the objective of this research was to investigate and compare the variations in disease severity, symptomatology, ICU hospitalizations, and mortality among SARS-CoV-2-infected elderly patients across these six COVID-19 pandemic waves.

Understanding the impact of the different pandemic waves on elderly patients is crucial due to their increased vulnerability to severe COVID-19 outcomes. By examining the severity and clinical characteristics of cases in this specific population, valuable insights can be gained to guide targeted interventions and healthcare resource allocation. Moreover, considering the evolving nature of the virus and the emergence of new variants, it is essential to assess how these changes influence disease progression in older adults, who may already have compromised immune systems and underlying health conditions.

By conducting a parallel comparison between the six pandemic waves, this research aims to provide a comprehensive overview of the trends and patterns in SARS-CoV-2 infection among elderly patients in Romania. The analysis will encompass factors such as the severity of cases, symptomatology, rates of ICU hospitalizations, and mortality. These findings have the potential to contribute to the development of targeted strategies for the prevention, management, and treatment of COVID-19 in this high-risk population. Additionally, they may shed light on the effectiveness of vaccination efforts and provide insights into the need for potential booster doses to combat waning immunity and emerging variants.

In summary, despite the global COVID-19 vaccination campaign, the efficacy of vaccination has shown some decline over time, potentially influenced by the continuous mutations of the SARS-CoV-2 virus. As a result, the severity and spread of the infection have varied across different pandemic waves. Understanding the dynamics of SARS-CoV-2 infection in elderly patients is critical due to their heightened vulnerability to severe outcomes. This research aims to address the knowledge gap by examining and comparing the severity, symptomatology, ICU hospitalizations, and mortality among SARS-CoV-2-infected elderly patients in Romania throughout the last six pandemic waves. The findings will provide valuable insights for targeted interventions and guide future vaccination strategies to protect this high-risk population effectively.

RESULTS

In this study, a total of 360 elderly patients, aged 70 years and above, were selected for data analysis, with the data as detailed in Table 5. These participants were compared with a control group, consisting of 234 adults who were younger than 70 years. The two groups were carefully matched based on two key factors: gender proportions and the number of comorbidities. By ensuring the similarity of these characteristics, the study aimed to mitigate confounding variables and draw more robust conclusions from the data.

An interesting detail of the study was the difference in the average age between the two groups. The control group had an average age of 60.9 years, whereas the group of interest, the elderly patients, had a higher average age of 73.6 years. This distinct age

difference was pivotal in the study as it allowed for an examination of the effects of aging on the variables being studied.

Despite the age difference, there were no significant disparities in the baseline characteristics between the two groups, with the exception of body mass index (BMI) and vaccination status. These two factors were notably higher in the group of elderly patients when compared with the younger adults. Specifically, the BMI was 25.6 in the older patients, which was significantly higher than the 24.2 BMI recorded in the younger adults (p-value = 0.002).

Additionally, the vaccination status also presented a significant difference between the two groups. Among the patients older than 70 years, 15.6% had been vaccinated. In contrast, only 9.8% of the younger adults were vaccinated, indicating a significant variation (p-value = 0.044). The most commonly used vaccine in the study was the BNT162b2, which was administered to 83.9% of the older patients. This compared to a lower usage rate of 60.9% in the control group, further highlighting the differences in health management practices between the age groups.

One of the key findings was a significant difference in white blood cell count. The control group, surprisingly, had a higher white blood cell count compared to the elderly patients, with 40.6% of samples falling outside the normal range, as opposed to 31.9% in the elderly group. This significant difference (p-value = 0.031) could suggest a more robust immune response in the control group or reflect underlying health conditions that aren't age-dependent. Furthermore, the study unveiled a difference in the lymphocyte count between the two groups. The percentage of elderly patients with a decreased lymphocyte count was 44.4%, whereas it was 54.3% in the control group. The lower lymphocyte count in the elderly (p-value = 0.019) may indicate a reduced capacity to mount an effective immune response, highlighting age as a potential factor affecting immune system functionality.

In terms of inflammatory markers, the study found significant differences in the levels of C-reactive protein (CRP), procalcitonin, and interleukin-6 (IL-6). These markers were statistically significantly more elevated in patients older than 70 years. This finding is critical as it suggests that older patients might experience more pronounced inflammatory responses, which could have implications for their overall health and the management of various diseases.

Interestingly, it was observed that older patients had a significantly lower number of symptoms upon admission compared to the younger group. Among the clinical signs and symptoms analyzed, it was found that patients above the age of 70 had a higher prevalence of digestive symptoms (16.4% vs. 8.5%, p-value = 0.005). Additionally, a greater proportion of older patients presented with dyspnea and confusion as their initial symptoms, with rates of 16.9% and 10.6%, respectively, compared to 10.3% and 4.7% in the younger group (p-value = 0.022 and p-value = 0.011, respectively). In contrast, fever was significantly more common among younger patients, with a prevalence of 75.6% compared to 66.1% in older patients (p-value = 0.013).

One of the striking observations was the difference in the severity of COVID-19 among hospitalized patients during these waves. Specifically, the third and fourth waves were characterized by a higher proportion of severe cases, 31.7% and 26.7% respectively. This was a significant increase in severity compared to the sixth wave, which saw only 13.3% of hospitalizations being classified as severe.

The study also noted significant variation in the mean duration of hospitalization across the six pandemic waves (p-value < 0.001). The fourth wave saw the longest hospital stays, with patients remaining in care for an average of 16.4 days. This was closely followed by the first wave, during which patients were hospitalized for an average of 15.3 days. In contrast, the shortest hospital stays were observed during the fifth and sixth waves, with patients being discharged after approximately 10.3 and 10.5 days, respectively. In addition to the duration of hospitalization, other key aspects of patient care varied significantly across the pandemic waves. These included the median duration of stay in the Intensive Care Unit (ICU) and the proportion of patients requiring oxygen supplementation. The longest median duration of ICU stay occurred during the first wave (7.1 days), which was followed by the second wave with

an average of 6.6 days. In contrast, the shortest median ICU stay was recorded during the fourth wave (5.2 days, p-value = 0.001).

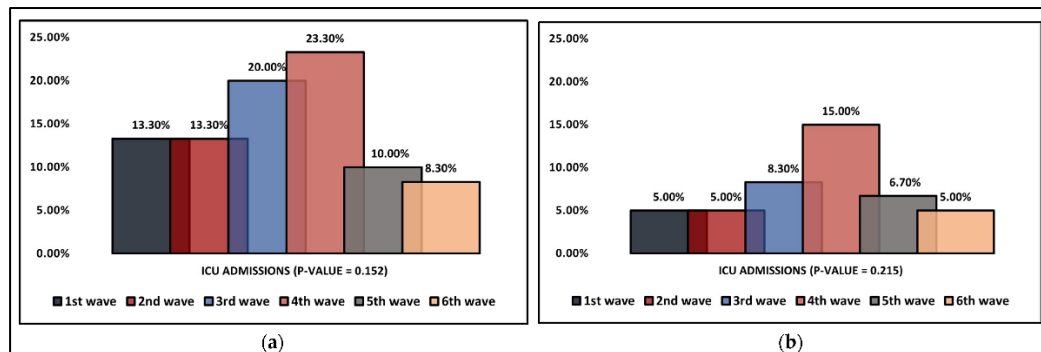


Figure 3 – Dynamic comparison of ICU admissions and mortality in elderly patients.

CONCLUSIONS

The impact of COVID-19 on elderly patients during hospitalization is often severe, largely due to the higher prevalence of comorbidities and general frailty within this demographic. A greater susceptibility to adverse health outcomes is typically observed in elderly patients compared to their younger counterparts. The various pre-existing conditions and the overall frail state of health in many elderly individuals tend to compound the risks associated with the virus, thereby exacerbating the severity of COVID-19 outcomes.

In this study, the six pandemic waves that were analyzed did not reveal significantly disproportionate differences in patient mortality rates. However, it was noted that during the fourth wave, there appeared to be a higher number of severe COVID-19 cases admitted to the hospital. This observation could be attributed to a variety of factors, one of which might be the presence of more contagious SARS-CoV-2 strains during that particular wave.

The hypothesis is that these more contagious viral strains could have led to a surge in infections, thereby overloading healthcare systems. This increased burden on healthcare facilities might explain the observed variations in patient admissions and disease severity during the fourth wave. However, this is merely a supposition, and further research would be required to substantiate this claim.

Interestingly, the biological parameters of the elderly patients did not show significant variations across the six pandemic waves that were analyzed. Nevertheless, it was found that patients over the age of 70 were more likely to present with symptoms such as dyspnea, confusion, and digestive issues. These symptoms were associated with lower lymphocyte levels and higher IL-6 levels, indicating a severe inflammatory response to the virus.

Diagnosing and treating SARS-CoV-2 infection in elderly people poses unique challenges due to their increased risk of developing severe clinical consequences. Therefore, a customized strategy is crucial, one that takes into account both the potential benefits and risks of various treatment options. This strategy should be tailored to the specific needs of older patients, considering their individual health status and the potential for adverse reactions to therapy.

As we continue to understand and adapt to the evolving situation, it becomes increasingly critical for healthcare facilities, including hospitals and long-term residential care facilities, to develop and implement appropriate healthcare plans for their older patients. Addressing the issue of frailty is essential to ensure that elderly COVID-19 patients have access to the most effective treatment options.

CHAPTER 3: OUTCOMES OF ELDERLY PATIENTS HOSPITALIZED WITH SARS-COV-2 OMICRON B.1.1.529 VARIANT: A SYSTEMATIC REVIEW.

CONTEXT

In light of the current situation concerning the vulnerability of certain demographics to the COVID-19 Omicron variant, there has been a growing concern that the standard immunization scheme may not yield significantly favorable outcomes for these groups [216,217]. Given the potential susceptibility of the elderly population, particularly those hospitalized due to Omicron infection, it is paramount to comprehend the course of the disease in this demographic. This understanding is vital not only to identify the risk factors contributing to a slow recovery rate but also to recognize protective elements that may aid in preventing the onset of the disease in the first place.

Therefore, we embarked on a systematic review, the primary objective of which is to scrutinize the clinical outcomes of hospitalized patients aged 65 and above, who have contracted the SARS-CoV-2 Omicron virus. The focus on this age group is deliberate, given that they are statistically among the most vulnerable to the more severe manifestations of the virus. By assessing the progression of the disease in this population, we aim to gain critical insights that can potentially inform more effective prevention and treatment strategies for this high-risk group.

Specifically, one crucial aspect that this review aims to examine is the impact of the patients' COVID-19 vaccination status on their clinical outcomes. The vaccination status, particularly regarding the reception of booster doses, could be a significant determinant of the disease's progression and severity in elderly patients. There is an urgent need to assess whether the current vaccination regimens are sufficient or if there's a need for modifications tailored to the specific needs of older patients, especially in the face of evolving virus variants.

By conducting this review, we hope to fill a vital gap in the current understanding of how the SARS-CoV-2 Omicron variant affects the elderly population. The findings could potentially provide healthcare practitioners and policymakers with evidence-based guidelines on how to improve the health outcomes of this vulnerable group, whether that involves modifying the existing vaccination protocols, introducing new preventative measures, or optimizing treatment approaches.

RESULTS

The systematic review incorporated articles with both a multicenter retrospective cohort study design and a multicenter prospective cohort study design. These designs were used to gather and analyze data from multiple centers, adding to the robustness of the studies. This approach was advantageous as it increased the diversity of the studied population and allowed for a broader generalization of the findings. The articles selected for this systematic review were sourced from various locations globally, ensuring a geographically diverse representation of data.

Two of the studies conducted were based in the United States, while the remaining research was carried out in different countries such as Israel, China, Belgium, and Australia. This geographical spread of the studies increases the global relevance of the systematic review, ensuring the findings are applicable to a broad demographic. The geographical variation also allowed for a more comprehensive understanding of the effects of the COVID-19 Omicron variant across different populations and healthcare systems.

In terms of sample size, the studies included a relatively high number of patients, ranging from 3056 to 445. The total patient population across all six studies amounted to 7398, a substantial sample size that contributes to the reliability and validity of the results. The mean age of participants varied across the studies, reported as between 65 and 80 years. However, one study did not provide a specific mean age, only identifying the sample as older than 65.

Despite the varying ages, there was an equal representation of males and females across all studies, reducing the potential for gender-based bias.

An important aspect of the patients' demographic profile was their health condition. Besides being infected with the COVID-19 Omicron variant, most patients included in the studies had multiple comorbidities. These included hypertension, chronic renal failure, chronic lung disease, cancer, immunosuppression, dementia, and diabetes. The presence of these comorbidities could potentially influence the outcomes of COVID-19 infection, making their consideration crucial in the analysis.

The analysis of the included studies was focused on several primary outcomes - the length of hospital stay, the requirement for intensive care unit (ICU) admission, the need for mechanical ventilation, and the mortality rate. These outcomes were selected for their relevance in evaluating the severity and impact of the COVID-19 Omicron variant on the patient population.

The length of hospital stay varied across the studies. Two studies reported a mean hospital stay of 6 days, while another two reported a mean stay of 8 days. The longest mean hospital stay was reported as 12.5 days. However, one study did not provide the mean number of days hospitalized for the entire cohort. The duration of hospital stay is a significant indicator of the severity of the illness and the recovery rate, contributing to the overall understanding of the disease's progression.

Another critical factor examined was the necessity for ICU admission. Two studies recorded the entire sample group needing ICU care. Excluding one study that did not specify the need for ICU, the others reported a part of their sample requiring ICU admission. Specifically, one study found that 26.5% of unvaccinated patients and 18.7% of fully vaccinated patients needed ICU care. Another study noted that 7% of their patient group required ICU admission. These statistics illustrate the severity of the COVID-19 Omicron variant and its impact on healthcare systems.

Mechanical ventilation requirements and mortality rates were also significant outcomes evaluated in this review. The percentage of patients requiring mechanical ventilation ranged from 6.7% to 11.6%, with one study reporting a notably lower rate of 1.8%. Mortality rates, on the other hand, spanned from 0.51% to a staggering 20.1%. Only one study reported a particularly high mortality rate of 47%, but this was within a sample group suffering from severe COVID-19 Omicron infection. These outcomes provide crucial insights into the disease's lethality and the extent of its impact on patients.

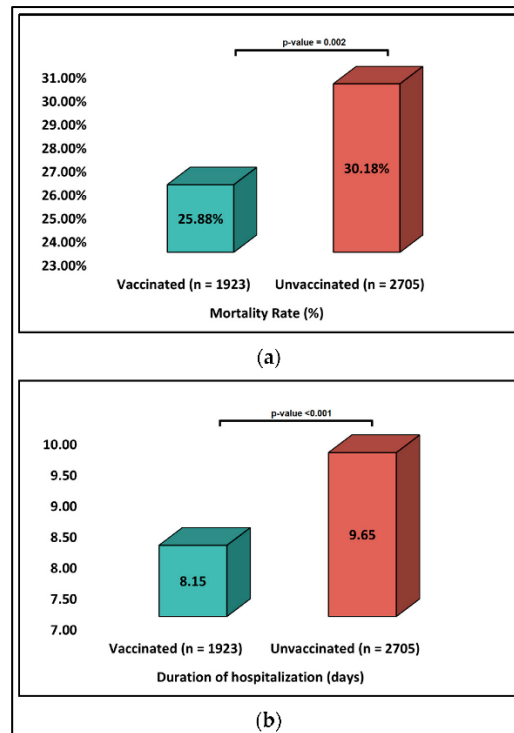


Figure 4 – Summary of findings (vaccinated vs. unvaccinated patients); (A) – Duration of hospitalization; (B) – Mechanical ventilation.

CONCLUSIONS

The pandemic that has been caused by the spreading of Coronavirus and its mutation has left specialists with a number of challenges to overcome in terms of developing strategies for the prevention and treatment of the various ways in which viruses manifest. Despite the fact that a large number of experts have collaborated over the course of the past few years in order to collect as much information as they possibly could regarding the origins of the virus, the most effective types of vaccines, prevention, and hospital management, there are still some aspects that remain unknown. This is because the most recent wave of the pandemic, which was caused by the Omicron variant of the virus, had the highest rate of transmission. Furthermore, despite the fact that the symptoms may have seemed to be less severe, there is still a significant portion of the population that comes into contact with this virus and experiences severe problems. These problems include increased mortality rates, admissions to intensive care units, and the requirement for mechanical ventilation.

These findings point to the necessity of finding effective treatments for the vulnerable population. The use of a series of booster vaccines is not a feasible option because there has been insufficient research done to evaluate the vaccine's long-term effectiveness and because it is unable to reach the global population because it requires a large number of doses to be distributed all over the world.