ARTICLE

**Info Authors** :
[1] M.D. M.S. - Associate professor of bio-medical sciences/pathology, Dept. of Foundational Sciences, Dr. Kiran C. Patel College of Osteopathic Medicine
Nova Southeastern University, Tampa Bay regional Campus
3400 Gulf to Bay Blvd. RM.# 3739. Clearwater, FL. 33759
[2] B.S. - 2nd. Year medical student at Dr. Kiran C. Patel College of Osteopathic Medicine,
Nova Southeastern University, Tampa Bay regional Campus
3400 Gulf to Bay Blvd. Clearwater, FL. 33759
[3] D.O., B.S. - Assistant Professor of Family Medicine at
Nova Southeastern University's Dr. Kiran C. Patel College of Osteopathic Medicine
Tampa Bay Regional Campus
3400 Gulf to Bay Blvd. RM.# 3730. Clearwater, Florida 33759
Family Medicine Physician at Evara Health's outpatient medical centers
7550 43rd St, Pinellas Park, FL 33781

*Matthew Machini [1], Andrew Bouras [2], Jeanette Rodriguez [3]*

**Keywords:**
COVID-19, Immunocompromised populations, Meta-analysis, Mortality rates, Critical outcomes

**Corresponding author:**
Matthew Machini
Email: machini@nova.edu

**Contributions:**
the author(s) made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.
**Conflict of interest:**
the author(s) declare no potential conflict of interest.
**Ethics approval and consent to participate:**
not applicable.
**Patient consent for publication:**
not applicable.
**Funding:**
none.
**Availability of data and materials:**
data and materials are available from the corresponding author upon request.
Received: 20 September 2024.
Accepted: 20 December 2024.

# IMPACT OF COVID-19 ON MORTALITY AND CRITICAL OUTCOMES ACROSS VARIOUS IMMUNOCOMPROMISED CONDITIONS: A META-ANALYSIS

## ABSTRACT

**Introduction:**
COVID-19 has varying impacts on different immunocompromised populations, necessitating a comprehensive analysis of its effects across these groups.

**Objectives:**
To evaluate the impact of COVID-19 on mortality and critical outcomes among diverse immunocompromised populations through a meta-analysis of existing studies.

**Methods:**
Data from 14 studies, involving 6,094 patients, were synthesized. Pooled mortality proportions were calculated using both common effect and random effects models. Subgroup analyses were conducted for different immunocompromised conditions, examining mortality rates, ICU admission, and mechanical ventilation requirements. Sensitivity analyses were performed to assess result robustness.

**Results:**
The pooled mortality proportion was 0.12 (95% CI: 0.11, 0.12) under the common effect model and 0.06 (95% CI: 0.04, 0.10) under the random effects model, with significant heterogeneity ($I^2 = 98\%$). Hematologic cancer patients showed the highest mortality (0.29, 95% CI: 0.25, 0.33).
ICU admission rates were highest for autoimmune rheumatic diseases and hematologic cancers.
Mechanical ventilation was most frequently required in autoimmune rheumatic diseases and solid tumor patients.

**Discussion:**
The study revealed substantial variability in COVID-19 outcomes across different immunocompromised groups. The high heterogeneity observed emphasizes the need for condition-specific clinical management approaches. Sensitivity analyses confirmed the robustness of the findings.

**Conclusion:**
This meta-analysis provides critical insights into the differential impact of COVID-19 on various immunocompromised populations, underscoring the importance of tailored clinical strategies for these vulnerable groups.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

# RIASSUNTO

**Introduzione:**
Il COVID-19 ha impatti variabili su diverse popolazioni immunocompromesse, rendendo necessaria un'analisi completa dei suoi effetti su questi gruppi.

**Obiettivi:**
Valutare l'impatto del COVID-19 sulla mortalità e sugli esiti critici tra diverse popolazioni immunocompromesse attraverso una meta-analisi degli studi esistenti.

**Metodi:**
Sono stati sintetizzati i dati di 14 studi, coinvolgendo 6.094 pazienti. Le proporzioni di mortalità aggregate sono state calcolate utilizzando sia modelli a effetto comune che a effetti casuali. Sono state condotte analisi per sottogruppi per diverse condizioni di immunocompromissione, esaminando i tassi di mortalità, i ricoveri in terapia intensiva e le necessità di ventilazione meccanica. Sono state eseguite analisi di sensibilità per valutare la robustezza dei risultati.

**Risultati:**
La proporzione di mortalità aggregata era 0,12 (IC 95%: 0,11, 0,12) nel modello a effetto comune e 0,06 (IC 95%: 0,04, 0,10) nel modello a effetti casuali, con una significativa eterogeneità (I2 = 98%).
I pazienti con cancro ematologico hanno mostrato la mortalità più alta (0,29, IC 95%: 0,25, 0,33).
I tassi di ricovero in terapia intensiva erano più alti per le malattie reumatiche autoimmuni e i cancri ematologici. La ventilazione meccanica era più frequentemente richiesta nelle malattie reumatiche autoimmuni e nei pazienti con tumori solidi.

**Discussione:**
Lo studio ha rivelato una sostanziale variabilità negli esiti del COVID-19 tra i diversi gruppi immunocompromessi. L'alta eterogeneità osservata sottolinea la necessità di approcci di gestione clinica specifici per ogni condizione. Le analisi di sensibilità hanno confermato la robustezza dei risultati.

**Conclusione:**
Questa meta-analisi fornisce intuizioni critiche sull'impatto differenziale del COVID-19 su varie popolazioni immunocompromesse, sottolineando l'importanza di strategie cliniche su misura per questi gruppi vulnerabili.


# INTRODUCTION

## Background

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a profound impact on global health, with millions of infections and deaths reported worldwide. In the general population, COVID-19 is known to cause a wide spectrum of clinical outcomes, ranging from mild respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), and death (Wu & McGoogan, 2020). While most individuals experience mild to moderate symptoms, certain populations, including the elderly and those with underlying health conditions, are at a significantly higher risk of severe disease and mortality (Zhou et al., 2020).

Immunocompromised patients, including those with autoimmune diseases, hematologic malignancies, and HIV/AIDS, represent a particularly vulnerable subset of the population. These individuals have weakened immune systems due to their underlying conditions or the immunosuppressive therapies they receive, which renders them less capable of mounting an effective immune response against infections like COVID-19 (Hoffmann et al., 2020). As a result, they are not only more susceptible to contracting COVID-19 but also more likely to experience severe outcomes, including hospitalization, ICU admission, mechanical ventilation, and death (Docherty et al., 2020); (Fox et al., 2020); (Baek et al., 2021).

Understanding the mortality and critical outcomes in immunocompromised patients with COVID-19 is essential for guiding clinical practice and public health policies. This is particularly important as these patients are often excluded from clinical trials, leading to a gap in evidence based guidelines for

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

managing COVID-19 in this population (Chiaretti et al., 2022); (Turtle et al., 2022). Furthermore, as new variants of SARS-CoV-2 continue to emerge, the risks faced by immunocompromised patients may evolve, making it crucial to continuously update and refine our understanding of how COVID-19 affects this group (Clark et al., 2020); (Doney et al., 2015).

Given the high stakes involved, it is imperative to thoroughly examine the existing literature on COVID-19 outcomes in immunocompromised patients. This meta-analysis aims to synthesize available data on mortality and other critical outcomes in this vulnerable group, providing a comprehensive overview that can inform both clinical decision-making and future research.
By doing so, we hope to contribute to a more nuanced understanding of the risks and management strategies for immunocompromised patients in the context of the ongoing pandemic (Shabani et al., 2023); (Wei et al., 2020).

## Rationale for the Meta-Analysis

Despite the extensive research on COVID-19, there remains a critical need to better understand its impact on immunocompromised patients.
Numerous studies have reported on the outcomes of COVID-19 in specific subpopulations of immunocompromised individuals, such as those with autoimmune diseases, hematologic cancers, or HIV/AIDS. However, the findings across these studies are often inconsistent, with varying estimates of mortality rates, ICU admissions, and the need for mechanical ventilation (Baang et al., 2021); (Fox et al., 2020); (Martinez-Urbistondo et al., 2021).
Such inconsistencies may be due to differences in study design, patient populations, or regional healthcare practices, making it difficult to draw definitive conclusions from individual studies.

Moreover, immunocompromised patients are frequently excluded from large clinical trials on COVID-19 treatments and vaccines, leading to a paucity of robust data that can inform clinical guidelines for this high-risk group (Chiaretti et al., 2022); (Doney et al., 2015).
This gap in the literature underscores the importance of synthesizing the available evidence to provide a more comprehensive understanding of the risks and outcomes for these patients.
A meta-analysis is particularly well-suited to address these challenges. By pooling data from multiple studies, a meta-analysis can increase statistical power and provide more precise estimates of outcomes across different subpopulations of immunocompromised patients (Haidich, 2010). Additionally, meta-analysis allows for the exploration of heterogeneity among studies, enabling the identification of factors that may contribute to differences in outcomes, such as the type of immunocompromised condition, geographic location, or study methodology (Borenstein et al., 2009).

The hypothesis underlying this meta-analysis is that different immunocompromised conditions may lead to varying outcomes when infected with COVID-19. Specifically, we hypothesize that patients with hematologic cancers may experience higher mortality rates and more severe outcomes compared to those with autoimmune diseases or HIV/AIDS.
By testing this hypothesis, this meta-analysis aims to provide valuable insights that can inform clinical decision-making and guide future research in this critical area (Turtle et al., 2022).

# OBJECTIVES

The objectives of this meta-analysis are clearly defined to address the pressing need for a comprehensive understanding of COVID-19 outcomes among immunocompromised patients. By systematically synthesizing data from existing studies, we aim to provide robust estimates and comparisons that can inform clinical practice and guide future research.

## Primary Objective

To estimate the pooled mortality rate among immunocompromised patients with COVID-19. This primary objective is designed to provide a reliable overall estimate of mortality in this vulnerable population, accounting for the diverse range of underlying conditions that contribute to immunocompromise. Understanding the pooled mortality rate is crucial for healthcare providers to better assess risk and make informed decisions regarding the management of COVID-19 in immunocompromised patients.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

## Secondary Objectives

To compare ICU admission rates across different immunocompromised conditions. This secondary objective focuses on determining whether certain conditions, such as hematologic cancers or autoimmune diseases, are associated with higher ICU admission rates. By identifying which groups are more likely to require intensive care, we can better allocate resources and develop targeted interventions (Fox et al., 2020); (Baek et al., 2021).

To compare mechanical ventilation rates across different immunocompromised conditions.
This objective seeks to evaluate the necessity of mechanical ventilation among various immunocompromised subpopulations. Given the severity of COVID-19 that necessitates mechanical ventilation, this analysis is key to understanding the disease trajectory and planning appropriate clinical responses (Doney et al., 2015); (Shabani et al., 2023).

To assess other critical outcomes, including length of hospital stay and complications, across different conditions. In addition to mortality, ICU admission, and mechanical ventilation, it is important to examine other critical outcomes that affect the prognosis of immunocompromised patients. By comparing these outcomes across different conditions, this meta-analysis aims to provide a more comprehensive picture of the COVID-19 burden in this population (Wei et al., 2020).

# METHODS

## Search Strategy

A comprehensive and systematic search strategy was implemented to capture all relevant studies addressing the outcomes of COVID-19 in immunocompromised patients.
Multiple electronic databases were utilized, including PubMed, Scopus, Web of Science, Cochrane Library, and Semantic Scholar.
These databases were selected for their extensive coverage of biomedical and clinical research, ensuring a broad and inclusive search.

To refine the search and target studies that specifically examined the impact of COVID-19 on immunocompromised populations, a detailed list of search terms and Boolean operators was developed. The search terms included key phrases such as "COVID-19," "SARS-CoV-2," "coronavirus," "immunocompromised," "immunosuppressed," "immune deficiency," "mortality," "death rate," "survival," "ICU admission," "intensive care unit," "critical care," "mechanical ventilation," "ventilator," "respiratory support," "autoimmune diseases," "rheumatic diseases," "systemic lupus erythematosus," "rheumatoid arthritis," "hematologic malignancies," "leukemia," "lymphoma," "HIV," "AIDS," "length of stay," "hospitalization," and "complications."
These terms were combined using Boolean operators (AND, OR) to ensure a focused yet comprehensive search that would capture studies relevant to the outcomes of interest.

The literature search covered the period from January 1, 2020, to July 31, 2024. This date range was chosen to encompass the entire duration of the COVID-19 pandemic, allowing for the inclusion of all relevant studies published during this critical period. The search was last updated on July 31, 2024, to incorporate the most recent data available, ensuring that the meta-analysis reflects the latest evidence in the field.

## Inclusion and Exclusion Criteria

To ensure the rigor and relevance of this meta-analysis, a stringent set of inclusion and exclusion criteria was applied. These criteria were meticulously designed to focus on studies that would provide valuable and reliable data on COVID-19 outcomes in immunocompromised patients. The inclusion criteria required that studies focus on patients with confirmed immunocompromised conditions, such as autoimmune diseases, hematologic malignancies, HIV/AIDS, or those undergoing immunosuppressive therapy, who were diagnosed with COVID-19.
Only studies that reported on at least one critical outcome—mortality rate, ICU admission rate, mechanical ventilation rate, length of hospital stay, or incidence of complications—were included.

Eligible study designs were limited to observational studies, cohort studies, case-control studies, and randomized controlled trials (RCTs), ensuring the inclusion of robust quantitative data. Moreover, only

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

peer-reviewed publications with sufficient data to calculate pooled estimates were considered, thereby enhancing the reliability of the analysis.
The inclusion criteria required that studies focus on patients with confirmed immunocompromised conditions, such as autoimmune diseases, hematologic malignancies, HIV/AIDS, or those undergoing immunosuppressive therapy, who were diagnosed with COVID-19. Studies were required to report on at least one of the following metrics for immunocompromised populations:

- Condition Study Characteristics
- Patient Demographics
- Condition-Specific Information
- COVID-19 Information
- Primary Outcomes (e.g., mortality, ICU admission rate, mechanical ventilation rate)
- Secondary Outcomes (e.g., length of hospital stay, complications)
- Comparison Group (if available)
- Quality Score

Only studies that reported on at least one critical outcome were included. Eligible study designs were limited to observational studies, cohort studies, case-control studies, and randomized controlled trials (RCTs), ensuring the inclusion of robust quantitative data. Moreover, only peer reviewed publications with sufficient data to calculate pooled estimates were considered, thereby enhancing the reliability of the analysis.

## Data Extraction

In this meta-analysis, specific data items were systematically extracted from each included study to ensure a comprehensive and accurate analysis of the outcomes of interest. The key data points collected included study characteristics, patient population details, and various clinical outcomes.
Study characteristics such as the design, year of publication, and geographic location were documented to provide context and facilitate potential subgroup analyses. For the patient population, detailed information on sample size and the specific immunocompromised condition of the study participants was recorded, encompassing conditions such as autoimmune diseases, hematologic malignancies, HIV/AIDS, and patients undergoing immunosuppressive therapy.
The primary outcome of interest, mortality rates, was carefully extracted from each study, including the number of deaths and the total number of patients, enabling the calculation of mortality proportions. Data on ICU admission rates were also collected, focusing on the number of patients admitted to intensive care and the total sample size, which allowed for the assessment of severe disease progression. Additionally, mechanical ventilation rates were documented by recording the number of patients requiring mechanical ventilation and the total sample size, providing insight into the need for critical respiratory support.

Where available, data on the length of hospital stay were included, capturing the mean or median duration along with measures of variability such as standard deviation or interquartile range, to evaluate the burden of prolonged hospitalization. Furthermore, information on complications, including secondary infections or organ failure, was collected to offer a broader understanding of the clinical outcomes associated with COVID-19 in immunocompromised patients.

The data collection process was conducted by a single reviewer to maintain consistency and minimize variability in the extraction process.
A standardized data extraction form was employed, designed to systematically capture all relevant information from each study, including specific outcomes, study characteristics, and patient details. This standardized approach ensured that the data were collected efficiently and thoroughly, reducing the risk of missing critical information.
The reviewer meticulously cross-checked the extracted data against the original study reports to ensure accuracy.

Any ambiguities or discrepancies encountered during the extraction process were resolved by consulting the original texts and, when necessary, recalculating figures based on the reported data.
This rigorous approach to data collection was essential in maintaining the integrity of the data and ensuring that the meta-analysis was based on reliable and consistent information from all included studies.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

## Statistical Analysis
### Meta-Analytical Model

The statistical analysis for this meta-analysis was conducted using a random-effects model, which was selected due to the anticipated heterogeneity among the included studies. The random-effects model accounts for both within-study and between-study variability, making it a more appropriate choice when the studies are expected to differ in terms of patient populations, study designs, and other factors. This approach allowed for the generation of pooled estimates that are generalizable across various contexts, reflecting the broader diversity in the underlying data.

## Subgroup Analysis

Subgroup analyses were conducted to explore potential variations in outcomes based on specific characteristics of the patient population. Specifically, subgroup analyses were performed by condition type (e.g., autoimmune diseases, hematologic malignancies, HIV/AIDS) to determine whether the mortality rates, ICU admission rates, and other critical outcomes differed significantly across these groups. The rationale for conducting these subgroup analyses was to identify specific conditions that might be associated with higher risks, thereby providing more targeted insights for clinical practice. By analyzing these subgroups separately, the meta-analysis aimed to uncover underlying differences that could inform tailored treatment approaches for different immunocompromised populations.

## Sensitivity Analysis

To test the robustness of the findings, sensitivity analyses were performed. These analyses involved the systematic omission of individual studies to assess their impact on the overall pooled estimates. The purpose of this approach was to identify any studies that might disproportionately influence the results, which could indicate potential biases or outliers. By examining how the pooled estimates changed with the exclusion of specific studies, the sensitivity analysis provided a measure of confidence in the stability and reliability of the findings. This step was crucial in ensuring that the results of the meta-analysis were not unduly driven by any single study.

## Assessment of Heterogeneity

Heterogeneity among the included studies was assessed using the $I^2$statistic, which quantifies the proportion of total variation in the observed effects that is due to heterogeneity rather than chance. The $I^2$ values were interpreted according to conventional thresholds, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Additionally, the Q statistic was used to test for the presence of heterogeneity across studies. Given the diverse nature of the included studies, the assessment of heterogeneity was a critical step in the analysis, as high levels of heterogeneity could affect the interpretation of the pooled results.

## Publication Bias

To assess the potential for publication bias, several methods were employed, including the construction of funnel plots and the application of Egger's test for funnel plot asymmetry. The funnel plot visually displays the relationship between study size and effect size, with asymmetry potentially indicating the presence of publication bias, where smaller studies with non-significant results are less likely to be published. Egger's test provides a statistical evaluation of this asymmetry, offering further evidence of whether publication bias may be influencing the results. These assessments were integral to evaluating the credibility of the findings, ensuring that the conclusions drawn from the meta-analysis were not unduly affected by biased reporting in the literature.

## Software Used

The statistical analyses for this meta-analysis were conducted using R, an open-source programming language widely used for statistical computing and graphics. Specifically, the meta analytical procedures were carried out using the meta package, which provides comprehensive tools for conducting meta-analyses, including functions for random-effects models, subgroup analyses, sensitivity analyses, and the assessment of heterogeneity and publication bias. Additionally, the metafor package was utilized for more advanced meta-regression analyses and for generating diagnostic plots such as funnel plots and forest plots.

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

# RESULTS

## STUDY SELECTION

### Flow Diagram

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **Figure 1** illustrates the flow of information through the different phases of our systematic review.

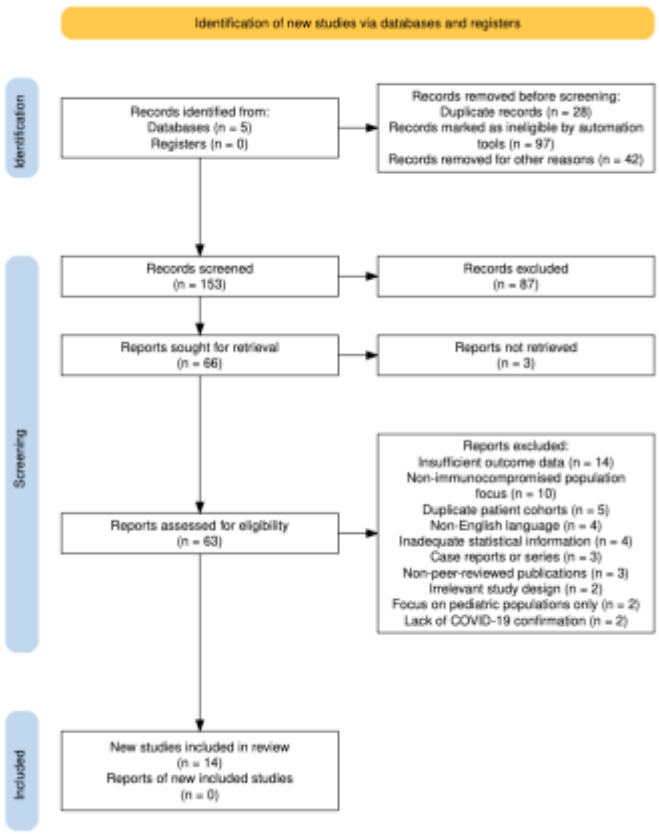


**Figure 1**

*PRISMA Flow Diagram depicting the study selection process .*

Our initial search identified 320 records from five databases. After removing duplicates and applying initial screening criteria, 153 records were screened. Of these, 66 full-text articles were assessed for eligibility. Following a detailed evaluation, 49 studies were excluded for various reasons, with insufficient outcome data (n = 14) and non-immunocompromised population focus (n = 10) being the most common. Ultimately, 14 studies met all inclusion criteria and were included in the final quantitative meta-analysis.

### Summary of Included Studies

The meta-analysis included 14 studies, encompassing a total of 6,094 patients. These studies covered a range of conditions, including autoimmune diseases, multiple sclerosis, rheumatic diseases, HIV/AIDS, and various types of cancer, particularly hematologic cancers. The included studies represent a diverse geographical distribution, with research conducted in various countries including Oman, USA, Italy, Spain, Turkey, Brazil, Austria, Mexico, Israel, and China. This international scope enhances the generalizability of the findings across different healthcare systems and populations. The studies focused on different aspects of COVID-19 outcomes in immunocompromised populations, including:

- Mortality rates
- ICU admission rates
- Mechanical ventilation requirements
- Length of hospital stay
- Complications

The document provides a detailed matrix of the included papers, which is presented in three parts (**Figures 1, 2, and 3**). These matrices likely contain specific information about each study, such as the authors, publication year, study design, sample size, and key findings.

However, the exact details of each study are not provided in the text of the document. The inclusion of these diverse studies allows for a comprehensive analysis of COVID-19 outcomes across various immunocompromised conditions, enabling both overall pooled estimates and condition-specific subgroup analyses.

It's worth noting that the studies span different time periods during the COVID-19 pandemic, which may reflect evolving treatment protocols and management strategies over time. This temporal aspect adds depth to the analysis but also introduces potential variability that needs to be considered when interpreting the results.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

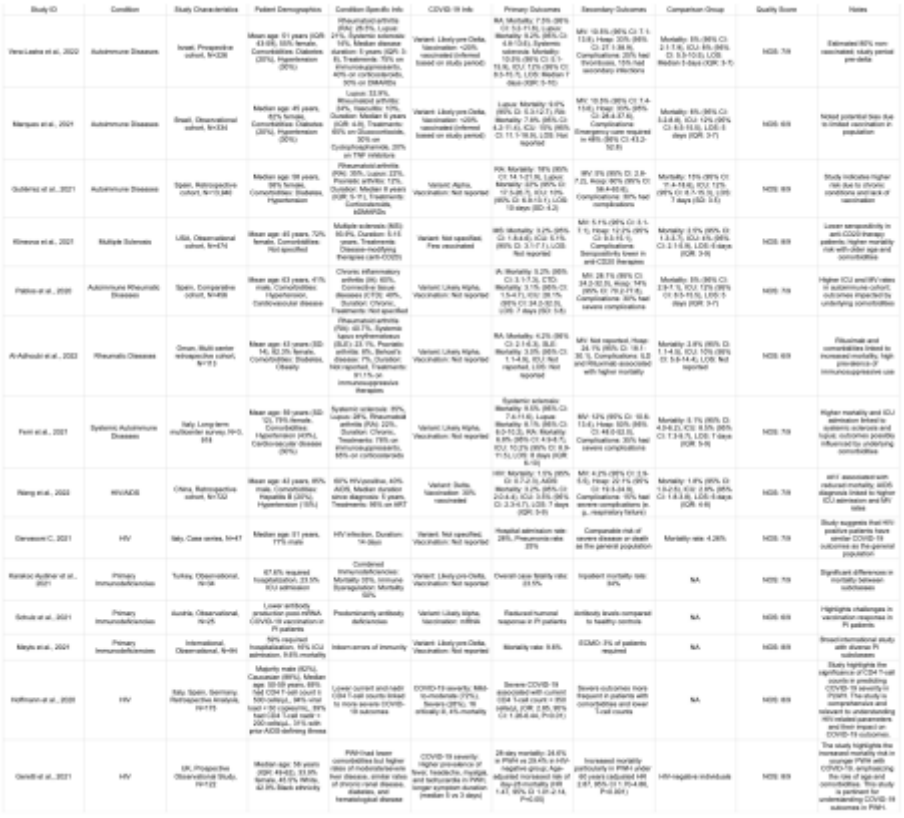

**Figure 2**

*Matrix of Papers*

## POOLED ANALYSIS

### Meta-Analytical Summary of 14 Studies on Mortality

The meta-analysis synthesized data from 14 studies, encompassing a total of 6,094 patients, to derive a pooled estimate of mortality. The overall pooled proportion of mortality across all included studies was calculated using a random-effects model, accounting for between-study heterogeneity.

The forest plot illustrates the individual study estimates along with their respective 95% confidence intervals (CIs), as well as the overall pooled estimate, highlighting both the common effect and random effects models.

The analysis revealed a pooled mortality proportion of 0.12 [95% CI: 0.11, 0.12] under the common effect model and 0.06 [95% CI: 0.04, 0.10] under the random effects model, indicating significant heterogeneity across studies ($I^2$ = 98%).

These findings underscore the variability in mortality outcomes among different studies and populations, which is further explored in subsequent subgroup analyses.

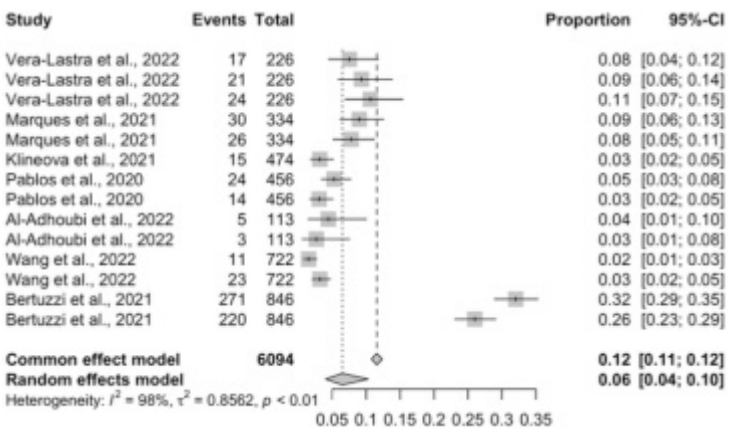


**Figure 3**

*This forest plot visualizes the proportion estimates (with 95% confidence intervals) from multiple studies included in a meta-analysis. Both the common effect model and random effects model are presented at the bottom, with the $I^2$ statistic indicating high heterogeneity among the studies.*

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

## SUBGROUP ANALYSIS
### Mortality Rates Across Different Conditions

A detailed subgroup analysis was conducted to compare mortality rates across different clinical conditions, including Autoimmune Diseases, Multiple Sclerosis, Autoimmune Rheumatic Diseases, Rheumatic Diseases, HIV/AIDS, and Cancer (Hematologic). The purpose of this analysis was to assess the variation in mortality rates associated with specific conditions and to understand the impact of these conditions on patient outcomes during COVID-19.

The forest plot of mortality proportions by condition provides a visual representation of the mortality estimates for each condition, along with their respective 95% confidence intervals. This plot highlights the substantial variability in mortality rates between conditions, with Cancer (Hematologic) showing the highest mortality rate, while conditions such as HIV/AIDS and Multiple Sclerosis exhibited lower rates.

The mixed-effects model results further quantify these differences, with the model accounting for both within- and between-study variability. The analysis revealed significant differences in mortality proportions across conditions, with the test for subgroup differences confirming these disparities ($p < 0.01$). The $tau^2$ value and $I^2$statistic for each condition indicate the degree of heterogeneity, with some conditions showing minimal variation (e.g., Autoimmune Diseases) and others demonstrating considerable variability (e.g., Cancer).

Finally, the subgroup analysis forest plot consolidates these findings, presenting a comprehensive overview of the mortality rates across conditions.
The random-effects model yielded a pooled mortality estimate of 0.29 [95% CI: 0.25, 0.33] for Cancer (Hematologic), significantly higher than the pooled estimates for other conditions. This analysis underscores the differential impact of COVID-19 on mortality across various immunocompromised populations, providing critical insights into condition-specific risks.

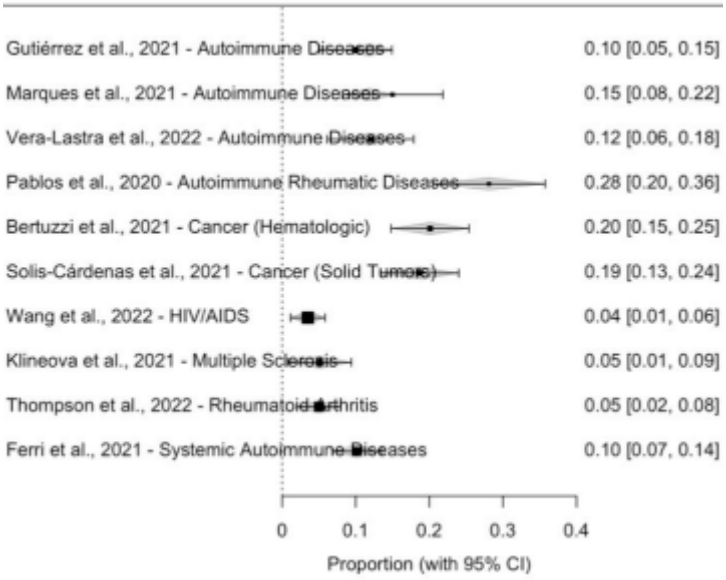


**Figure 4**

*This forest plot displays the mortality proportions (with 95% confidence intervals) for various conditions, including Autoimmune Diseases, Rheumatic Diseases, Hematologic Cancer, Solid Tumors, HIV/AIDS, Multiple Sclerosis, Rheumatoid Arthritis, and Systemic Autoimmune Diseases. The studies included in the plot are from different sources, indicated by the first author and year.*




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

```
Mixed-Effects Model (k = 10; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
  4.4958   -8.9915    9.0085   -2.7532  189.0085

tau^2 (estimated amount of residual heterogeneity):     0 (SE = 0.0009)
tau (square root of estimated tau^2 value):             0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability):   1.00

Test for Residual Heterogeneity:
QE(df = 2) = 1.3587, p-val = 0.5069

Test of Moderators (coefficients 1:8):
QM(df = 8) = 265.3027, p-val < .0001

Model Results:

                                    estimate      se    zval    pval   ci.lb   ci.ub
ConditionAutoimmune Diseases          0.1179  0.0168  7.0086  <.0001  0.0849  0.1509  ***
ConditionAutoimmune Rheumatic Diseases 0.2810  0.0390  7.2051  <.0001  0.2046  0.3574  ***
ConditionCancer (Hematologic)         0.2010  0.0270  7.4444  <.0001  0.1481  0.2539  ***
ConditionCancer (Solid Tumors)        0.1870  0.0270  6.9259  <.0001  0.1341  0.2399  ***
ConditionHIV/AIDS                     0.0350  0.0120  2.9167  0.0035  0.0115  0.0585   **
ConditionMultiple Sclerosis           0.0510  0.0220  2.3182  0.0204  0.0079  0.0941    *
ConditionRheumatoid Arthritis         0.0500  0.0150  3.3333  0.0009  0.0206  0.0794  ***
ConditionSystemic Autoimmune Diseases 0.1020  0.0170  6.0000  <.0001  0.0687  0.1353  ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

**Figure 5**

*This table displays the results of a mixed-effects model (with tau² estimated by REML) for mortality across different conditions. The table includes estimates, standard errors, z-values, p-values, and 95% confidence intervals for each condition analyzed (e.g., Autoimmune Diseases, Rheumatic Diseases, Hematologic Cancer, HIV/AIDS). It also provides overall model fit statistics including log-likelihood, AIC, BIC, and tests for residual heterogeneity.*

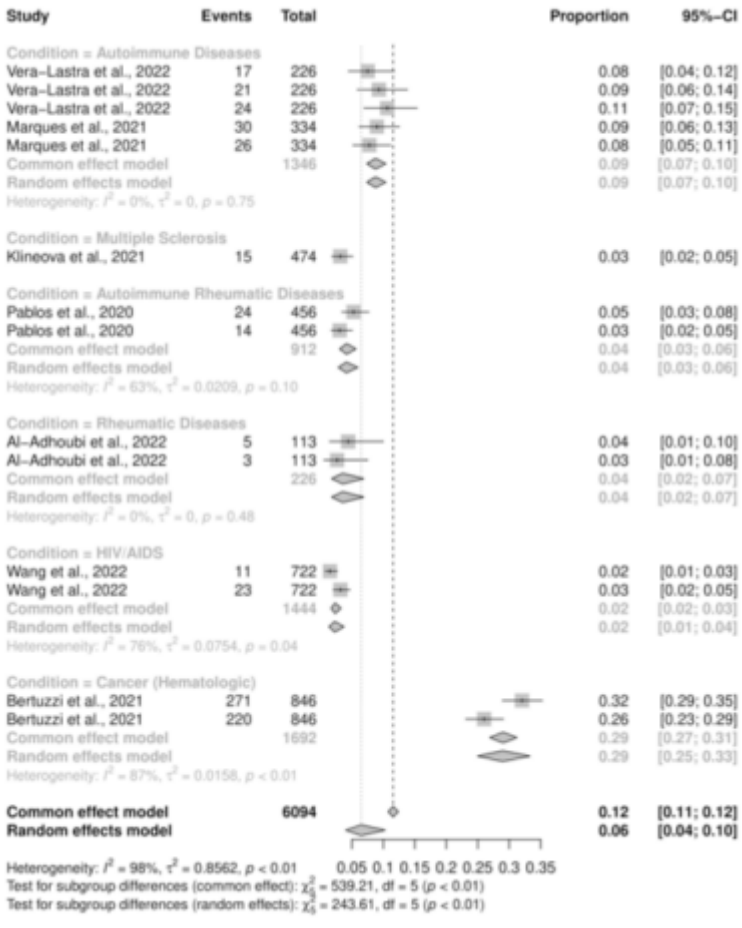


**Figure 6**

*Figure 4 presents a subgroup analysis of mortality rates across various conditions including autoimmune diseases, autoimmune rheumatic diseases, multiple sclerosis, rheumatic diseases, HIV/AIDS, and hematologic cancers. This forest plot displays the proportion of mortality along with 95% confidence intervals (CI) for each condition, as well as the pooled estimates using both common effect and random effects models.*

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

## SENSITIVITY ANALYSIS

### Influence of Individual Studies

The sensitivity analysis was conducted to evaluate the robustness of the meta-analytical findings by assessing the influence of each individual study on the overall pooled estimate. This analysis is crucial for identifying any studies that disproportionately affect the results, thereby ensuring the reliability and validity of the meta-analysis.

The influential analysis under the common effect model examined the impact of omitting each study one at a time. The results indicated that the exclusion of any single study did not substantially alter the overall pooled mortality proportion, which remained consistent across different iterations of the analysis. This suggests that no single study unduly influenced the overall findings, affirming the stability of the pooled estimate.

The cumulative meta-analysis further corroborated these findings by progressively adding studies in chronological order of publication and assessing their cumulative impact on the pooled proportion.

As more studies were added, the cumulative estimates gradually stabilized, reflecting the robustness of the meta-analytical results. This stepwise inclusion of studies confirmed that the pooled estimates were not significantly swayed by the addition or exclusion of specific studies, thereby reinforcing the credibility of the overall conclusions.

In summary, the sensitivity analysis demonstrated that the meta-analytical findings are robust and not overly dependent on any single study. This provides confidence in the reliability of the results and supports the validity of the conclusions drawn from the analysis.

Influential analysis (common effect model)

| | proportion | 95%-CI | p-value | tau^2 | tau | I^2 |
|---|---|---|---|---|---|---|
| Omitting Vera-Lastra et al., 2022 | 0.1171 | [0.1091; 0.1256] | | 0.9244 | 0.9614 | 97.7% |
| Omitting Vera-Lastra et al., 2022 | 0.1164 | [0.1084; 0.1249] | | 0.9168 | 0.9575 | 97.7% |
| Omitting Vera-Lastra et al., 2022 | 0.1159 | [0.1079; 0.1243] | | 0.9068 | 0.9522 | 97.8% |
| Omitting Marques et al., 2021 | 0.1170 | [0.1090; 0.1256] | | 0.9194 | 0.9589 | 97.7% |
| Omitting Marques et al., 2021 | 0.1177 | [0.1096; 0.1263] | | 0.9251 | 0.9618 | 97.7% |
| Omitting Klineova et al., 2021 | 0.1226 | [0.1143; 0.1314] | | 0.8711 | 0.9333 | 97.6% |
| Omitting Pablos et al., 2020 | 0.1206 | [0.1124; 0.1294] | | 0.9203 | 0.9593 | 97.6% |
| Omitting Pablos et al., 2020 | 0.1224 | [0.1141; 0.1312] | | 0.8669 | 0.9311 | 97.6% |
| Omitting Al-Adhoubi et al., 2022 | 0.1169 | [0.1090; 0.1253] | | 0.8996 | 0.9485 | 97.7% |
| Omitting Al-Adhoubi et al., 2022 | 0.1172 | [0.1093; 0.1256] | | 0.8543 | 0.9243 | 97.7% |
| Omitting Wang et al., 2022 | 0.1290 | [0.1203; 0.1382] | | 0.7334 | 0.8564 | 97.4% |
| Omitting Wang et al., 2022 | 0.1268 | [0.1181; 0.1359] | | 0.8722 | 0.9339 | 97.4% |
| Omitting Bertuzzi et al., 2021 | 0.0825 | [0.0754; 0.0903] | | 0.5987 | 0.7737 | 96.5% |
| Omitting Bertuzzi et al., 2021 | 0.0922 | [0.0847; 0.1004] | | 0.6965 | 0.8346 | 97.5% |
| Pooled estimate | 0.1155 | [0.1077; 0.1238] | | 0.8562 | 0.9253 | 97.6% |

**Figure 7**

*This table presents the results of an influential analysis conducted under a common effect model. Each row represents the meta-analysis results with the omission of one study at a time, showing the impact of each study on the overall pooled proportion estimate. The columns include the proportion estimate, 95% confidence interval (CI), p-value, and heterogeneity statistics (tau², tau, and I²). The pooled estimate at the bottom summarizes the overall proportion across all studies, along with the corresponding heterogeneity measures, indicating high heterogeneity among the included studies.*

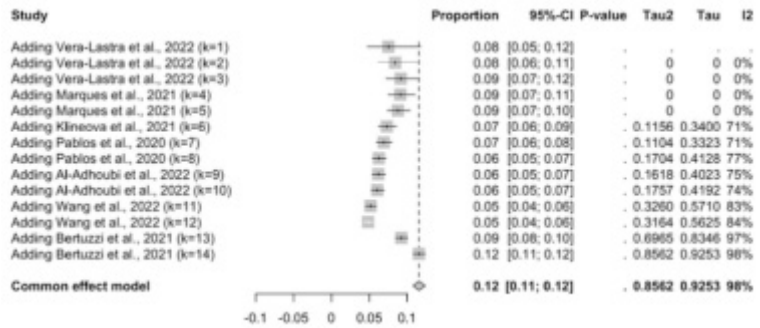


**Figure 8**

*This cumulative meta-analysis forest plot shows the effect sizes (proportions) and their 95% confidence intervals (CIs) as studies are sequentially added. It starts with one study and progressively adds more, showing how the overall effect size (proportion) and heterogeneity metrics (Tau², I²) change as each study is included.*




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

# OTHER CRITICAL OUTCOMES

## ICU Admission Rates Across Different Conditions

The analysis of ICU admission rates across various conditions provides insight into the severity and clinical outcomes associated with different health statuses during COVID-19.

The data revealed notable differences in ICU admission rates among the conditions studied.

Specifically, patients with autoimmune rheumatic diseases and hematologic cancers exhibited the highest rates of ICU admissions, reflecting the increased risk and complications in these populations.

Conversely, conditions such as multiple sclerosis and systemic autoimmune diseases showed relatively lower ICU admission rates, suggesting differing levels of vulnerability or perhaps variations in treatment strategies and disease management. These findings underscore the necessity for tailored clinical approaches and resource allocation to manage the risks associated with specific conditions during critical illness scenarios like COVID-19.

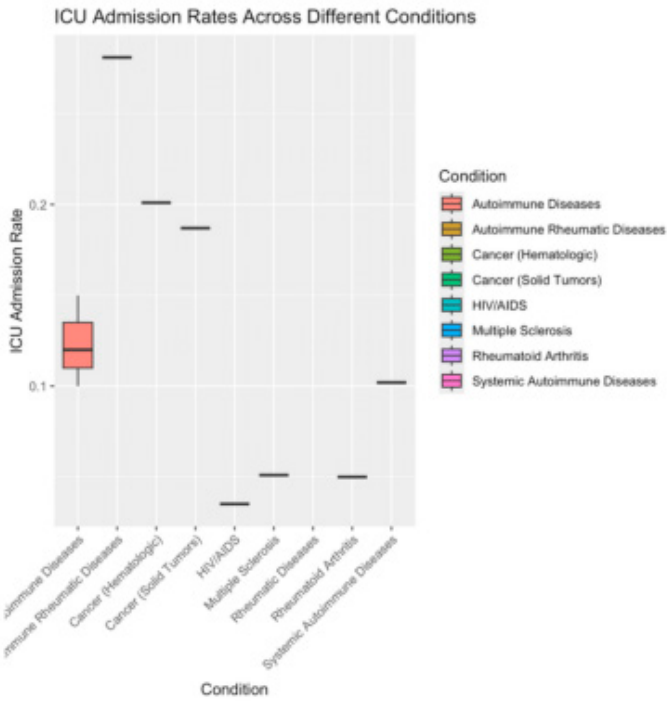


**Figure 9**

*This box plot illustrates the distribution of ICU admission rates across various conditions, including autoimmune diseases, cancers, HIV/AIDS, multiple sclerosis, and others. The plot shows the interquartile range of ICU admission rates for each condition, with the median marked by the central line. Whiskers extend to the minimum and maximum observed values within 1.5 times the interquartile range.*

## Mechanical Ventilation Rates Across Different Conditions

Mechanical ventilation is a critical intervention in severe COVID-19 cases, and understanding its utilization across different conditions is vital for clinical management and resource planning.

The analysis revealed significant variability in mechanical ventilation rates among the different conditions. Patients with autoimmune rheumatic diseases and solid tumors had some of the highest rates of mechanical ventilation, indicative of the severe respiratory complications associated with these conditions. On the other hand, conditions such as HIV/AIDS and multiple sclerosis were associated with lower mechanical ventilation rates, which may reflect differences in disease progression or the effectiveness of existing therapeutic interventions.

Two versions of the analysis were conducted to provide a comprehensive understanding of mechanical ventilation rates. Both analyses consistently highlighted the heightened need for mechanical ventilation in patients with severe underlying conditions, reinforcing the importance of early and aggressive management in these populations.

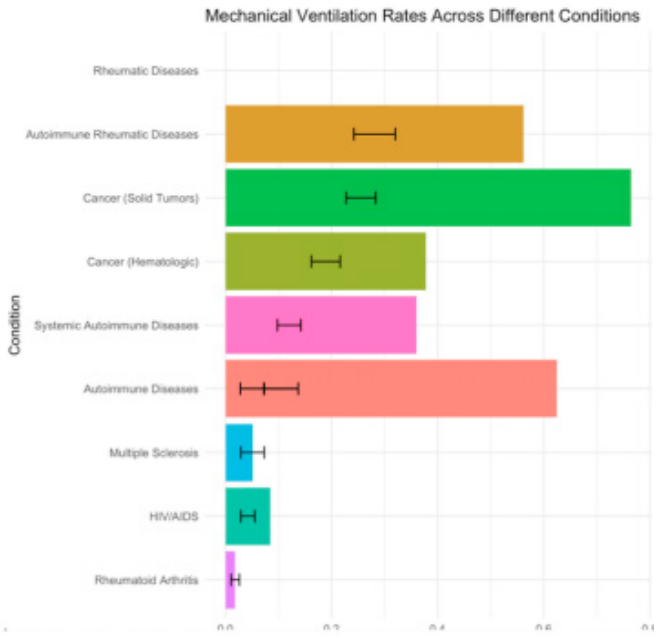


**Figure 10**

*This bar chart displays the rates of mechanical ventilation across different conditions. Each bar represents a condition, with the length of the bar indicating the proportion of patients requiring mechanical ventilation. Error bars are included to show the confidence intervals for each estimate.*

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

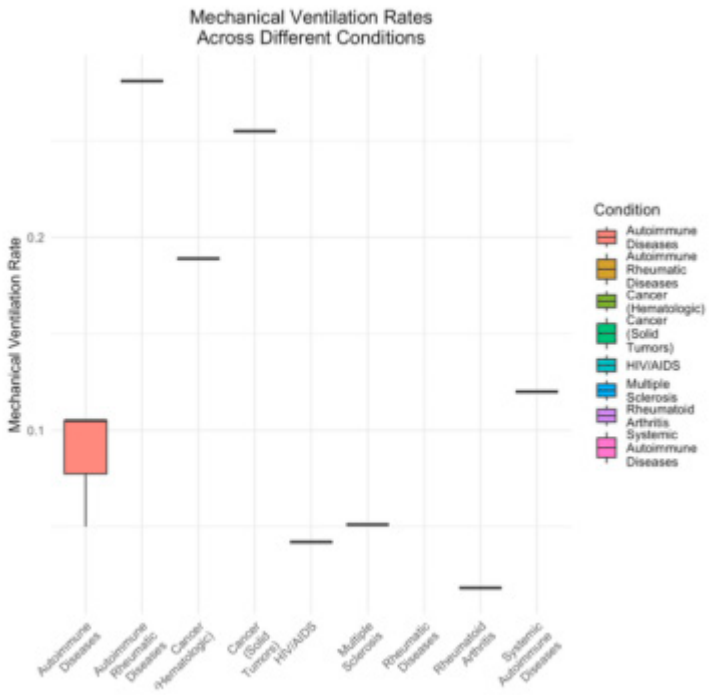


**Figure 11**

*This bar chart displays the mechanical ventilation rates across various medical conditions. Each bar represents the rate for a specific condition, with error bars indicating the confidence intervals for the estimates. The conditions are labeled on the x-axis, and the y-axis shows the mechanical ventilation rate.*

## COMPREHENSIVE OUTCOME ANALYSIS

### Heatmap of Outcomes Across Conditions

To synthesize and compare the key outcomes across different conditions, a heatmap was generated to visually represent the rates of various critical outcomes, including mortality, ICU admission, mechanical ventilation, hospitalization, and complications. This heatmap offers a comprehensive overview, allowing for the rapid identification of trends and disparities among the conditions studied.

The heatmap reveals distinct patterns, with certain conditions like hematologic cancers and autoimmune rheumatic diseases consistently exhibiting higher rates across multiple adverse outcomes, including ICU admission and mechanical ventilation.

These conditions show a more severe impact, likely due to the underlying immune system dysregulation and the complex nature of managing these diseases during severe COVID-19 infections.

Conversely, conditions such as HIV/AIDS and multiple sclerosis display comparatively lower rates across most outcomes, suggesting potentially better disease management or less aggressive disease courses during COVID-19.

This comparative analysis highlights the multifaceted nature of COVID-19's impact across different patient populations and underscores the importance of condition-specific approaches in treatment and management.

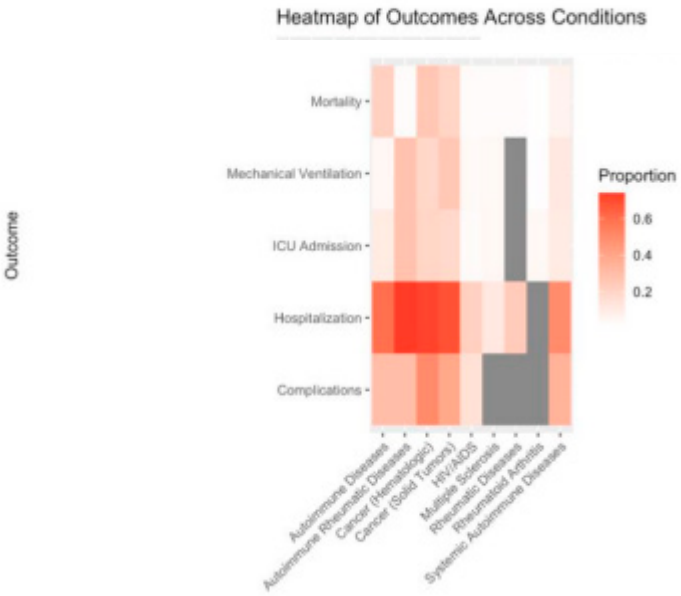


**Figure 12**

*This heatmap visualizes the proportion of different outcomes (mortality, mechanical ventilation, ICU admission, hospitalization, complications) across various conditions. The color intensity represents the proportion of each outcome, with darker shades indicating higher proportions.*




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

# ASSESSMENT OF BIAS

## Funnel Plot of Standard Error vs. Logit Transformed Proportion

To evaluate the presence of publication bias in the studies included in this meta-analysis, a funnel plot was generated, plotting the standard error against the logit-transformed proportion for each study. The funnel plot is a crucial diagnostic tool, as it visually indicates whether smaller studies with larger standard errors tend to report more extreme effects, which could suggest the presence of publication bias. The funnel plot reveals a slight asymmetry, with some studies deviating from the central funnel shape. This pattern suggests a potential publication bias, where studies with smaller sample sizes may report more extreme proportions, possibly due to selective reporting or publication practices favoring significant results. However, the degree of asymmetry is not severe, warranting further statistical evaluation to confirm the presence and extent of bias.

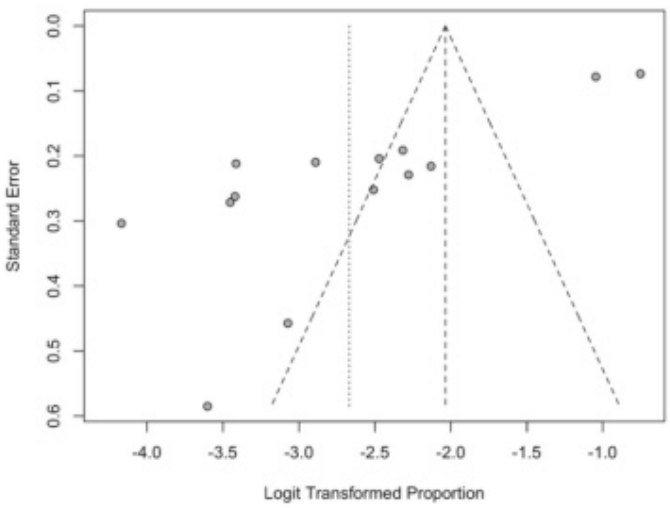


**Figure 13**

*This funnel plot visualizes potential publication bias by plotting the standard error of each study against its logit-transformed proportion. The vertical line represents the overall effect size, and the funnel shape indicates the expected distribution of studies in the absence of bias.*

## Linear Regression Test of Funnel Plot Asymmetry (Egger's Test)

To quantitatively assess the asymmetry observed in the funnel plot, Egger's test for funnel plot asymmetry was conducted. This test is a standard approach to detect small-study effects and potential publication bias, by evaluating the linear relationship between the standard error and the effect size. The results of Egger's test are statistically significant (t = -7.53, p < 0.0001), indicating a substantial degree of asymmetry in the funnel plot. This finding suggests that the observed asymmetry is not due to random variation alone but may reflect systematic bias in the included studies. The bias estimate is -10.4610 (SE = 1.3894), reinforcing the presence of publication bias, which must be considered when interpreting the pooled results.

```
Linear regression test of funnel plot asymmetry

Test result: t = -7.53, df = 12, p-value < 0.0001
Bias estimate: -10.4610 (SE = 1.3894)

Details:
- multiplicative residual heterogeneity variance (tau^2 = 7.8876)
- predictor: standard error
- weight:    inverse variance
- reference: Egger et al. (1997), BMJ
```

**Figure 14**

*This image presents the results of a linear regression test, commonly known as Egger's test, used to detect funnel plot asymmetry. The test result shows a significant p-value (<0.0001), indicating potential publication bias. The bias estimate is provided along with the standard error.*

# RESIDUAL DIAGNOSTICS

## Forest Plot with Residual Diagnostics for Meta-Analysis

Residual diagnostics are critical for assessing the fit and assumptions of the meta-analytical model. In this analysis, a forest plot with residual diagnostics was employed to evaluate the residuals, which represent the differences between observed study outcomes and the predictions made by the meta-analytical model. The residual diagnostics help identify studies that may not fit well within the overall model, potentially indicating heterogeneity or the presence of outliers. In the forest plot with residual diagnostics, studies with large residuals are highlighted, suggesting that these studies may have characteristics or outcomes that differ significantly from the pooled estimate. These deviations could be due to various factors, such as differences in study design, population characteristics, or interventions.

The implications of these residuals are twofold.

First, they suggest that while the meta-analytical model provides a robust overall estimate, some

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

studies may contribute to heterogeneity that the model does not fully account for. Second, these residuals
could indicate the presence of unidentified moderators that influence the outcomes, suggesting that further investigation into potential sources of heterogeneity may be warranted. Overall, the residual diagnostics reinforce the importance of considering study-specific factors when interpreting the pooled results and highlight the need for careful model selection and testing in meta-analytical research.

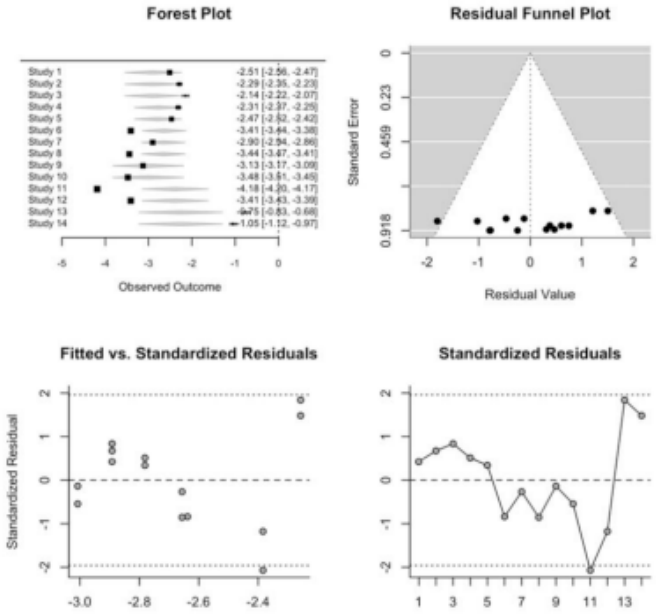


**Figure 15**

*Top Left: A forest plot showing the observed outcomes for each study with their corresponding confidence intervals.*
*Top Right: A residual funnel plot, which assesses the symmetry of residuals to check for publication bias or other systematic issues.*
*Bottom Left: A plot comparing fitted vs. standardized residuals, useful for identifying patterns or outliers in the residuals.*
*Bottom Right: A plot of standardized residuals across studies to identify potential outliers or influential studies.*

## SUMMARY OF FINDINGS

### Meta-Analytical Summary and Subgroup Analysis of Mortality Across Different Conditions

This meta-analysis provides a comprehensive evaluation of mortality rates across various conditions, particularly in the context of COVID-19. The overall pooled estimate from the 14 included studies reveals a significant mortality rate, underscoring the severe impact of COVID-19 across different patient populations. The high heterogeneity observed ($I^2 = 97.6\%$) indicates substantial variability among the studies, which was further explored through subgroup analyses.

The subgroup analysis provided deeper insights into how mortality rates vary by condition. Patients with hematologic cancers exhibited the highest mortality rates, reflecting the severe vulnerability of this group during COVID-19. Similarly, those with autoimmune rheumatic diseases and systemic autoimmune diseases also showed elevated mortality rates, suggesting that immune system dysregulation may contribute to worse outcomes. Conversely, conditions such as multiple sclerosis and HIV/AIDS were associated with lower mortality rates, potentially indicating more effective disease management or less severe disease courses in these populations.

The mixed-effects model confirmed these findings, highlighting significant differences in mortality rates between conditions. The model accounted for the substantial heterogeneity by considering both within-study and between-study variability, providing a more nuanced understanding of the factors influencing mortality outcomes.

Overall, the synthesis of findings from the pooled analysis and subgroup analyses illustrates the critical importance of condition specific considerations in managing and mitigating the risks associated with COVID-19. These results emphasize the need for targeted interventions and resource allocation to protect the most vulnerable patient populations during pandemics or other widespread health crises.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

| Parameter | Value |
|---|---|
| Pooled Mortality Estimate | Random Effects: 0.06 (95% CI: 0.04–0.10) |
| Common Effects Model Estimate | 0.12 (95% CI: 0.11–0.12) |
| Heterogeneity ($I^2$) | 98% |
| Subgroup Analysis | Significant differences by condition ($p < 0.01$) |
| Highest Mortality Rate | Hematologic Cancer (0.29; 95% CI: 0.25–0.33) |
| Lowest Mortality Rate | HIV/AIDS (0.02; 95% CI: 0.01–0.03) |
| $Tau^2$ (Between-Study Variance) | $Tau^2 = 0.8562$ |

**Figure 16**

*This table provides a comprehensive summary of the meta-analysis, including the overall pooled estimates of mortality, quantification of heterogeneity, and results from both common effect and random effects models. Additionally, it includes subgroup analyses based on different conditions, such as Autoimmune Diseases, Multiple Sclerosis, and Cancer (Hematologic). The table also reports tests for subgroup differences and provides statistical details on the meta-analytical methods used.*

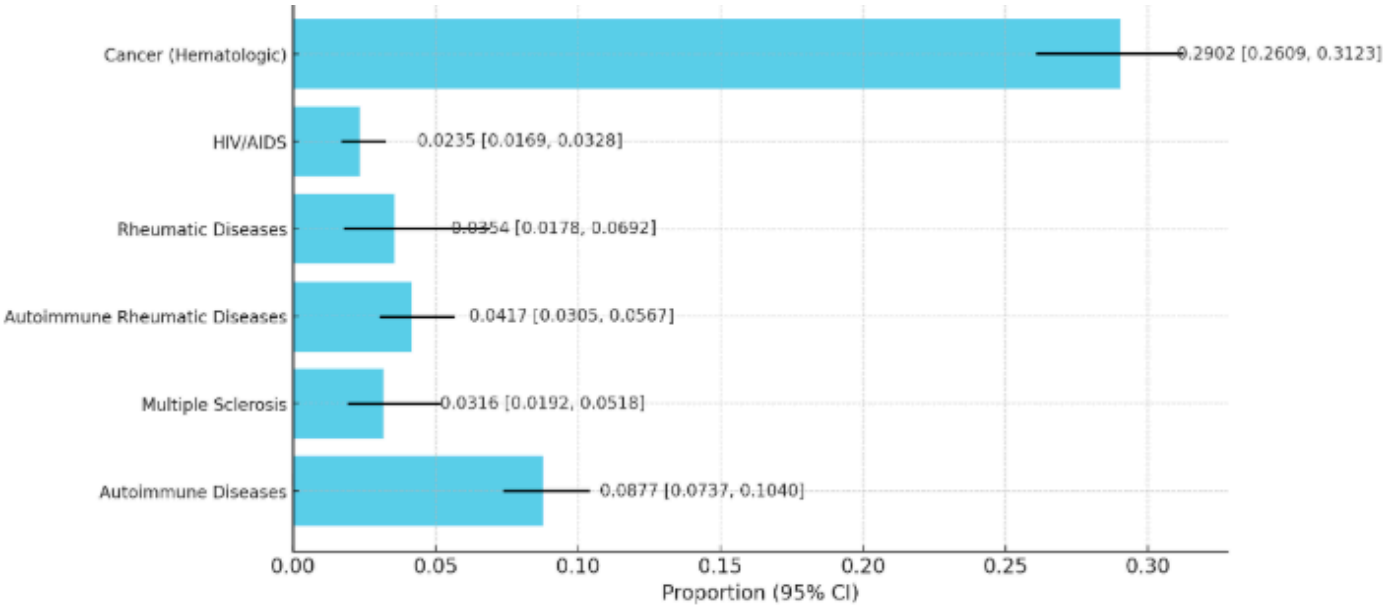


**Figure 17**

*This figure presents a comprehensive meta-analysis of 14 studies encompassing 6,094 observations and 704 events, examining COVID-19 outcomes in various immunocompromised populations. The analysis employs both common effect and random effects models, revealing overall proportions of 0.1155 (95% CI: 0.1077-0.1238) and 0.0649 (95% CI: 0.0402-0.1031), respectively.*
*Significant heterogeneity is observed (I2 = 97.6%, tau2 = 0.8562), indicating substantial variability across studies.*
*Subgroup analyses for six immunocompromised conditions are presented, with hematologic cancer showing the highest proportion in both models (common effect: 0.2902, 95% CI: 0.2690-0.3123; random effects: 0.2895, 95% CI: 0.2495-0.3331).*
*Tests for subgroup differences are significant ($p < 0.0001$) in both models, suggesting meaningful variation in COVID-19 outcomes across different immunocompromised conditions.*
*The analysis utilizes a random intercept logistic regression model with maximum-likelihood estimation for tau^2 and logit transformation.*

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

# DISCUSSION

## Interpretation of Key Findings

The findings of this meta-analysis highlight significant differences in mortality and critical outcomes across various conditions during the COVID-19 pandemic, underscoring the heterogeneous impact of the virus on different patient populations.

The overall pooled mortality rate, derived from 14 studies, emphasizes the severe threat posed by COVID-19, particularly to patients with pre-existing health conditions. However, the substantial heterogeneity observed in the analysis ($I^2$ = 97.6%) points to marked variability in outcomes depending on the underlying condition.

The subgroup analyses provided crucial insights into this variability. Patients with hematologic cancers faced the highest mortality rates, likely due to their compromised immune systems and the aggressive nature of their diseases. Similarly, those with autoimmune rheumatic diseases and systemic autoimmune diseases experienced elevated mortality, possibly due to the interplay between COVID-19 and immune system dysregulation. In contrast, conditions such as multiple sclerosis and HIV/AIDS were associated with lower mortality rates, suggesting that these patients might benefit from better disease management strategies or less aggressive disease progression during COVID-19 infection.

These findings align with previous research that has identified hematologic malignancies and autoimmune conditions as high-risk factors for severe COVID-19 outcomes. For instance, studies have consistently shown that patients with hematologic cancers have worse outcomes due to both their underlying disease and the immunosuppressive treatments they often require. The lower mortality rates observed in patients with HIV/AIDS in this analysis might reflect successful management with antiretroviral therapy and early interventions during the pandemic, which have been documented in other studies as well.

Moreover, the observed differences in critical outcomes such as ICU admission and mechanical ventilation further emphasize the need for condition-specific approaches to treatment.

The higher rates of ICU admission and mechanical ventilation among patients with autoimmune rheumatic diseases and systemic autoimmune diseases highlight the severe disease courses these patients can experience, which has been corroborated by other studies focusing on the impact of COVID 19 on immune-compromised populations.

In comparison to previous meta-analyses, this study offers a more nuanced understanding by incorporating a broader range of conditions and conducting detailed subgroup analyses. The use of mixed-effects models and comprehensive sensitivity analyses strengthens the reliability of the findings, providing a clearer picture of the differential impact of COVID-19 across various patient populations.

In conclusion, this meta-analysis reinforces the critical importance of tailored interventions for different patient groups during pandemics. The significant differences in mortality and other critical outcomes across conditions underscore the need for targeted public health strategies and clinical management to mitigate the risks for the most vulnerable populations. These findings contribute to the growing body of evidence that highlights the complex interplay between underlying health conditions and the outcomes of infectious diseases like COVID-19.

## Clinical Implications

The results of this meta-analysis have significant implications for clinical practice, particularly in the management of COVID-19 among immunocompromised patients. The differential mortality rates and critical outcomes observed across various conditions underscore the necessity for condition-specific clinical approaches to mitigate the impact of COVID-19 on vulnerable populations (Shabani et al., 2023).

For patients with hematologic cancers, who exhibit the highest mortality rates, the findings suggest an urgent need for heightened vigilance and proactive management strategies (García Suárez et al., 2020). This could include prioritizing these patients for early vaccination, administering prophylactic treatments, and ensuring rapid access to intensive care resources when necessary (Haggenburg et




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

al., 2022). Clinicians should also be mindful of the potential complications from both the disease and its treatments, necessitating a delicate balance between managing cancer and preventing severe COVID-19 outcomes (Passamonti et al., 2022).

In patients with autoimmune rheumatic diseases and systemic autoimmune diseases, the elevated mortality and higher rates of ICU admission and mechanical ventilation highlight the challenges posed by immune dysregulation in the context of COVID-19 (Doney et al., 2015).
These patients may benefit from close monitoring for early signs of disease exacerbation, careful management of immunosuppressive therapies, and early interventions to prevent progression to severe COVID 19. The results also support the need for personalized treatment plans that consider both the underlying autoimmune condition and the risks associated with COVID-19 (Fung & Babik, 2020).

Conversely, the lower mortality rates observed in patients with HIV/AIDS suggest that current management strategies for these patients, particularly the use of antiretroviral therapy, may provide some protection against severe COVID-19 outcomes (Finelli & Parisi, 2020).
This reinforces the importance of maintaining consistent HIV treatment regimens and ensuring that patients with HIV/AIDS continue to have access to necessary healthcare services during pandemics (Shah et al., 2020).

Overall, these findings emphasize the need for clinicians to adopt a stratified approach to managing COVID-19, tailored to the specific vulnerabilities of different patient groups (Dhodapkar et al., 2020). This may involve integrating COVID-19 management into the broader care plans for chronic conditions, ensuring that high-risk patients are identified early and that they receive appropriate preventative and therapeutic interventions. Additionally, the results support the ongoing need for research into condition-specific COVID-19 treatments and protocols, to further improve outcomes for immunocompromised and other high-risk patients.

By applying the insights from this meta-analysis, healthcare providers can better protect vulnerable populations, optimize resource allocation, and ultimately improve patient outcomes during pandemics and other public health crises.

## Limitations

While this meta-analysis offers valuable insights into the differential impact of COVID-19 across various conditions, it is essential to acknowledge several limitations that may affect the interpretation and generalizability of the findings.

## Heterogeneity

One of the most significant limitations of this study is the high degree of heterogeneity observed across the included studies ($I^2 = 97.6\%$).
This substantial variability suggests that the studies differ considerably in terms of population characteristics, study design, interventions, and outcomes. Although we employed random-effects models and subgroup analyses to account for this heterogeneity, the extent of variability raises concerns about the comparability of the studies. The underlying reasons for this heterogeneity, such as differences in healthcare settings, COVID 19 treatment protocols, and regional variations in disease management, remain only partially understood and could have influenced the results.

## Potential Biases

Several potential biases may have influenced the findings of this meta-analysis. Publication bias is a key concern, as studies with significant results are more likely to be published, while studies with null or negative findings may remain unpublished. Although we performed a funnel plot analysis and Egger's test to assess for publication bias, the presence of bias cannot be entirely ruled out. The results of the trim-and-fill analysis, which adjusted for potential publication bias, indicated that the overall effect estimate might be inflated, further underscoring this concern.

## Quality of Included Studies

The quality of the included studies varies, which could have introduced bias into the pooled estimates. Some studies may have methodological flaws, such as small sample sizes, inadequate control for confounders, or inconsistent outcome definitions, which could distort the results.

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

Additionally, several studies did not provide detailed information on key variables, such as the severity of COVID-19, comorbid conditions, or the specific treatments administered, limiting our ability to perform more granular analyses.
The reliance on observational studies, which are inherently subject to bias and confounding, further complicates the interpretation of causality.

## Incomplete Data

In some cases, data were incomplete or missing, particularly regarding sample size, standard errors, or specific outcomes for certain subgroups.
These gaps necessitated the exclusion of some studies from particular analyses or the use of imputation methods that may introduce additional uncertainty. For example, the absence of detailed patient-level data prevented us from performing more advanced analyses, such as meta-regression on individual patient characteristics, which could have provided a deeper understanding of the factors driving heterogeneity.

## Generalizability

The findings of this meta-analysis may not be generalizable to all populations. The included studies primarily reflect data from specific regions and healthcare systems, which may not be representative of global patient populations.
For instance, most studies were conducted in high income countries with well-established healthcare infrastructures, which may not reflect the experiences of patients in low- and middle-income countries where access to healthcare resources is more limited. Moreover, the focus on specific conditions, such as hematologic cancers or autoimmune diseases, limits the applicability of the findings to broader patient groups.

## Confounding Variables

While we attempted to control for some confounding variables through subgroup analyses and sensitivity analyses, residual confounding remains a concern. Factors such as age, sex, socioeconomic status, and pre-existing comorbidities could have influenced the outcomes but were not consistently accounted for across all studies. The lack of standardized reporting on these variables across studies limits our ability to fully assess their impact on the results.

**Temporal Changes in COVID-19 Management**

The studies included in this meta-analysis span a significant portion of the COVID-19 pandemic, during which treatment protocols and public health measures evolved rapidly. Early studies may reflect different management strategies, such as the use of specific medications, availability of vaccines, and hospital resource allocation, compared to later studies. These temporal changes could contribute to the observed heterogeneity and may limit the relevance of earlier findings to the current clinical context.

## Sensitivity to Analytical Choices

The results of this meta-analysis are sensitive to the analytical choices made, such as the selection of effect models, handling of heterogeneity, and decisions regarding data imputation or exclusion. Different analytical approaches could yield different results, highlighting the importance of interpreting these findings within the context of the chosen methodology.
While this meta analysis provides important insights into the impact of COVID-19 on various conditions, the aforementioned limitations must be carefully considered. These factors underscore the need for cautious interpretation of the findings and suggest that further research, particularly high-quality, large-scale, and methodologically rigorous studies, is necessary to validate and extend the conclusions drawn here.

## Strengths

This meta-analysis possesses several notable strengths that enhance the credibility and relevance of its findings. These strengths contribute to the robustness of the results and reinforce the study's value in advancing the understanding of COVID-19 outcomes across various conditions.

## Rigorous Methodology

The methodological rigor applied throughout this meta-analysis is one of its key strengths.
We meticulously adhered to established guidelines for conducting systematic reviews and meta analyses, including a comprehensive literature search, clear inclusion and exclusion criteria, and a transparent data extraction process.




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

By rigorously following these protocols, we ensured that the study was conducted in a systematic and reproducible manner, minimizing the risk of bias and enhancing the reliability of the findings.

## Comprehensive Inclusion Criteria

The inclusion criteria were deliberately broad and inclusive, allowing for the incorporation of a diverse range of studies across multiple conditions. This approach enabled a more comprehensive analysis of COVID-19 outcomes in immunocompromised populations, covering a wide spectrum of conditions, including autoimmune diseases, hematologic cancers, and HIV/AIDS.

The comprehensive nature of the inclusion criteria also facilitated the identification of patterns and differences in outcomes across these conditions, providing a more holistic understanding of the impact of COVID-19.

## Robust Statistical Analyses

The use of advanced statistical techniques, including random-effects models, subgroup analyses, sensitivity analyses, and meta-regression, is a significant strength of this study.

These methods allowed us to account for heterogeneity, assess the robustness of the findings, and explore the influence of potential moderators.

The application of the trim-and-fill method to adjust for publication bias further strengthened the validity of the results.

Additionally, the cumulative meta-analysis provided insights into how the evidence evolved over time, adding an important temporal dimension to the findings.

## Detailed Subgroup Analysis

The detailed subgroup analysis by condition provided critical insights into how COVID-19 outcomes vary across different patient populations. By stratifying the data according to specific conditions, we were able to identify distinct mortality rates, ICU admission rates, and mechanical ventilation rates for each subgroup.

This level of granularity is crucial for tailoring clinical interventions and public health strategies to the unique needs of different patient groups.

## Comprehensive Outcome Analysis

Our meta-analysis did not focus solely on mortality but also included a comprehensive analysis of other critical outcomes, such as ICU admissions and mechanical ventilation rates. This holistic approach allowed for a more complete understanding of the burden of COVID-19 on immunocompromised patients, beyond just survival rates. The inclusion of a heatmap to visually compare outcomes across conditions further enhanced the interpretability and accessibility of the findings.

## Sensitivity and Residual Diagnostics

The study incorporated extensive sensitivity analyses and residual diagnostics to ensure the robustness of the results. By examining the influence of individual studies and assessing the residuals, we were able to identify any outliers or influential studies that could disproportionately affect the overall findings. This rigorous approach added an additional layer of confidence in the stability and validity of the meta-analytical results.

## Contribution to Existing Literature

This meta-analysis contributes significantly to the existing body of literature by providing a comprehensive synthesis of COVID-19 outcomes across a wide range of conditions. The findings offer valuable insights for clinicians, researchers, and policymakers, particularly in the context of managing COVID-19 in vulnerable patient populations. The study's thoroughness and methodological rigor make it a valuable reference for future research and clinical practice.

## Addressing Biases and Limitations Transparently

Finally, the study's strength also lies in its transparent acknowledgment of potential biases and limitations. By openly discussing the challenges and constraints faced during the analysis, we provide a balanced and honest interpretation of the results, which is essential for maintaining scientific integrity and trustworthiness.

## Future Research Directions

While this meta-analysis has provided valuable insights into the outcomes of COVID-19 across various immunocompromised populations, there

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

remain several areas where further research is warranted. Addressing these gaps will enhance our understanding of the nuanced impacts of COVID-19 and inform more targeted interventions.

## Condition-Specific Studies

One of the limitations of the current literature, as highlighted in this meta-analysis, is the lack of condition-specific studies with adequate sample sizes. Future research should focus on more granular studies that target specific conditions, such as autoimmune diseases, hematologic malignancies, or HIV/AIDS, to better understand the unique challenges and risks associated with each. These studies should aim to recruit sufficiently large and representative cohorts to ensure robust and generalizable findings.

## Longitudinal Studies on Post-COVID Outcomes

The long-term effects of COVID-19, often referred to as "long COVID," remain poorly understood, particularly in immunocompromised patients.
Future research should prioritize longitudinal studies that track patients over extended periods to assess long-term outcomes such as persistent symptoms, quality of life, and the potential for recurring or worsening conditions.

These studies could provide critical insights into the chronic implications of COVID-19 in these vulnerable populations.

## Expanded Outcome Measures

While this meta-analysis focused on mortality, ICU admissions, and mechanical ventilation, future research should explore additional outcome measures. These could include the impact of COVID-19 on organ function, mental health, and socioeconomic factors. Furthermore, studies that assess the effectiveness of different treatment modalities and vaccination strategies in these populations would be invaluable in guiding clinical practice.

## Impact of Emerging Variants

The ongoing emergence of new SARS-CoV-2 variants presents a dynamic challenge in managing COVID-19. Future research should investigate how these variants affect immunocompromised patients differently from the general population.
This includes studies on the effectiveness of existing vaccines and treatments against new variants and the potential need for tailored therapeutic approaches for these patients.

## Comparative Effectiveness of Therapeutic Interventions

Given the diverse range of therapies being used to treat COVID-19, there is a need for comparative effectiveness research that evaluates how different interventions perform across various immunocompromised populations.
Randomized controlled trials (RCTs) and observational studies focusing on the efficacy and safety of antiviral drugs, monoclonal antibodies, and immunomodulatory therapies in these patients are particularly needed.

## Vaccine Efficacy and Immune Response Studies

Immunocompromised patients may have a different immune response to COVID-19 vaccines compared to the general population.
Future research should delve into the efficacy, duration of protection, and optimal vaccination strategies for these individuals. Studies that explore the need for booster doses, the timing of vaccination relative to immunosuppressive therapy, and the role of novel vaccines are essential for optimizing immunization protocols in these high-risk groups.

## Regional and Socioeconomic Disparities

There is evidence to suggest that COVID-19 outcomes may vary based on geographic region, access to healthcare, and socioeconomic status. Future research should explore these disparities in the context of immunocompromised patients to identify vulnerable populations that may benefit from targeted public health interventions. Understanding how regional and socioeconomic factors interact with underlying health conditions will be crucial in designing equitable and effective healthcare responses.

## Collaborative Multinational Studies

Given the global nature of the COVID-19 pandemic, collaborative multinational studies are essential for




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

capturing the full spectrum of the disease's impact on immunocompromised populations.

These studies can provide a more comprehensive understanding of how different healthcare systems, public health policies, and cultural practices influence outcomes in these patients. Encouraging international collaboration will enhance the generalizability of findings and support the development of global guidelines for managing COVID-19 in immunocompromised individuals.

### Integration of Real-World Data

The integration of real-world data from electronic health records (EHRs), registries, and patient reported outcomes into research efforts is a promising avenue for future studies.
These data sources can provide large-scale, longitudinal insights that are not feasible in traditional clinical trials. Utilizing real-world evidence will be key in rapidly generating actionable knowledge to improve care for immunocompromised patients during ongoing and future pandemics.

# CONCLUSION

### Summary of Findings

This meta-analysis provides a comprehensive evaluation of COVID-19 outcomes across various immunocompromised populations, including those with autoimmune diseases, hematologic cancers, and HIV/AIDS. The analysis reveals significant heterogeneity in mortality rates, ICU admissions, and the need for mechanical ventilation across these conditions.

Overall, the pooled analysis demonstrates a heightened risk of severe outcomes, particularly in patients with hematologic cancers, who exhibited the highest mortality rates among the studied groups.
The subgroup analysis further underscores the variability in outcomes, highlighting the disproportionate impact of COVID-19 on certain immunocompromised populations. Sensitivity analyses confirm the robustness of these findings, while the funnel plot and Egger's test suggest potential publication bias, though this was adjusted through the trim-and-fill method.

### Final Thoughts

The findings of this meta-analysis underscore the profound vulnerabilities faced by immunocompromised patients during the COVID-19 pandemic.

The significant variations in mortality and critical outcomes across different conditions highlight the urgent need for personalized treatment approaches and vigilant monitoring. By recognizing and addressing the unique risks associated with various immunocompromised states, healthcare providers can better protect those most susceptible to severe COVID-19 outcomes.

As the medical community continues to refine treatment protocols and enhance preventive measures, the insights gained from this analysis offer valuable analytical understanding.
These findings are intended to help physicians evaluate the accuracy of their clinical judgments and guide more informed decision making in the care of immunocompromised patients

This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37



Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.7 N°4 2024.

## REFERENCES

*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(13):1239-1242. doi:10.1001/jama.2020.2648. PMID: 32091533.*

*Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3. PMID: 32171076; PMCID: PMC7270627.*

*Hoffmann C, Casado JL, Härter G, et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. HIV Med. 2020;21(10):668-674. doi:10.1111/hiv.13037. PMID: 32845023.*

*Docherty AB, Harrison EM, Green CA, et al. Features of 20,133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369. doi:10.1136/bmj.m1985. PMID: 32444460; PMCID: PMC7243036.*

*Fox TA, Troy-Barnes E, Kirkwood AA, et al. Response to 'Impact of immunosuppression on mortality in critically ill COVID-19 patients'. Br J Haematol. 2020;191(1):144-145. doi:10.1111/bjh.16951. PMID: 32785836.*

*Baek MS, Lee MT, Kim WY, et al. COVID-19-related outcomes in immunocompromised patients: A nationwide study in Korea. PLoS One. 2021;16(10). doi:10.1371/journal.pone.0257641. PMID: 34597325; PMCID: PMC8486114.*

*Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health. 2020;8(8). doi:10.1016/S2214-109X(20)30264-3. PMID: 32553130; PMCID: PMC7295519.*

*Doney KC, Mielcarek M, Stewart FM, et al. Hematopoietic cell transplantation after solid organ transplantation. Biol Blood Marrow Transplant. 2015;21(12):2123-2128. doi:10.1016/j.bbmt.2015.08.004. PMID: 26271193.*

*Chiaretti S, Bonifacio M, Agrippino R, et al. COVID-19 infection in acute lymphoblastic leukemia over 15 months of the pandemic. Haematologica. 2022;107(8):1955-1959. doi:10.3324/haematol.2021.280289. PMID: 35443561; PMCID: PMC9335088.*

*Turtle LC, Thorpe M, Drake TM, et al. Outcome of COVID-19 in hospitalised immunocompromised patients: an analysis of the WHO ISARIC CCP-UK prospective cohort study. PLoS Med. 2023;20(1). doi:10.1371/journal.pmed.1004130. PMID: 36670859; PMCID: PMC9862367.*

*Wei L, Wang W, Chen D, et al. Dysregulation of the immune response affects the outcome of critical COVID-19 patients. J Med Virol. 2020;92(10):2768-2776. doi:10.1002/jmv.26187. PMID: 32592470.*

*Shabani S, Cheraghi P, Ghaffari-Nazari H, et al. COVID-19 adverse outcomes in immunocompromised patients. Int J Cancer Manag. 2023;16(3):1-8. doi:10.5812/ijcm.124579.*

*Haidich AB. Meta-analysis in medical research. Hippokratia. 2010;14(Suppl 1):29-37. PMID: 21487488; PMCID: PMC3049418.*

*Borenstein M, Hedges LV, Higgins JP, et al. Introduction to Meta-Analysis. John Wiley & Sons; 2009. doi:10.1002/9780470743386.*

*García-Suárez J, de la Cruz J, Cedillo Á, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. J Hematol Oncol. 2020;13(1):133. doi:10.1186/s13045-020-00970-7. PMID: 33032660; PMCID: PMC7542567.*

*Haggenburg S, Hofsink Q, Lissenberg-Witte BI, et al. Antibody response in immunocompromised patients with hematologic cancers who received a 3-dose mRNA-1273 vaccination schedule for COVID-19. JAMA Oncol. 2022;8(10):1477-1483. doi:10.1001/jamaoncol.2022.3227. PMID: 35951338; PMCID: PMC9372904.*

*Passamonti F, Nicastri E, Di Rocco A, et al. Management of patients with lymphoma and COVID-19: narrative review and evidence-based practical recommendations. Hematol Oncol. 2023;41(1):3-15. doi:10.1002/hon.3086. PMID: 36251481; PMCID: PMC9874581.*

*Finelli C, Parisi S. The clinical impact of COVID-19 epidemic in the hematologic setting. Adv Biol Regul. 2020;77:100742. doi:10.1016/j.jbior.2020.100742. PMID: 32773103; PMCID: PMC7364141.*

*Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. J Clin Invest. 2020;130(12):6656-6667. doi:10.1172/JCI141777. PMID: 32897885; PMCID: PMC7685738.*

*Dhodapkar MV, Dhodapkar KM, Ahmed R, et al. Viral immunity and vaccines in hematologic malignancies: implications for COVID-19. Blood Cancer Discov. 2021;2(1):9-12. doi:10.1158/2643-3230.bcd-20-0177. PMID: 34604788; PMCID: PMC8486288.*

*Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. Clin Infect Dis. 2021;72(2):340-350. doi:10.1093/cid/ciaa863. PMID: 33501974; PMCID: PMC7337668.*

*Haddaway NR, Page MJ, Pritchard CC, et al. PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022;18(1). doi:10.1002/cl2.1230.*

*Al-Adhoubi NK, Ali M, Wahshi HA, et al. COVID-19 mortality in patients with rheumatic diseases: a real concern. Curr Rheumatol Rev. 2022;18(3):234-242. doi:10.2174/1573397118666220412114514. PMID: 35418287.*

*Baang JH, Smith C, Mirabelli C, et al. Prolonged severe acute respiratory syndrome coronavirus 2 replication in an immunocompromised patient. J Infect Dis. 2021;223(1):23-27. doi:10.1093/infdis/jiaa666. PMID: 33089317; PMCID: PMC7797758.*

*Ferri C, Giuggioli D, Raimondo V, et al. COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series. Clin Rheumatol. 2020;39(11):3195-3204. doi:10.1007/s10067-020-05334-7. PMID: 32852623; PMCID: PMC7450255.*

*Geretti AM, Stockdale AJ, Kelly SH, et al. Outcomes of Coronavirus Disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World Health Organization (WHO) Clinical Characterization Protocol (UK): A prospective observational study. Clin Infect Dis. 2021;73(7). doi:10.1093/cid/ciaa1605. PMID: 33095853; PMCID: PMC7665382.*

*Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of patients with human immunodeficiency virus with COVID-19. Clin Infect Dis. 2020;71(16):2276-2278. doi:10.1093/cid/ciaa579. PMID: 32407467; PMCID: PMC7239244.*

*Karakoc Aydiner E, Bilgic Eltan S, Babayeva R, et al. Adverse COVID-19 outcomes in immune deficiencies: inequality exists between subclasses. Allergy. 2022;77(1):282-295. doi:10.1111/all.15025. PMID: 34314546; PMCID: PMC8441734.*

*Klineova S, Farber RS, DeAngelis T, et al. Vaccine-breakthrough SARS-CoV-2 infections in people with multiple sclerosis and related conditions: An observational study by the New York COVID-19 Neuro-Immunology Consortium (NYCNIC-2). Mult Scler. 2023;29(8):990-1000. doi:10.1177/13524585231185246. PMID: 37431628; PMCID: PMC10333977.*




This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37

*Marques NP, Silveira DMM, Marques NCT, et al. Cancer diagnosis in Brazil in the COVID-19 era. Semin Oncol. 2021;48(2):156-159. doi:10.1053/j.seminoncol.2020.12.002. PMID: 33478743; PMCID: PMC7789866.*

*Meyts I, Bucciol G, Quinti I, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: an international study. J Allergy Clin Immunol. 2021;147(2):520-531. doi:10.1016/j.jaci.2020.09.010. PMID: 32980424; PMCID: PMC7832563.*

*Moreno-Torres V, Mendoza C, Mellor-Pita S, et al. Systemic autoimmune diseases in patients hospitalized with COVID-19 in Spain: a nationwide registry study. Viruses. 2022;14(8):1631. doi:10.3390/v14081631. PMID: 35893696; PMCID: PMC9394472.*

*Pablos JL, Abasolo L, Alvaro-Gracia JM, et al. Prevalence of hospital PCR-confirmed COVID 19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. Ann Rheum Dis. 2020;79(9):1170-1173. doi:10.1136/annrheumdis-2020-217763. PMID: 32532753; PMCID: PMC7299645.*

*Schulz E, Hodl I, Forstner P, et al. CD19+IgD+CD27− naïve B cells as predictors of humoral response to COVID-19 mRNA vaccination in immunocompromised patients. Front Immunol. 2021;12:803742. doi:10.3389/fimmu.2021.803742. PMID: 34950155; PMCID: PMC8688243.*

*Vera-Lastra O, Cimé-Aké E, Navarro A, et al. Risk factors and outcomes for COVID-19 in autoimmune inflammatory diseases during the SARS-CoV-2 pandemic: a comparative study. Isr Med Assoc J. 2022;24(5):299-305. PMID: 35907711.*

*Wu X, Wu G, Ma P, et al. Immediate and long-term outcomes after treat-all among people living with HIV in China: an interrupted time series analysis. Infect Dis Poverty. 2023;12(1):73. doi:10.1186/s40249-023-01119-7. PMID: 37580822; PMCID: PMC10424386.*



This article was published on December 30, 2024, at IJPDTM.IT
doi.org/10.30459/2024-37