# **Introduction**

The COVID-19 pandemic transforming impact on societies across the globe. In 2019, the virus spread rapidly overwhelming our healthcare systems, shutting down economies, and forcing many into isolation. These drastic changes required us to adapt to lockdowns, remote work and education, and a new social norms. Although the acute phase of the pandemic has largely subsided, and vaccination campaigns have significantly reduced the severity of transmission. The long-term consequences, such as disruption of routine healthcare for non- COVID-19 patients during the lockdown period, still persist (1).

The pandemic also challenged our medical and scientific communities, prompting global levels of collaboration and innovation to meet the rapid demands of aiding the crisis quickly. Vaccines were developed and distributed promptly, and treatment protocols evolved swiftly as new data emerged. However, despite these milestones, much about the virus remains unknown, particularly in terms of its long-term health impacts. While many individuals recover quickly from COVID-19, others experience prolonged symptoms, a condition known as "Long COVID," which symptoms of persistent fatigue and respiratory issues. (2) The risk factors, cause and long-term implications of long COVID are still under investigation.

## Objectives

Although the global threat of COVID-19 has diminished, long-term morbidity remains unclear. Clinicians are tasked not only with managing acute cases but also addressing the chronic conditions that may follow infection. Understanding these long-term medical consequences across multiple clinical domains is essential in improving the healthcare of our patients.

The objective of this literature review is to evaluate and compare the morbidity outcomes in patients with COVID-19 infection versus those without, across various clinical and demographic settings. This review focuses in identifying patterns in diseases among varied clinical domain to assess long-term health complications associated with COVID-19, and determine whether COVID-19 infection is linked to increased morbidity relative to non-infected populations. The findings will help clarify the extent of COVID-19’s long-term impact on health and guide future research and healthcare planning.

This literature review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines to ensure credibility, consistency and transparency throughout the selection process. This review specifically addresses components including rationale, objectives, eligibility criteria, information sources, search strategy, selection process, data collection process, data items, synthesis methods, study selection, study characteristics, risk of bias in studies, discussion, and results of individual studies.

# **Methods**

## Information sources

We searched MEDLINE (PubMed) use of MeSH-based search strategy**:  
 (((COVID-19[MeSH Terms]) AND (non-COVID[Title/Abstract])) ) AND (morbidity[Title/Abstract])**This strategy aimed to identify studies comparing morbidity outcomes between patients with and without COVID-19.

## Search strategy & Selection Process

The initial database search returned **137 results.** After excluding **22 articles** due to the unavailability of abstracts or full texts, **115 articles** remained.  
Titles were screened for relevance, resulting in the exclusion of **61 articles.**  
Abstract screening was then performed on the remaining **54 articles,** of which **32** did not meet our inclusion criteria.  
Among the **22 studies** selected for full-text review, **5** were excluded due to insufficient data or methodological limitations.  
A final total of **17 articles** published between **September 2020 and April 2025** were included in the final analysis.

## Eligibility criteria & Study selection

The studies published between 2020 and 2025 included in this review compared morbidity outcomes between populations exposed to COVID-19 with non-infected populations across the following medical domains General Hospital/ICU, Cardiovascular, Pulmonary, Neurologic, Trauma, Rheumatology, Obstetric/Pregnancy.

Inclusion Criteria:

* Studies published between 2020 and 2025
* Studies comparing morbidity outcomes in COVID-19 positive versus non-infected populations

Exclusion Criteria:

* Studies lacking a comparison/control group
* Non-English language studies
* Studies missing Abstracts, case reports, or opinion pieces

## Data collection process

Data extraction was performed manually by a single reviewer using standardized Microsoft Excel spreadsheet. The PMC ID Converter tool was used to obtain full-text articles and citation information. No automation tools were used during the extraction process.

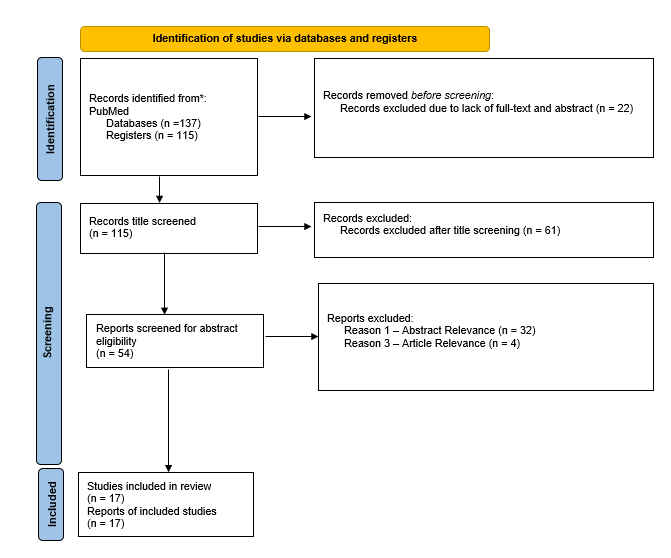
## Data Items

For each included study, the following data were extracted:

* **Study characteristics** (authors, year of publication, country, study design)
* **Population characteristics** (sample size, age, gender)
* **Medical Domain** (e.g., cardiovascular, endocrinology, general hospital, neurologic, obstetric/pregnancy, pulmonary, rheumatologic, and trauma)
* **Reported morbidity outcomes** (COVID vs. non-COVID groups)
* **Comparative findings** between different diseases (if available: comorbidities and illness severity)

## Figure 1

PRISMA flow Diagram



# **Synthesis Methods**

To assess morbidity outcomes associated with COVID-19 infection, data were synthesized according to clinical domain (e.g., cardiovascular, endocrinology, general hospitalization, neurologic, obstetric/pregnancy, pulmonary, rheumatologic, and trauma). This review included studies that provided comparative morbidity data for COVID-positive and non-COVID population, with specific focus on ICU admission, hospitalization, mortality, or clinical complications. Studies lacking control groups or defined morbidity outcomes were excluded.

Due to variability in outcome measurement tools, study design, duration, morbidity definitions, a formal meta-analysis was not possible. Instead, a descriptive summary approach was used. Where applicable, morbidity rates were recalculated from available data (e.g., percentages, clinical scores such as the modified Rankin Scale [mRS]) or estimated using contextual information for meta-analysis. Any missing, inconsistent or unclear data were noted in the limitation column of the summary table.

# **Results**

Findings were organized into a structured summary table (Table1), capturing key variables such as reported outcomes, COVID-positive vs non-COVID morbidity rate, percent change, source references, and study characteristics (e.g., region, duration, population size). Visual arrow indicators (↑ increase, ↓ decrease) were used in the “% Morbidity Rate” column to illustrate trends. After tabulation, results were analyzed to identify consistent patterns of increased or decreased morbidity with each clinical domain. Discrepancies or inconclusive findings are highlighted in the “Reported Outcomes” column of Table 1.

## Table 1. Morbidity Data Summary

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medical Domain** | **Reported Outcomes** | **COVID-19 Morbidity Rate** | **Non-COVID Morbidity Rate** | **% Morbidity Rate** | **Key References (PMID/PMCID)** | **Duration** | **Region** | **Study Type** | **Population** | **Limitations** |
| **Cardiovascular** | ICU admission by CAD status | 4% - without CAD ICU 44% - with CAD ICU | Non-COVID excluded | N/A | Li X, Tian Y, Cao H, et al, 2025 [PMID: 40197291] | 12/20/2022 to 01/20/2023 |  | Retrospective Analysis | 143 patients with coronary atherosclerosis disease(CAD) (75 COVID-19 positive) (50 CAD, 25 without CAD) (68 non-COVID) (35 with CAD, 33 without CAD) | Age differences; small sample; lack of randomization |
| **Cardiovascular** | Highlight risk in delay of services contributing to morbidity and mortality rates | N/A | N/A | ↑58% COPD ↑52% Pneumonia | Chaudhry HW, Strini T, Rogers K, et al., 2022 [PMIID: 36481398] | 3/2020 to 8/2021 | Canada | Retrospective Analysis | Long-term care (LTC) Canadian residents | Age differences; small sample; lack of randomization |
| **Cardiovascular** | Higher risk of mortality and in-hospital complications | 66.10% | 12% | ↑437.4% | Ludvigson et al., 2021 [PMID: 33462815] | 3/2020 -5/2020 (2 months) | United Kingdom | Cohort Study | 12,958 hospitalized with Acute Coronary Syndrome  (517 COVID-positive)  (12441 non-COVID) | Use of ICD-10 codes unclear; ACS patients not routinely tested; no medical history or social determinants considered ACS patients were not routinely tested to predict virus exposure. Patient medical history and social determinants were not considered in this study. |
| **Endocrinology** | Results inconclusive, more data needed | data too variable to summarize | data too variable to summarize | data too variable to summarize | Wong R, Lam E, Bramante CT, et al., 2023 [PMID: 37284921] | 2021 to 2023 | US and Europe | Retrospective Analysis | Wide data from EHR; HbA1c >6.5% | ICD-10/9 codes used; no medical history or social determinants considered |
| **General Hospital/ICU** | Caution in use of SOFA score as triage tool | 67.9 % SOFA | 73.5% SOFA | ↓7.6% SOFA (decrease) | Sherak RAG, Sajjadi H, Khimani N, et al. , 2024 [PMID: 38758942] | 2014 to 20215 3/29/2020 to 8/1/202 (4months) | US | Retrospective Analysis | 268 hospital patients (96 COVID-positive) 75,601 (non-COVID-19 patients) from eICU Collaborative Research Database | Age differences; small sample; lack of randomization |
| **General Hospital/ICU/Stoke** | ICU admission, mortality, Stroke risk increase in COVID-19 patients | 80.60% | mRS at discharge = 1.86 ± 1.52 mRS = 2 --> No significant disability, able to carry out all usual duties (2 - 1.86) / 1.52 = 0.092 (Z table Calculator) = 46.3% | ↑74% | Evans et al., 2023 [PMID: 37514546] | 6/2020–8/2020 (3 months) | Bengaluru, South India | Retrospective Study | 62 hospital patients, age 42.46–68.86 (mean 55.66 years) | Retrospective, bias due to isolation precautions and staff shortage; small urban city; no medical history or social determinants considered |
| **Neurologic** | Poor outcomes and higher mortality due to stroke | 79.8% poor outcomes 38.7% mortality | 66.7% poor outcomes 18.4% mortality | ↑19.6% mortaility | Jabbour P, Dmytriw AA, Sweid A, et al. ,2022 [PMIID: 35238817] | 1/2018 to 12/2020 | Finland | Retrospective Analysis | 575 patients with Large Vessel Occlusion (LVO) (194 COVID-19 positive) (62.5 + 15.3 years)  (381 non-COVID) (71.2 + 15.9 years) | Age differences; small sample; lack of randomization |
| **Obstetric/Pregnancy** | More likely preterm labor, miscarriages, fetal distress | 89% adverse outcomes | 10% | ↑150% | Parazzini F, Bortolus R, Mauri PA, et al., 2020 [PMID: 32732059] | 2/2020–4/2020 (2 months) | United Kingdom | Cohort Study | 6679 pregnant patients  (23 COVID-positive) (6756 non-COVID)  age 16–40 (mean 29); ethnicity details (16 Asian, 3 Eastern Europe, 1 Black, 3 White British) | Small sample, single source; no medical history or social determinants considered |
| **Obstetric/Pregnancy** | Increased C-section, preterm labor, ICU, mortality | 32.5 % C-section 16.4% PreTerm 5.2 % ICU 0.10% mortality | 32.3% C-section 11.5% PreTerm 0.9% ICU 0.01% mortality | ↑478% ICU ↑9% mortality | Chinn J, Sedighim S, Kirby KA, et al. ,2021 [PMIID: 34379123] | 3/1/2020-2/28/2021 | US | Cohort Study | 869,079 pregnant woman(18 to 30 years) (18,715 COVID-19 positive) (850,364 non-COVID) | Age differences; small sample; lack of randomization |
| **Pulmonary** | Increased corticosteroid, central venous catheter, mechanical ventilation use | 20.5% Corticosteroid 74.4% Central Venous Catheter 53.8% Mechanical Ventilation | 8.9% Corticosteroid 57.3% Central Venous Catheterr 50.9% Mechanical Ventilation | ↑130%- Corticosteroid increase ↑30% Central Venous Catheterr increase ↑6% Mechanical Ventilation ↑27% Morbidity | 17. Shin SU, Bae S, Cho D, et al. , 2024 [PMID: 39732640] | 1/1/2020to 12/31/2022 | South Korea | Retrospective Analysis | 355 Candidaemia patients (39 COVID-19 positive) (non-COVID) | Age differences; small sample; missing data |
| **Pulmonary** | No increase in mortality or ICU admissions | 8% | 11.90% | ↓32% (decrease) | El Naamani K, Kharroubi S, Eid AH, et al., 2021 [PMID: 33741787] | 2020 (6 months) | Germany | Cohort Study | 100 sickle cell anemia patients (50 COVID-positive) (M:F 27:23) (50 non-COVID) (M:F 29:21) | Small sample; no medical history or social determinants considered |
| **Pulmonary (ARDS)** | No significant difference in morbidity/mortality for ARDS | N/A | N/A | N/A | Bernard A, Serna-Higuita LM, Martus P, et al., 2023 [PMID: 36740717] | 7/2019 to 5/2021 | Germany | Cohort Study | 150 patients with Acute Respiratory Distress Syndrome (ARDS) (58.5 + 14.4 years) (144 COVID-19 positive)  (44 non-COVID) | Limitation among age group difference between comparison cohorts with small scope of patients’ lack of randomization. |
| **Pulmonary (fungal infections)** | Increased  Rhizopus oryzae Aspergillus fumigatus Absidia mucor | 44.44% Rhizopus oryzae 33.33% Aspergillus fumigatus  11.11% Absidia mucor | 18.42% Rhizopus oryzae 26.32% Aspergillus fumigatus  2.63% Absidia mucor | ↑18.42% Rhizopus oryzae ↑26.63% Aspergillus fumigatus  ↑322% Absidia mucor | Ismaiel WF, Abdelazim MS, Eldsoky I, et al., 2021 [PMID: 34022619] | 2017 to 2020 | Egypt | Cohort Study | 56 patients with Acute invasive fungal rhino sinusitis (AIFRS) (18 COVID-19 positive) (38 non-COVID) | Small sample; no medical history or social determinants considered |
| **Pulmonary(ILD)** | Increased adverse outcomes in ILD/IPF patients | 6.9% - ILD - ICU 3% - IPF - ICU | 5.5% - ILD - ICU 2.1% - IPF - ICU | ↑0.2% - ILD ICU ↑.42% - IPF ICU | Vaeli Zadeh A, Dinparastisaleh R, Vaezi A, et al., 2022 [PMID: 38134434] | 1/2020 to 10/30/2021 | US | Retrospective Analysis | ILD/IPF patients ≥18 years from PearlDriver database | ICD codes used; older COVID population; no medical history or social determinants considered |
| **Pulmonary/Postoperative** | While the data suggest a slight increase in morbidity rate the author suggest this is mild and had no significate impact on patient outcomes and more research is needed for validation. | 21.4 % Minor Complications 6.2% Major Complications | 25.5 % Minor Complications 0 % Major Complications | ↑6.2% Major Complications | Ahmed A, Vellanki VS, Nalluri H, et al., 2022 [PMID: 35554331] | 11/2018 to 9/2021 | Ankara, Turkey | Cohort Study | Among 30 with Pneumonia 14 COVID-19 positive, 16 non-COVID M:F, 21:9 mean age 62.1+8.91 years | Age differences; small sample; lack of randomization |
| **Rheumatologic** | Increased risk of hospitalization, ICU, death | 0.64% | 0.40% | ↑32% | Gianfrancesco M, Hyrich KL, Al-Adely S, et al.,2020 [PMID: 33622688] | 3/2020 to 9/2020 (6 months) | Sweden | Retrospective Analysis | 53,455 patients with Inflammatory Join Disease (IJDs) | ICD-10 codes only; death defined by tax agency; no medical history or social determinants considered |
| **Trauma/Postoperative** | Dramatic mortality increase | 9.4% mortality 73% ICU | 1.9% mortality 63% ICU | ↑394% mortality rate ↑16% ICU | Müller M, Krämer N, Dufner B, et al. 2022 [PMIID: 34031703] | 1/1/2019–6/30/2019 and 1/1/2020–6/30/2020 | California US | Retrospective Analysis | 20,448 trauma patients (53 COVID-19 positive) (106 non-COVID) | Small sample; no medical history or social determinants considered |

# Risk of Bias

The methodological to quantify potential for bias in the 17 included studies were evaluated using the ROBINS-I- V2 (Risk Of Bias In Non-randomized Studies - of Interventions) tool as recommended on Duke’s University assessing bias for systematic review (3,4).This framework considers bias across seven domains particularly relevant to observational studies (5). Overall, most studies were categorize with moderate to serious risk of bias, in the following domains: due to confounding, selection of participants, and missing data and demographic differences between COVID-positive and non-COVID cohorts.

1. **Bias Due to Confounding**  
   This bias was found in most of the studies. Many studies failed to adjust for critical confounders such as age, comorbidities (e.g., diabetes, hypertension), socioeconomic status, and baseline severity of illness. For example, several studies (e.g., trauma and cardiovascular cohorts) included older or sicker COVID-19 patients without matching or statistical adjustment, increasing the likelihood of overestimating COVID-related morbidity rates.
2. **Bias in Classification of Interventions**  
   Exposure (COVID-19 status) was generally well defined via PCR testing or ICD codes. However, some studies relied solely on ICD-10/ICD-9 coding, which may be prone to misclassification bias if COVID status was under/miss coded or inconsistently reported across institutions.
3. **Bias in Selection of Participants into the Study**  
   Several studies had non-representative or convenience samples, including single-center cohorts or small subpopulations (e.g., obstetric or rheumatologic patients). Additionally, the exclusion of patients due to missing data or lack of testing early in the pandemic may have introduced selection bias, particularly in studies that did not routinely screen asymptomatic individuals for COVID-19.
4. **Bias Due to Deviations from Intended Interventions**  
   This domain was generally low risk across most studies, as the intervention (COVID-19 exposure) was not manipulated and there was no deviation in treatment assignment.
5. **Bias Due to Missing Data**  
   A moderate level of bias was present due to incomplete reporting of outcomes or loss to follow-up, especially in studies with retrospective chart reviews or administrative databases. Some studies failed to report attrition rates or did not explain missing data handling, potentially skewing outcome rates.

### **Bias Arising from Measurement of Outcomes** Outcomes were generally clinical and objectively measured (e.g., ICU admission, mortality). However, variability in morbidity definitions, especially in domains like endocrinology and post-operative complications, posed a moderate risk of measurement bias. In some cases, non-standardized scales or proxy indicators (e.g., use of mechanical ventilation) were used instead of validated morbidity scores.

### **Bias in Selection of the Reported Result** Reporting bias was possible in several studies due to selective outcome reporting, particularly in those lacking prespecified protocols or preregistered designs. Some studies appeared to emphasize statistically significant findings without reporting all measured outcomes.

### **Overall Assessment**

* **Low Risk**: 1 study
* **Moderate Risk**: 9 studies
* **Serious Risk**: 7 studies

Given these findings, we need to be cautious interpreting aggregated morbidity patterns. While the majority of studies suggest a consistent trend of increased morbidity among COVID-19 patients across several clinical domains, the observed associations may be influenced by varied confounding, outcome definitions, and sample selection methods. Future studies using prospective designs with better confounder control and standardized outcome reporting are needed to strengthen conclusive inferences.

# Discussion

This literature review focused on long-term morbidity outcomes among individuals with COVID-19 infection compared to those without, across different clinical domains. While the majority of included studies reported an increase of poor outcomes among COVID-19-positive patients, increased ICU admissions, mortality rates, and clinical complications. A few studies found little or no significant difference or even slight decreases in morbidity, highlighting the inconsistency in the results.

One of the major challenges in interpreting these results is the variability in how morbidity was defined and measured, even within the same clinical domains. For example, in the pulmonary category, one study emphasized mechanical ventilation usage, while others measured fungal infections or ICU admissions, complicating comparison efforts to draw a generalized conclusion about the impact of COVID-19.

In addition, methodological limitations were common across the included studies. Many studies used retrospective design methods and relied heavily on ICD coding and administrative databases, which often lack detailed clinical context and may not account full spectrum of patient history. Few studies adequately accounted for key confounding variables, such as comorbid conditions, age, and pre-existing health conditions. But these inconsistencies limits our ability to inference COVID-19 infection with long-term morbidity outcomes.

The ROBINS-I-V2 assessment indicated a generally moderate to serious overall risk of bias across the reviewed studies, due to confounding and missing data. While these biases does not invalidate the reported findings, we need to interpret the results with caution and highlighting the need for more rigorous study designs.

# Conclusion

While many of the reports trends toward increased long-term morbidity among COVID-19-positive patients across several clinical domains, the variability in outcome measures and methodological limitations prevents us from defining conclusive conclusion. Differences in morbidity definitions, retrospective data collection methods, and inconsistent control for confounders further hinder comparability and reliability.

Future research should focus on inclusion of social determinants of health, such as socioeconomic status and access to care, with standardized definitions of morbidity and comprehensive adjustment for confounding factors. This will enable more accurate assessments of patient outcomes.

As the healthcare system continues to evolve, reliable and standardized data will be crucial for informing public health policy, clinical decision-making, and healthcare resource allocations.

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