

REVIEW

Hospitalised versus outpatient COVID-19 patients' background characteristics and comorbidities: A systematic review and meta-analysis

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Abstract

This study aimed to systematically assess COVID-19 patient background characteristics and pre-existing comorbidities associated with hospitalisation status. The meta-analysis included cross-sectional, cohort, and case-series studies with information on hospitalisation versus outpatient status for COVID-19 patients, with background characteristics and pre-existing comorbidities. A total of 1,002,006 patients from 40 studies were identified. Significantly higher odds of hospitalisation were observed in Black individuals (OR = 1.33, 95% CI: 1.04–1.70), males (OR = 1.59, 95% CI: 1.43–1.76), and persons with current/past smoking (OR = 1.59, 95% CI: 1.34–1.88). Additionally, individuals with pre-existing comorbidities were more likely to be hospitalised [asthma (OR = 1.22, 95% CI: 1.02–1.45), COPD (OR = 3.68, 95% CI: 2.97–4.55), congestive heart failure (OR = 6.80, 95% CI: 4.97–9.31), coronary heart disease (OR = 4.40, 95% CI: 3.15–6.16), diabetes (OR = 3.90, 95% CI: 3.29–4.63), hypertension (OR = 3.89, 95% CI: 3.34–4.54), obesity (OR = 1.98, 95% CI: 1.59–2.46) and renal chronic disease (OR = 5.84, 95% CI: 4.51–7.56)]. High heterogeneity and low publication bias among all factors were found. Age was not included due to the large variability in the estimates reported. In this systematic review/meta-analysis for patients with COVID-19, Black patients, males, persons who smoke, and those with pre-existing comorbidities were more likely to be hospitalised than their counterparts. Findings provide evidence of populations with higher odds of hospitalisation for COVID-19.

KEYWORDS

background characteristics, co-morbidities, COVID-19, demographics, hospitalisation, meta-analysis

1 | INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel beta coronavirus that can be manifested as a mild to severe respiratory infection in humans along with asymptomatic transmission.¹ Emergence of the SARS-CoV-2 in late 2019, which became referred to as coronavirus disease-2019 or COVID-19, originated in Wuhan, China, and proceeded to escalate into a global pandemic, leaving more than 154 million people infected and 3.23 million people deceased.² Transmission of COVID-19 has been identified to be primarily facilitated through close contact air droplets and physical contact in addition to aerosol exposure in enclosed spaces.³ Of particular concern is the number of infected individuals who require hospitalisation as debilitating and potentially deadly clinical complications such as acute respiratory distress and respiratory failure are more prevalent among hospitalised individuals.⁴

Recorded hospitalisation rates due to COVID-19 are prone to significant variation week-to-week, which may be characterised by certain time intervals with larger peaks in hospitalisations.⁵ The burden placed on local hospital systems due to increased rates of patients requiring admittance for COVID-19 complications is a pressing matter as this creates an additional burden on the available capacity for hospitals to treat new patients.⁶ Furthermore, the burden placed upon the healthcare systems and the exposure to healthcare workers due to rates of hospitalisations and ICU transfers is not identical across the world, and identifying methods for minimising this burden are key.^{7,8}

Several characteristics of healthcare systems have been identified that may be at play when examining burden of COVID-19 hospitalisations on individual healthcare systems, such as timing of outbreaks and more isolated, rural locations of health centres.⁹ Prior evidence has suggested that patients admitted due to COVID-19 may experience longer durations of hospitalisation, increased reliance on oxygen therapy or invasive mechanical ventilation, and more intensive care unit (ICU) need compared to seasonal influenza patients.¹⁰

In addition, COVID-19 hospitalisation has been identified to vary significantly depending on several predictors such as background characteristics and the presence of certain pre-existing comorbidities.¹¹ The range of factors that have been identified among COVID-19 patients requiring hospitalisation is extensive; background characteristics have been primarily based on differences in age, ethnicity/race, smoking history, and sex. Prior research conducted on hospitalised COVID-19 patients has shown that individuals requiring admission are typically of older age, from an ethnic or racial minority group, and male.¹²

For example, research shows an independent predictor of COVID-19 hospitalisation includes age 65 years or older.¹³ A variety of factors ranging from immune system strength to other chronic health conditions that are more prevalent among older individuals may increase the susceptibility to infection and subsequent hospitalisation.¹⁴ Higher infection rates and need for hospitalisation among specific ethnic and racial groups, such as Hispanic and Black individuals, has been attributed to socio-economic differences,

including living situations, employment status, and associations with pre-existing conditions.¹⁵ Furthermore, male patients have also been shown to have higher risk for hospitalisation in multiple samples.¹⁶

Observations of COVID-19 hospitalisation in association with pre-existing comorbidities has been well-documented in existing COVID-19 research. Prior systematic reviews have identified chronic conditions including cardiovascular conditions, diabetes mellitus, respiratory diseases, and kidney diseases, as critical chronic conditions associated with hospitalisation for COVID-19.¹⁷ Additionally, elevated body mass index (BMI) has been associated to COVID-19 hospitalisation; individuals with BMI over 25 kg/m² (overweight) and over 30 kg/m² (obese) have been shown to require hospitalisation from COVID-19 at higher odds in comparison to individuals at healthy weights.¹⁸

Considering the preliminary results found in the literature for COVID-19 patients, a robust systematic review and meta-analysis was conducted to determine the background characteristics and pre-existing comorbidities associated with hospitalisation for COVID-19 patients. This will help identify the most vulnerable populations for severe COVID-19 infections that would require hospitalisation.

2 | METHODS

2.1 | Study selection and inclusion criteria

This study focused on the clinical outcome (hospitalisation vs outpatient) of COVID-19 in association with background characteristics (i.e., ethnicity/race, sex, and smoking status) and preexisting comorbidities (i.e., diabetes mellitus, cardiovascular diseases, respiratory diseases, obesity, hypertension, and renal chronic disease). We conducted a broad literature search in three datasets: (1) PubMed, (2) Web of Science, and (3) Cochrane Library, that comprised preprint and published papers from December 2019 to December 2020. The search was not geographically limited, and included papers written in English, Spanish, or Chinese. Additionally, we searched the reference lists of relevant systematic reviews and meta-analyses to identify potential supplemental studies (one paper was included from this search). This systematic review and meta-analysis followed the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) consensus statement.¹⁹ The protocol of this study is registered in PROSPERO (CRD42021235460).

The keywords and MESH terms in English comprised in this search included: 'coronavirus', 'COVID-19', 'novel coronavirus', 'sars-cov-2', '2019-ncov', 'severe acute respiratory syndrome related coronavirus' AND 'clinical characteristics', 'epidemiologic characteristics', 'clinical features', 'epidemiologic features', 'demographic features', 'demographic characteristics', 'comorbidities', 'diabetes mellitus', 'cardiovascular', 'respiratory', 'obesity', 'hypertension', and 'renal chronic disease', AND 'outpatient', 'ambulatory', 'inpatient' and 'hospitalised'.

Cross-sectional, cohort (retrospective/prospective), and case-series studies with laboratory-confirmed diagnoses for COVID-19

(according to World Health Organisation guidance), which examined patient demographic factors such as ethnicity/race, sex, smoking status, and pre-existing comorbidities including cardiovascular diseases (CVD) (coronary heart disease and congestive heart failure), diabetes mellitus, hypertension, obesity, renal chronic disease, and respiratory diseases (asthma and chronic obstructive pulmonary disease (COPD)) were included in this meta-analysis. Age was not included in this analysis due to the variability in the estimates reported.

For external validity and relevance to the general population, inclusion criteria encompassed studies conducted in patients aged 18 years or older. Studies in subpopulation specific samples were excluded (e.g., children, adolescents, pregnant women, nursing homes, institutionalised individuals, HIV-only, COPD-only, cardiomyopathic-only, renal-only, hepatic-only).

2.2 | Data collection and quality assessment

Following the PRISMA guidelines, one investigator (PMM) identified the studies that potentially met the inclusion criteria, by screening the title and abstract for the searching results, after excluding duplicate papers. Non-relevant studies and those that met exclusion criteria were removed. This initial review was inclusive to reduce the chance of omitting eligible studies (Figure 1).

Two investigators (PMM and CB), independently assessed the full text of initially screened studies and identified the potentially eligible studies based on inclusion and exclusion criteria. Additionally, two investigators (CC and CO) assessed the reference lists of published systematic reviews and meta-analyses to capture any potential study that could have been missed. The investigators (PMM and CB), independently, then proceeded with the methodological qualitative assessment of the studies using the NIH (National Institutes of Health) Study Quality Assessment Tools. These tools were based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality's, the Cochrane Collaboration, the U.S. Preventive Services Task Force, the Scottish Intercollegiate Guidelines Network, and the National Health Service Centre for Reviews and Dissemination. NIH quality assessment tools include specific scales for observational, case-series and experimental studies. The scales were applied based on the study design.²⁰ For observational designs, papers with scores of 0–4 were graded as poor, 5–8 were graded as fair, and more than 9 were graded as good. For case-series and reports, papers with scores of 0–3 were graded as poor, 4–6 were graded as fair, and more than 7 were graded as good. The scores of each study were compared, and any discrepancies were assessed by a third investigator (CC). After the quality assessment, the two investigators proceeded with the data extraction, comparing between the investigators for validity and accuracy. Any discrepancies were again assessed by a third investigator (CC). Data extraction included the following information from each study: title, study design, publication stage, study period, location, first author, publication year, total positive cases, and total number for hospitalised patients and

outpatients. For each condition we collected the number of events for hospitalised and outpatients. Crude odds ratios were included when available. The PRISMA checklist of the manuscript is available in the supplementary material.

2.3 | Statistical analysis

The association of background characteristics and pre-existing comorbidities with hospitalisation was assessed. Exposure variables were demographics (i.e., ethnicity/race, sex, smoking) and pre-existing comorbidities extracted from the papers. Each ethnicity/race category was coded as a non-mutually exclusive binary outcome due to the variability in definitions among the included studies (e.g., White vs Non-White). Our outcome variable was hospitalisation status (hospitalised vs outpatients). We estimated the odds ratios (ORs) with 95% confidence interval (95% CI) for COVID-19 hospitalised patients to one of the potential factors compared to COVID-19 outpatients from the extracted raw data or reported crude ORs. A random effect model was utilised to calculate pooled odds ratios when the test of heterogeneity (I^2 statistic) was moderate (50%–74%) or high ($\geq 75\%$) in the pooled estimates.²¹ Due to high heterogeneity between studies for all the background characteristics and pre-existing comorbidities, random-effects models were used for the meta-analysis of hospitalisation. In addition, subgroup and sensitivity analyses were conducted to look into heterogeneity. These analyses were determined *a priori* by (1) study design (i.e., case series, cohort, cross-sectional) and (2) publication stage (i.e., published, pre-print), as these could have been potential causes of heterogeneity in the results. Publication bias and small study effect were assessed with the Egger's regression test and the Harbord's modified test which accounted for the heterogeneity and binary outcomes.^{22,23} To reduce publication bias, we included both published studies and literature published in medRxiv. All statistical analyses were conducted with Stata, Version 15²⁴ with an alpha at the 0.05 level.

3 | RESULTS

3.1 | Study characteristics

A total of 14,623 records were identified in databases, during the initial search. We identified 14,586 papers on PubMed, 35 new papers from Cochrane, and 2 papers from the meta-analyses/systematic review references. After removing duplicates and applying our exclusion criteria, a title and abstract analysis was performed for 134 papers. Only 40 papers included the number of events for both hospitalised patients and outpatients. The 40 papers^{25–64} underwent the quality assessment and were included in our meta-analysis (Figure 1).

The systematic review identified a total of 1,002,006 patients (188,597 hospitalised patients and 813,409 outpatients). The studies included 26 cohort studies,^{26–30,32,34–37,42,44–46,48,49,51–56,60,62–64} 7 cross-sectional studies,^{33,38,39,41,47,50,61} and 7 reports and case series^{25,31,40,43,57–59} that were developed between December 2019 and

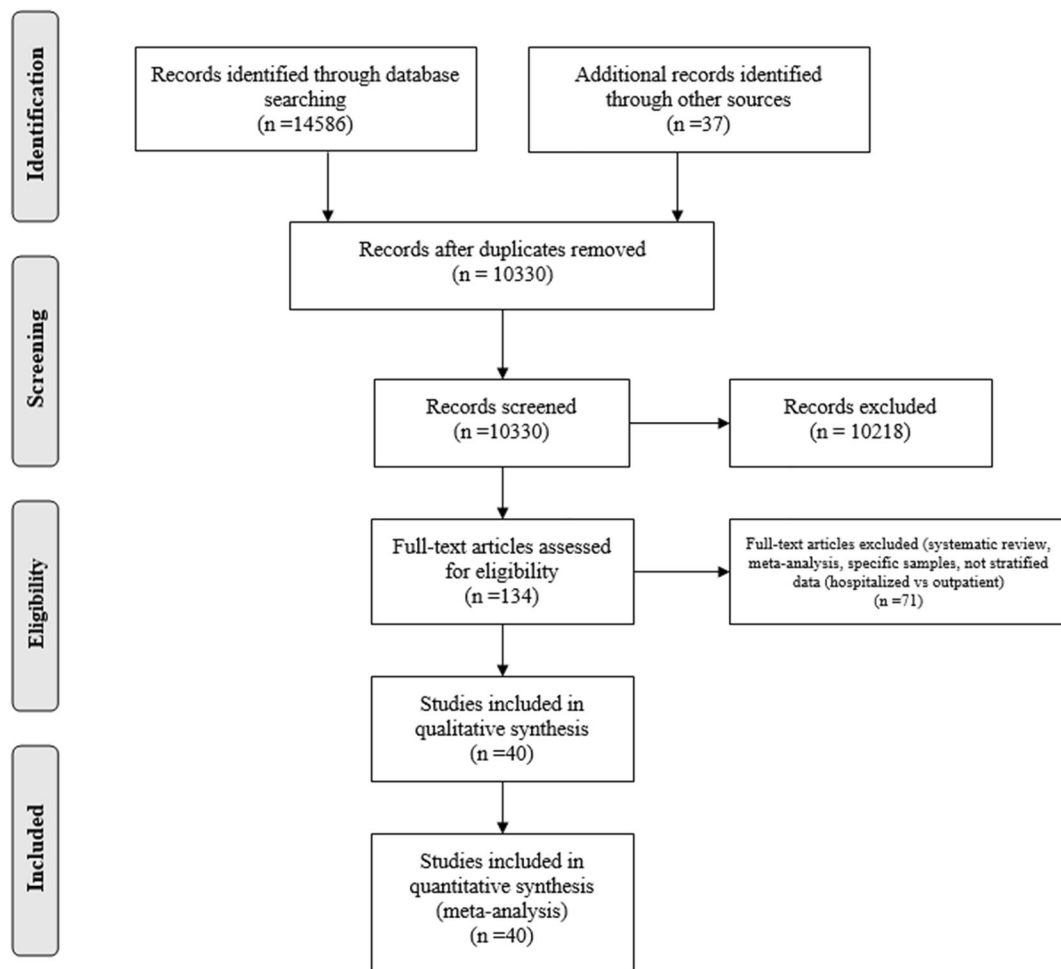


FIGURE 1 Flowchart for literature search

December 2020. The included studies were conducted in the United States (27 studies),^{25,26,28,30-33,35,36,38,40,42-46,48,49,52,54-60,62} Mexico,^{39,51} United Kingdom,^{37,63} Spain^{29,41} (2 studies conducted in each country), Brazil,⁴⁷ Chile,⁶¹ Denmark,⁵³ France,⁵⁰ Honduras,⁶⁴ Italy,³⁴ and Turkey,²⁷ (1 study conducted in each country). A total of 4 pre-print articles^{28,37,46,54} were included in the meta-analysis (Table 1). Age was not assessed in our analysis, due to high variation in the descriptive statistics on age. For example, a total of 11 papers reported mean age (range 44–68.8 years),^{32,37,39,41,46,49,55-57,60,63} 11 papers reported median age (range: 41–66.1 years),^{25,30,35,36,44,48,51-54,58} and 18 papers did not have available data on age for the total sample.^{26-29,31,33,34,38,40,42,43,45,47,50,59,61,62,64}

Overall, 33 papers were graded as fair,^{25,27-34,36,37,39-52,54,56,57,59-62,64} and 7 papers were graded as good^{26,35,38,53,55,58,63} (Table S1).

3.2 | Patient background characteristics and comorbidities

Black patients (OR = 1.33, 95% CI: 1.04–1.70), males (OR = 1.59, 95% CI: 1.43–1.76), and patients with a current or past smoking status had higher odds of hospitalisation (Table 2; Figures S1, S2, and S3).

No significant association was found for Hispanic or White patients and hospitalisation (Table 2; Figures S4 and S5). All pre-existing comorbidities were significantly associated with hospitalisation [asthma (OR = 1.22, 95% CI: 1.02–1.45), COPD (OR = 3.68, 95% CI: 2.97–4.55), congestive heart failure (OR = 6.80, 95% CI: 4.97–9.31), coronary heart disease (OR = 4.4, 95% CI: 3.15–6.16), diabetes (OR = 3.90, 95% CI: 3.29–4.63), hypertension (OR = 3.89, 95% CI: 3.34–4.54), obesity (OR = 1.98, 95% CI: 1.59–2.46), and renal chronic disease (OR = 5.84, 95% CI: 4.51–7.56)] (See Table 3 and Figures S6, S7, S8, S9, S10, S11, S12, and S13).

After conducting the subgroup analyses by study design and printing stage, we found that the association for Black patients in case-series and cohort studies remained significant but was not the case for cross-sectional studies (Figure S14). For asthma, the association remained positive in cohort studies, but we found no significant association in case-series, and a significant inverse association in cross-sectional studies. It is worth noting that only 2 cross-sectional studies included asthma (Figure S15). All other associations did not change.

We found a potential small-study effect bias in the analysis for White race and Hispanic ethnicity, for both the Egger's and Harbord's test ($p < 0.01$ respectively). In addition, publication bias was

TABLE 1 Main Characteristics of the studies included in the analyses

Author	Date	Stage of printing	Type of study	Location	Included positive cases (n)	Hospitalised patients (n)	Outpatients (n)	Age of total positive cases (Median/Mean [IQR/SD])
Argenziano, et al.	March 11th–April 6th	Print	Case series	US	1,000	850	150	63.0 [50.0–75.0]
Argyropoulos, et al.	March 12th–March 18th	Print	Retrospective cohort	US	205	40	165	NA
Avci, et al.	March 11th–April 21st	Print	Retrospective cohort	Turkey	1,197	215	982	NA
Baidal, et al.	March 1–May 14	Pre-print	Retrospective cohort	US	8,055	5,136	2919	NA
Bermejo-Martin, et al.	March 16th–April 15th	Print	Prospective cohort	Spain	250	200	50	NA
Blair, et al.	April 21st–June 23rd	Print	Prospective cohort	US	118	9	109	56.0 [50.0–63.0]
CDC COVID-19 response team	February 12th–March 28th	Print	Report	US	6,637	1,494	5143	NR
Ebinger, et al.	March 8th–March 21st	Print	Retrospective cohort	US	442	214	228	52.7 [19.6]
Fan, et al.	February 28th–May 14th	Print	Cross-sectional	US	88,747	27,062	61,685	NR
Giorgi Rossi, et al.	February 27th–April 2nd	Print	Prospective cohort	Italy	2,653	1,075	1578	NR
Gottlieb, et al.	March 4th–June 21st	Print	Retrospective cohort	US	8,673	1,483	7190	41.0 [29.0–54.0]
Gu, et al.	March 10th–April 22th	Print	Retrospective cohort	US	1,139	523	616	53.0 [39.0–66.0]
Hamer, et al.	March 16th–April 26th	Pre-print	Prospective cohort	UK	387,109	760	386,349	57.1 [9.0]
Hao, et al.	March 4th–April 13th	Print	Cross-sectional	US	2,566	929	1637	NA
Hernandez-Galdamez, et al.	June	Print	Cross-sectional	Mexico	211,003	65,495	145,508	45.7 [16.3]
Hsu, et al.	March 1st to May 18th	Print	Report	US	2,631	1,088	1543	NR
Izquierdo-Dominguez, et al.	March 21st–April 18th	Print	Cross-sectional	Spain	846	649	197	56.8 [15.7]
Jehi, et al.	March 8th to June 5th	Print	Retrospective cohort	US	4,536	958	3578	NA
Killerby, et al.	March 1st–April 7th	Print	Report	US	531	220	311	NA
Marcello, et al.	March 5th–April 9th	Print	Retrospective cohort	US	13,442	6,248	7194	52.7 [39.5–64.5]

(Continues)

TABLE 1 (Continued)

Author	Date	Stage of printing	Type of study	Location	Included positive cases (n)	Hospitalised patients (n)	Outpatients (n)	Age of total positive cases (Median/Mean [IQR/SD])
McPadden, et al.	March 1st–April 30th	Pre-print	Retrospective cohort	US	7,995	2,154	5841	NR
Mendy, et al.	March 13th–May 31st	Print	Retrospective cohort	US	689	216	473	44.4 [1.2]
Menezes Soares, et al.	February 29th–June 11th	Print	Cross-sectional	Brazil	10,713	1,152	9561	NR
Mikami, et al.	March 13th–April 17th	Print	Retrospective cohort	US	6,493	3,708	2785	59.0 [43.0–72.0]
Miller, et al.	March 7th–April 30th	Print	Retrospective cohort	US	3,633	2,316	1317	58.4 [18.1]
Nouchi, et al.	March 23rd–March 27th	Print	Cross-sectional	France	390	198	192	NA
Ortiz-Brizuela, et al.	February 26th–March 23rd	Print	Prospective cohort	Mexico	309	140	169	43.0 [33.0–54.0]
Petrilli, et al.	March 1st–May 5th	Print	Prospective cohort	US	5,279	2,741	2538	54.0 [38.0–66.0]
Reilev, et al.	February 27th–May 19th	Print	Retrospective cohort	Denmark	11,122	2,254	8868	48.0 [33.0–62.0]
Rentsch, et al.	February 8th–March 30th	Pre-print	Retrospective cohort	US	585	297	288	66.1 [60.4–71.0]
Shah, et al.	March 20th–April 22nd	Print	Prospective cohort	US	77	22	55	44.0 [19.0]
Singer, et al.	March 12th–April 14th	Print	Retrospective cohort	US	1,651	737	914	50.0 [18.0]
Suleyman, et al.	March 9th–March 27th	Print	Case series	US	463	355	108	57.5 [16.8]
Tenforde, et al.	April 15th–May 24th	Print	Report	US	350	79	271	43.0 [32.0–57.0]
Thompson, et al.	February 29th–June 1st	Print	Report	US	203,792	54,211	149,581	NR
Van Gerwen, et al.	March–May	Print	Retrospective cohort	US	3,703	2,015	1688	56.8 [18.2]
Vial, et al.	March 3rd–April 4th	Print	Cross-sectional	Chile	381	88	293	NA
Yan, et al.	March 3rd–April 8th	Print	Retrospective cohort	US	128	26	102	NA
Zhang, X., et al.	March 16th–June 29th	Print	Prospective cohort	UK	1,596	1,020	576	68.8 [9.2]
Zuniga-Moya, et al.	March 17th–May 4th	Print	Retrospective cohort	Honduras	877	220	657	NR

Note: NA: the data was not available the total sample, but reported stratified by group (hospitalised, Intensive Care Unit (ICU), outpatient); NR: not reported means or medians. Data was collected in categories.

TABLE 2 Quantitative data synthesis for the association of background characteristics and hospitalisation of COVID-19

Background characteristic	Number of studies	Total cases	OR	CI	p value ^a	I ² (%)	Tau ²
Ethnicity/race							
Black versus non-Black	27	377,636	1.33	1.04–1.70	0.03	99.2%	0.37
Hispanic versus non-Hispanic	22	361,413	1.01	0.76–1.33	0.97	99.2%	0.39
White versus non-White	27	764,312	0.92	0.80–1.05	0.22	97.3%	0.10
Sex							
Male versus female	38	785,233	1.59	1.43–1.76	<0.001	95.4%	0.08
Smoking							
Current and former versus never	24	740,896	1.59	1.34–1.88	<0.001	96.8%	0.13

Note: Each Ethnicity/race category was used as a binary variable due to the variability of how ethnic groups and races were captured across all 40 studies (i.e., not mutually exclusive groups).

Abbreviations: CI, confidence interval; OR, odds ratio.

^ap < 0.05.

TABLE 3 Quantitative data synthesis for the association of comorbidities and hospitalisation of COVID-19

Comorbidity	Number of studies	Total cases	OR	CI	p value ^a	I ² (%)	Tau ²
Asthma	21	350,437	1.22	1.02–1.45	0.03	92.5%	0.11
Chronic obstructive pulmonary disease	24	361,466	3.68	2.97–4.55	<0.001	94.8%	0.17
Congestive heart failure	17	161,879	6.80	4.97–9.31	<0.001	95.9%	0.35
Coronary heart disease	15	135,539	4.40	3.15–6.16	<0.001	96.8%	0.36
Diabetes	34	786,373	3.90	3.29–4.63	<0.001	98.3%	0.21
Hypertension	31	768,334	3.89	3.34–4.54	<0.001	98.0%	0.15
Obesity	26	372,468	1.98	1.59–2.46	<0.001	99.0%	0.27
Renal disease	27	391,522	5.84	4.51–7.56	<0.001	97.4%	0.35

Abbreviations: CI, confidence interval; OR, odds ratio.

^ap < 0.05.

found for congestive heart failure (Egger's $p = 0.006$, Harbord's $p = 0.04$) and asthma (Egger's $p = 0.04$, Harbord's $p = 0.03$). A discrepancy was found between tests for coronary heart disease and renal disease (with a significant publication with the Egger's test only) (Table S2).

4 | DISCUSSION

This meta-analysis compared background characteristics and pre-existing comorbidities between COVID-19 hospitalised patients and outpatients. There were higher odds for hospitalisation with Covid-19 for Black patients, males, and persons with current and former smoking, compared to the reference groups. Assessment of how ethnic and racial groups differ in hospitalisation incidence indicates that minority groups present with higher odds of inpatient status compared to non-Hispanic Whites.⁶⁵ Prior studies have indicated that higher hospitalisation ratios for minority groups may be due in part to relevant social determinants of health including geographic locations, living environments, employment settings, or

underlying health conditions.⁶⁶ Additionally, chronic cardiovascular diseases such as hypertension and heart disease are more prevalent in the Black community and may play a key role in observing higher hospitalisation from COVID-19.⁶⁷ Nonetheless, this meta-analysis did not indicate similar findings from previous studies and meta-analyses for Hispanic patients and odds of hospitalisation. Previous studies indicated that Hispanic patients show higher odds of hospitalisation when compared to non-Hispanic White patients in addition to higher mortality risk, higher rates of ICU transfers, and higher need for more invasive interventions such as mechanical ventilation in COVID-19.⁶⁸ The evidence of publication bias within this study for Hispanic COVID-19 patients could be reflected of smaller study sizes for Hispanic populations, and therefore, of the difference in the results when compared to previous studies.

The observation of higher odds for COVID-19 hospitalisation in males is similarly supported through prior meta-analyses.⁶⁹ This may be explained through a combination of immunological and humoral differences, including a more robust T cell response in females compared to males, as well as a higher cytokine response (e.g.,

interleukins IL-6 and IL-1).⁷⁰ Additionally, associations between males and several chronic conditions ranging from cardiovascular complications to obesity may be important to consider in this observation, as these conditions have been associated with higher odds of COVID-19 hospitalisation.⁷¹

Smoking status also showed a significantly positive association with COVID-19 hospitalisation, as persons with current or former smoking had higher odds of hospital admission versus those who had never smoked. Associations between smoking and respiratory illness based upon prior research has supported the findings of smoking showing significant increase in the odds of COVID-19 hospitalisation due to increased possibility of inflammation in the respiratory system.⁷² While some researchers have discussed a smoker's paradox in COVID-19, the limited data about this effect is dubious, and the results in this meta-analysis are supported by the previous findings about the association of smoking and COVID-19 susceptibility and worse prognosis.⁷³

In addition, hospitalised individuals were at higher odds of presenting pre-existing comorbidities compared to outpatients. The findings of this meta-analysis are supported by similar meta-analyses; a relative risk for poor COVID-19 clinical outcomes have been shown to be significantly associated with hypertension, CVD, chronic kidney disease, obesity, and diabetes.⁷⁴

Potential biological explanations have been generally focused on the impact that cardiovascular complications, diabetes, renal disease, obesity, and respiratory disease can have on immune system strength and respiratory functioning.⁷⁵ Functioning of cardiovascular tissues and organs has significant interplay with innate immune components and consistent communication between both systems is often facilitated via cytokines and hormones.⁷⁶ Cytokines are utilised in the body to assist with intercellular communication and inflammatory responses,⁷⁶ which may have significant impact on clinical severity of SARS-CoV-2 infection and an increased risk of hospitalisation. This connection is key to consider, as risk of comorbidities, and particularly, cardiovascular diseases, which have been linked to higher activity involving innate immune system functions.⁷⁶ Significant interplay can also be observed in prior studies, as pre-existing chronic conditions such as obesity may additionally have strong associations with other prognostic factors for worse COVID-19 outcomes such as CVD, respiratory disease, diabetes, and renal disease.⁷⁷

Due to the heterogeneity and variability among the factors in the included studies, one of the limitations of this study is the estimation of unadjusted odds ratios when analysing the potential factors. Our pooled estimates account for the crude odds ratios, as it was not possible to account for potential confounders. There was also a high level of heterogeneity between the included studies, which might reduce the strength the precision of the pooled point estimates even after conducting the subgroup analysis. Several factors could account for this heterogeneity, including sample size, location, time during the pandemic, and individual variability which could have increased the variation of estimates for hospitalisation.⁷⁸ Furthermore, some of the

investigated factors had smaller samples size in some of the strata. In addition, discrepancies were found between the coefficients and confidence intervals of both tests for bias due to unknown potential sources of bias and confounding that were not considered in this study.⁷⁹ Lastly, we expect the COVID-19 pandemic to continue to evolve and expect our findings to only generalise to 2020 (e.g., due to advancement in vaccination and/or newer and more effective treatments).

5 | CONCLUSION

To our knowledge, this is the first meta-analysis to report the pooled estimates for factors and hospitalisation status, which helps to provide stronger support for findings from individual studies that examined background characteristics and pre-existing comorbidities associated with COVID-19 hospitalisation. Black individuals, males, and persons with former and current smoking had a higher odds of COVID-19 hospitalisation. Persons with chronic conditions were significantly associated with COVID-19 hospitalisation as well. As vaccinations are slowly underway around the world, social restrictions by local governments are reduced, new strains emerged, and the burden on the healthcare systems remain, it is vital to identify the most vulnerable populations that will require hospitalisation due to COVID-19.

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CONFLICT OF INTEREST STATEMENT

The authors whose names are listed in this document, certify that they have no affiliation with or involvement in any organisation or entity with financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS

Every person who meets the authorship criteria are listed as authors, and all authors certify their participation in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Additionally, the authors certify that this material has not been published and not will be submitted or published in any other journal. Author Parker designed the study. Authors Begle, Matthey-Mora, Owusu, and Chen conducted the systematic review and participated in all drafts of the paper. Author Matthey-Mora performed the data analysis. All authors have approved the final article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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