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COVID-19

Age-Adjusted Risk Factors Associated with Mortality and Mechanical Ventilation Utilization Amongst COVID-19 Hospitalizations—a Systematic Review and Meta-Analysis

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Abstract

The increasing COVID-19 cases in the USA have led to overburdening of healthcare in regard to invasive mechanical ventilation (IMV) utilization as well as mortality. We aim to identify risk factors associated with poor outcomes (IMV and mortality) of COVID-19 hospitalized patients. A meta-analysis of observational studies with epidemiological characteristics of COVID-19 in PubMed, Web of Science, Scopus, and medRxiv from December 1, 2019 to May 31, 2020 following MOOSE guidelines was conducted. Twenty-nine full-text studies detailing epidemiological characteristics, symptoms, comorbidities, complications, and outcomes were included. Meta-regression was performed to evaluate effects of comorbidities, and complications on outcomes using a random-effects model. The pooled correlation coefficient (r), 95% CI, and OR were calculated. Of 29 studies (12,258 confirmed cases), 17 reported IMV and 21 reported deaths. The pooled prevalence of IMV was 23.3% (95% CI: 17.1–30.9%), and mortality was 13% (9.3–18%). The age-adjusted meta-regression models showed significant association of mortality with male (r: 0.14; OR: 1.15; 95% CI: 1.07–1.23; I^2: 95.2%), comorbidities including pre-existing cerebrovascular disease (r: 0.35; 1.42 (1.14–1.77); I^2: 96.1%), and chronic liver disease (r: 0.08; 1.08 (1.01–1.17); I^2: 96.23%), complications like septic shock (r: 0.099; 1.10 (1.02–1.2); I^2: 78.12%) and ARDS (r: 0.04; 1.04 (1.02–1.06); I^2: 90.3%), ICU admissions (r: 0.03; 1.03 (1.03–1.05); I^2: 95.21%), and IMV utilization (r: 0.05; 1.05 (1.03–1.07); I^2: 89.80%). Similarly, male (r: 0.08; 1.08 (1.02–1.15); I^2: 95%), comorbidities like pre-existing cerebrovascular disease (r: 0.29; 1.34 (1.09–1.63); I^2:93.4%), and cardiovascular disease (r: 0.28; 1.32 (1.1–1.58); I^2: 89.7%) had higher odds of IMV utilization. COVID-19 patients with comorbidities including cardiovascular disease, cerebrovascular disease, and chronic liver disease had poor outcomes. Diabetes and hypertension had higher prevalence

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but no association with mortality and IMV. Our study results will be helpful in right allocation of resources towards patients who need them the most.

Keywords COVID-19 · Coronavirus disease · SARS-CoV-2 · 2019-nCoV · Severe acute respiratory syndrome · Mortality · Mechanical ventilation · COVID-related complications · COVID risk factors

Introduction

The first confirmed case of coronavirus disease 2019 (COVID-19) in the USA was reported on 20 January 2020 [1]. The USA now has more confirmed cases than any other country in the world. The number of cases exceeds 1.2 million with a death toll crossing 70,000 [2]. COVID-19 disease affects mainly the respiratory system [3] but there are studies showing the involvement of other systems as well [4, 5]. Studies have shown that a large number of admitted patients required mechanical ventilation [3, 6, 7]. The common point that these studies show is that the majority of these patients had some associated comorbid condition. The prevalence of diabetes is 10.5% [8] and hypertension is 29% [9] in the USA indicating how widespread some of these conditions are. Some other studies revealed that certain risk factors like pre-existing cardiovascular, cerebrovascular diseases, age ≥ 65, CD3+CD8+ T cells ≤ 75 cell/μL, and cardiac troponin $I \geq 0.05$ ng/mL and d-dimer > 1 μg/mL are associated with increased in-hospital mortality [5, 10–12]. Predicting the risk factors associated with the need for IMV and poor prognosis are thus of utmost importance given the overwhelming number of admissions of critical patients to the hospitals.

Studying the correlation of various factors like demographics, comorbidities, and complications in COVID-19 patients with IMV utilization can help to redirect the limited resources towards patients who require them the most. The other aim of the paper is to identify predictors of mortality adjusted by age based on the same parameters. The predictors of mortality will also help clinicians in early identification of such patients in the course of admission which can save lives and decrease mortality due to COVID-19. The objective of this study was to evaluate the risk factors including comorbidities, and complications associated with the poor outcomes amongst COVID-19 patients.

Method

Endpoints

Primary aim of this study was to evaluate the risk factors (age-adjusted) associated with poor outcomes (IMV and mortality) amongst patients with confirmed COVID-19 infection. Secondary outcome of the study was to evaluate demographic and clinical characteristics, comorbidities, and complications of COVID-19 patients. We have not considered recovery and ICU admission as outcomes due to variability in the definitions of recovery and utilization of IMV outside ICU.

Search Strategy and Selection Criteria

A systematic review was performed using MOOSE guidelines [13]. We searched PubMed, Web of Science, Scopus, and medRxiv for observational studies that described characteristics of COVID-19 from December 1, 2019 to May 31, 2020 following keyword/MESH terms: ((COVID-19[Title/Abstract]) OR coronavirus[Title/Abstract]) OR SARS-CoV-2[Title/Abstract] OR 2019-nCoV[Title/Abstract]. All studies describing epidemiology of COVID-19 were included. Literature other than observational studies, non-English literature, non-full text, and animal studies were excluded. Flow diagram of literature search and study selection process is described in eSupplemental file (1).

Study Selection

Abstracts were reviewed, and articles were retrieved and reviewed for availability of data on epidemiology of COVID-19. Studies mentioned details on IMV and mortality had been selected for quantitative analysis. UP and PM independently screened all identified studies and assessed full texts to decide eligibility. Any disagreement was resolved through discussion with other reviewers (SU and DM).

Data Collection

From the included studies, data relating to patient characteristics like age and sex, symptoms like headache, fever, cough, diarrhea, dyspnea hemoptysis, myalgia/fatigue, nausea/vomiting, sore throat, nasal congestion/rhinorrhea, and sputum production, comorbidities and risk factors like smoker, diabetes, hypertension, malignancy, pulmonary disease, chronic liver disease, cerebrovascular disease, and cardiovascular disease, complications like pneumonia, acute respiratory distress syndrome, septic shock, secondary infections, and cardiac complications, details on discharged/recovery and ICU admission, and outcomes like mortality and needs for IMV were collected using prespecified data collection forms by two authors (UP and PM) with a common consensus of

authors (SU and TJ) upon disagreement. We have presented the study characteristics like publication year, country of origin, and sample size. Data on the following outcomes which were IMV utilization and mortality were extracted.

Assessment of Risk of Bias

The Newcastle-Ottawa Quality Assessment Scale [14] was used to evaluate the quality of the included studies and the risk of bias.

Statistical Analysis

We used all studies containing details on epidemiological characteristics in order to calculate pooled prevalence, 95% confidence interval (CI), and weights of demographic features, symptoms, comorbidities, risk factors, and complications rate amongst COVID-19 patients precisely. Meta-regression was performed to evaluate the effects of comorbidities, risk factors, and complications on outcomes of COVID-19 patients. We used comprehensive meta-analysis software to estimate correlation coefficient (r) and 95% confidence interval (95% CI) and odds ratios (OR) (e^coefficient) with corresponding 95% CI were pooled using a random-effects model. The proportion of total between-study variance explained by the model identified using analogous index (R^2) and statistical heterogeneity across studies was reported using the I^2 statistics. The I^2 statistic of > 75% was considered significant heterogeneity. $p < 0.05$ was considered significant. Age-adjusted and unadjusted meta-regression were performed. Sensitivity analysis was also performed using the "leave-one-out method" to probe sources of heterogeneity.

Results

As of May 31, 2020, we included 29 observational studies (eSupplemental file (2)) with 12,258 confirmed cases of COVID-19 patients detailing epidemiological characteristics, symptoms, comorbidities or risk factors, complications, and outcomes including mortality and IMV. Of those 29 studies, 17 studies have reported IMV utilization and 21 studies have reported deaths. The pooled prevalence of IMV was 23.3% (95% CI: 17.1–30.9%; $p < 0.001$; 1789/8804 patients), and mortality was 13% (95% CI: 9.3–18%; $p < 0.001$; 1267/11252 patients) (Table 1).

In our pooled cohort of confirmed cases of COVID-19, pooled prevalence of male was 57.3% (95% CI: 55.1–59.4%; $p < 0.001$; 7198/12247 patients). The most common clinical symptoms of COVID-19 patients were fever with pooled prevalence of 85.6% (95% CI: 73.6–92.7%; $p < 0.001$; 5172/9163) followed by cough 64.7% (95% CI: 57.4–71.4%; $p < 0.001$; 2464/3863), myalgia or fatigue 43.3% (95% CI: 35.8–51.2%; $p < 0.096$; 1848/3813), sputum production or expectoration 33.4% (95% CI: 29.1–38.1%; $p < 0.001$; 968/2846), and dyspnea 32% (95% CI: 23.9–41.3%; $p < 0.001$; 1259/3629). Other clinical symptoms included sore throat with pooled prevalence of 17.3% (95% CI: 9.1–30.3%; $p < 0.001$; 192/1344), headache 10.7% (95% CI: 7.9–14.3%; $p < 0.001$; 306/2738), diarrhea 9.4% (95% CI: 6.2–14.1%; $p < 0.001$; 400/3428), nausea or vomiting 7% (95% CI: 4.4–10.8%; $p < 0.001$; 265/3258), nasal congestion 7.5% (95% CI: 3.1–17.4%; $p < 0.001$; 50/1082), and hemoptysis 2% (95% CI: 1.1–3.9%; $p < 0.001$; 29/1804).

Most common coexisting comorbidities were hypertension with pooled prevalence of 28.2% (95% CI: 22.1–35.1%; $p < 0.001$; 4858/11626), diabetes 15.4% (95% CI: 12–19.4%; $p < 0.001$; 2897/11680), cardiovascular diseases 12.2% (95% CI: 8.9–16.6%; $p < 0.001$; 204/11664), and smoking 8.9% (95% CI: 4.2–17.9%; $p < 0.001$; 3003/8410). Most common complications of COVID-19 infection were pneumonia (68.1%; 95% CI: 38.8–78.8%; $p = 0.221$; 1518/2113), acute respiratory distress syndrome (29.9%; 95% CI: 18.5–44.7%; $p = 0.009$; 470/2518), cardiac complications (22.3%; 95% CI: 12.8–36.1%; $p < 0.001$; 357/1246), and secondary infection (13.8%; 95% CI: 5.8–29.3%; $p < 0.001$; 218/1187) (Table 2).

Meta-Regression

Meta-regression random-effects models quantified the study level impact of comorbidities, risk factors, and complications in COVID-19 patients on IMV utilization, and mortality. Amongst COVID-19 patients, the age-adjusted meta-regression models showed strong association of mortality with male (r: 0.14; OR: 1.15; 95% CI: 1.07–1.23; $p = 0.0001$; I^2: 95.2%), comorbidities including pre-existing cerebrovascular disease (r: 0.35; OR: 1.42; 95% CI: 1.14–1.77; $p = 0.0018$; I^2: 96.1%), and chronic liver disease (r: 0.08; OR: 1.08; 95% CI: 1.01–1.17; $p = 0.0259$; I^2: 96.23%), complications like septic shock (r: 0.099; OR: 1.10; 95% CI: 1.02–1.2; $p = 0.0149$; I^2: 78.12%), and acute respiratory distress syndrome (ARDS) (r: 0.04; OR: 1.04; 95% CI: 1.02–1.06; $p = 0.0005$; I^2: 90.3%). Mortality odds were higher amongst patients in intensive care unit patients (r: 0.03; OR: 1.03; 95% CI: 1.03–1.05; $p = 0.0001$; I^2: 95.21%) and utilized IMV (r: 0.05; OR: 1.05; 95% CI: 1.03–1.07; $p < 0.0001$; I^2: 89.80%). Similarly, in age-adjusted meta-regression analysis, male (r: 0.08; OR: 1.08; 95% CI: 1.02–1.15; $p = 0.0140$; I^2: 95%), comorbidities like pre-existing cerebrovascular disease (r: 0.29; OR: 1.34; 95% CI: 1.09–1.63; $p = 0.0038$; I^2: 93.4%), cardiovascular disease (r: 0.28; OR: 1.32; 95% CI: 1.1–1.58; $p = 0.0028$; I^2: 89.7%), chronic liver disease (r: 0.08; OR: 1.08; 95% CI: 1.03–1.17; $p = 0.0033$; I^2: 94.4%), and acute respiratory distress syndrome (correlation coefficient: 0.04; OR: 1.04; 95% CI: 1.03–1.06; $p = 0.0000$; I^2: 77.34%) had higher odds of IMV utilization amongst COVID-19 patients. Pre-existing diabetes mellitus (r: 0.02;

Table 1 Study characteristics describing details on COVID-19

Study	Country	Sample size total study (n) = 29	Mortality (events; event rate (%) (95% CI)*; weight (%)#) total study (n) = 21	Mechanical ventilation (events; event rate (%) (95% CI)*; weight (%)#) total study (n) = 17
Huang et al., Jan 2020	China	41	6; 14.6 (6.7–29); 4.9	4; 9.8 (3.7–23.3); 4.99
Guan et al., Feb 2020	China	1099	15; 1.4 (0.8–2.3); 5.87	67; 6.1 (4.8–7.7); 7.54
Zhao et al., Mar 2020	China	19	NA	0; 2.5 (0.2–29.8); 1.51
Young et al., Mar 2020	Singapore	18	NA	1; 5.6 (0.8–30.7); 2.48
Wang et al., Feb 2020	China	138	6; 4.3 (2–9.3); 5.04	17; 12.3 (7.8–18.9); 6.85
Ng et al., Mar 2020	Singapore	100	0; 0.5 (0–7.4); 1.47	NA
Spiteri et al., Mar 2020	Europe	38	1; 2.6 (0.4–16.5); 2.36	1; 2.6 (0.4–16.5); 2.53
COVID-19 National Incident Room Surveillance Team, Mar 2020	Australia	71	2; 2.8 (0.7–10.6); 3.47	NA
Xu et al., Feb 2020	China	62	0; 0.8 (0–11.5); 1.46	1; 1.6 (0.2–10.6); 2.55
Bajema et al., Feb 2020	USA	11	1; 9.1 (1.3–43.9)[a]; 2.26	NA
Chen et al., Jan 2020	China	99	11; 11.1 (6.3–19); 5.57	NA
Yang et al., Feb 2020	China	52	32; 61.5 (47.8–73.7)[b]; 5.75	37; 71.2 (57.5–81.8); 6.54
Wang et al., Mar 2020	China	69	5; 7.2 (3–16.3); 4.78	NA
Mo et al., Mar 2020	China	155	NA	36; 23.2 (17.2–30.5); 7.25
Arentz et al., Mar 2020	USA	21	11; 52.4 (31.8–72.1)[c]; 4.93	15; 71.4 (49.2–86.6); 5.29
Wu et al., Mar 2020	China	201	44; 21.9 (16.7–28.1); 6.24	67; 33.3 (27.2–40.1); 7.44
Zhou et al., Mar 2020	China	191	54; 28.3 (22.3–35.1); 6.28	58; 30.4 (24.3–37.3); 7.41
Wang et al., Mar 2020	China	339	65; 19.2 (15.3–23.7); 6.35	80; 23.6 (19.4–28.4); 7.53
Guo et al., Mar 2020	China	187	43; 23 (17.5–29.6); 6.23	45; 24.1 (18.5–30.7); 7.35
Richardson et al., Apr 2020	USA	5700	553; 9.7 (9–10.5); 6.53	1151; 20.2 (19.2–21.3); 7.76
Goyal et al., Apr 2020	USA	393	40;10.2 (7.6–13.6); 6.26	130; 33.1 (28.6–37.9); 7.6
Ruan et al., Mar 2020	China	150	68; 45.3 (37.6–53.4)[d]; 6.27	79; 52.7 (44.7–60.5); 7.38
Qian et al., Mar 2020	China	91	0;0.5 (0–8.1); 1.47	NA
Paranjpe et al., Apr 2020	USA	2199	310; 14.1 (12.7–15.6); 6.51	NA
Lauer et al., Mar 2020	China	181	NA	NA
Chang et al., Feb 2020	China	13	NA	NA
Kim et al., Feb 2020	South Korea	28	NA	NA
Qin et al., Mar 2020	China	452	NA	NA
Zhang et al., Feb 2020	China	140	NA	NA
Total		12,258	1267; 13 (9.3–18); 100	1789; 23.3 (17.1–30.9); 100

Total number (n =) of patients included for COVID-19 epidemiology evaluation 12,258, mortality prevalence 11,252, and for mechanical ventilation utilization 8804

* Statistically significant at $p < 0.001$ except (a) $p = 0.028$, (b) $p = 0.099$, (c) $p = 0.827$, and (d) $p = 0.254$

Weight (%) = relative weight (random)

OR: 1.02; 95% CI: 0.94–1.11; $p = 0.6027$; I^2: 96.08%) and hypertension (r: 0.001; OR: 1.00; 95% CI: 0.94–1.06; $p = 0.9685$; I^2: 95.99%) had not been associated with increased odds of mortality or needs for IMV (Table 3).

Figures 1 and 2 show a forest plot of age-adjusted factors contributing poor outcomes amongst COVID-19 patients. Sensitivity analysis showed that the removal of any single study did not change the significance of the results. Unadjusted relationships are mentioned in the eSupplemental file (3).

eSupplemental file (4) shows age-adjusted meta-regression suggests incremental association between mortality (log-event) and pooled prevalence of male, ICU admission, IMV utilization, cerebrovascular disease, chronic liver disease, acute respiratory distress syndrome, septic shock, and cardiac complications. eSupplemental file (5) shows age-adjusted meta-regression suggests incremental association between IMV utilization (log-event) and pooled prevalence of male, cerebrovascular disease, chronic liver disease, cardiovascular disease, and acute respiratory distress syndrome.

Table 2 Demographics, clinical features, and outcomes of patients with COVID-19

Variable	Number of patients affected	Total number of patients	Pooled percentage % (95% CI)*	Heterogeneity (I^2) %
Patient demographics				
Age in years (median, range)	52.5 (41–70)	12,247	–	–
Female	5042	12,247	42.6 (40.4–44.8)	66.6
Males	7198	12,247	57.3 (55.1–59.4)	66.4
Clinical features				
Headache	306	2738	10.7 (7.9–14.3)	79.1
Fever	5172	9563	85.6 (73.6–92.7)	98.8
Cough	2464	3863	64.7 (57.4–71.4)	93.7
Diarrhea	400	3428	9.4 (6.2–14.1)	92.2
Dyspnea	1259	3629	32 (23.9–41.3)	95.8
Hemoptysis	29	1804	2.1 (1.1–3.9)	56.8
Myalgia/fatigue	1848	3813	43.3 (35.8–51.2)[a]	94.5
Nausea/vomiting	265	3258	7 (4.4–10.8)	90.6
Sore throat	192	1344	17.3 (9.1–30.3)	85.9
Nasal congestion/rhinorrhea	50	1082	7.5 (3.1–17.4)	88.1
Sputum production	968	2846	33.4 (29.1–38.1)	79.4
Comorbidities				
Smoker	3003	8410	8.9 (4.2–17.9)	98.8
Diabetes	2897	11,680	15.4 (12–19.4)	95.8
Hypertension	4858	11,626	28.2 (22.1–35.1)	97.8
Malignancy	578	11,486	4 (3.1–5.2)	76.6
Pulmonary disease	1371	11,402	5.5 (3.8–7.7)	94.1
Chronic liver disease	116	8830	3 (1.4–6.1)	92.6
Cerebrovascular disease	244	4987	4.4 (2.9–6.5)	83.6
Cardiovascular disease	2044	11,664	12.2 (8.9–16.6)	96.8
Complications				
Pneumonia	1518	2113	68.1 (38.8–87.8)[b]	98.3
Acute respiratory distress syndrome	470	2518	29.9 (18.5–44.7)[c]	96.6
Septic shock	68	1920	3.6 (0.9–13.8)	96.1
Secondary infection	218	1187	13.8 (5.8–29.3)	96.1
Cardiac complications	357	1246	22.3 (12.8–36.1)	95.1
Others	268	2180	21.2 (7.4–47.6)	97.9
Clinical outcomes				
Discharged/recovery	3906	11,083	36.6 (28.9–44.9)[d]	97.6
ICU	2038	10,230	18.8 (14.7–23.8)	92.5
Mechanical ventilation	1789	8804	23.3 (17.1–30.9)	95.6
Mortality	1267	11,252	13 (9.3–18)	95.6

For the accuracy of the epidemiological characteristics, we have considered all the studies ($n = 29$) mentioning COVID-19 epidemiology with or without outcomes

*Statistically significant at $p = < 0.001$ except (a) $p = 0.096$, (b) $p = 0.009$, (c) $p = 0.009$, and (d) $p = 0.002$

Heterogeneity (I^2) Statistics

The heterogeneity analysis of the age-adjusted mortality and IMV showed 67–96% and 77–96% dispersion observed between studies, respectively. Additionally, overall studies had moderate risk of bias (eSupplemental file (6)).

Discussion

In our meta-regression analysis of 29 observational studies with 12,258 confirmed cases of COVID-19 patients, the pooled prevalence of IMV was 23.3%, and mortality was 13%. Male (57.3%) and those with pre-existing hypertension

Table 3 Age-adjusted factors associated with mortality and needs of mechanical ventilator amongst COVID-19 patients

Covariate	Mortality				Mechanical ventilation			
	Correlation coefficient (95% CI); *p* value	Odds ratio e^coefficient	Analogous index (R^2)	Heterogeneity I^2 (%)#; Cochran's Q_{model}; $Tau^2_{unexplained}$	Correlation coefficient (95% CI); *p* value	Odds ratio e^coefficient	Analogous index (R^2)	Heterogeneity I^2 (%)#; Cochran's Q_{model}; $Tau^2_{unexplained}$
Male vs. female	0.14 (0.07–0.21); 0.0001	1.15 (1.07–1.23)	0.28	95.24; 35.08; 0.49	0.08 (0.02–0.14); 0.0140	1.08 (1.02–1.15)	0	95.16; 23.57; 0.55
Intensive care unit	0.03 (0.02–0.05); 0.0001	1.03 (1.03–1.05)	0.24	95.21; 27.4; 0.52	0.02 (− 0.0003–0.05); 0.0531	1.02 (0.9997–1.05)	0.15	92.45; 23.72; 0.69
Mechanical ventilation	0.05 (0.03–0.07); 0.0000	1.05 (1.03–1.07)	0.68	89.80; 44.64; 0.30	–	–	–	–
Comorbidities								
Smoking	− 0.08 (− 0.13–-0.03); 0.0021	0.9 (0.88–0.97)	0.32	94.18; 13.48; 0.65	− 0.05 (− 0.07–0.02); 0.0000	0.95 (0.93–0.98)	0.75	80.45; 35.99; 0.12
Diabetes mellitus	0.02 (− 0.06–0.10); 0.6027	1.02 (0.94–1.11)	0	96.08; 9.63; 0.69	0.02 (− 0.07–0.11); 0.6664	1.02 (0.93–1.12)	0	96.39; 9.06; 0.80
Hypertension	0.001 (− 0.06–0.06); 0.9685	1 (0.94–1.06)	0	95.99; 4.44; 0.78	0.01 (− 0.07–0.09); 0.8161	1.01 (0.93–1.09)	0	95.98; 5.70; 0.64
Malignancy	− 0.16 (− 0.34–0.03); 0.0945	0.85 (0.71–1.03)	0.04	96.59; 9.49; 0.54	− 0.18 (− 0.40–0.04); 0.1169	0.84 (0.67–1.04)	0	96.51; 8.92; 0.54
Pulmonary disease	0.0002 (− 0.05–0.06); 0.9955	1 (0.95–1.06)	0	96.58; 8.23; 0.62	0.01 (− 0.05–0.07); 0.7233	1.01 (0.95–1.07)	0	96.83; 9,53; 0.74
Cerebrovascular disease	0.35 (0.13–0.57); 0.0018	1.42 (1.14–1.77)	0.32	96.11; 16.46; 0.73	0.29 (0.09–0.49); 0.0038	1.34 (1.09–1.63)	0.57	93.43; 14.74; 0.57
Chronic liver disease	0.08 (0.01–0.16); 0.0259	1.08 (1.01–1.17)	0.27	96.23; 13.65; 0.85	0.08 (0.03–0.13); 0.0033	1.08 (1.03–1.17)	0.38	94.40; 26.83; 0.38
Cardiovascular disease	− 0.01 (− 0.13–0.11); 0.8772	0.99 (0.88–1.12)	0	96.31; 1.4; 1.71	0.28 (0.1–0.46); 0.0028	1.32 (1.1–1.58)	0.34	89.69; 11.67; 0.43
Complications								
Pneumonia	− 0.003 (− 0.03–0.02); 0.8204	0.997 (0.97–1.02)	0	96.13; 6.84; 1.83	− 0.01 (− 0.03–0.02); 0.5806	0.99 (0.97–1.02)	0	96.37; 7.1; 1.53
Acute respiratory distress syndrome	0.04 (0.02–0.06); 0.0005	1.04 (1.02–1.06)	0.60	90.28; 23.16; 0.47	0.04 (0.03–0.06); 0.0000	1.04 (1.03–1.06)	0.88	77.34; 51.89; 0.1362
Septic shock	0.099 (0.02–0.18); 0.0149	1.10 (1.02–1.2)	0.77	78.12; 11.93; 0.38	*			
Secondary infection	− 0.01 (− 0.11–0.08); 0.7953	0.99 (0.90–1.08)	0	96.22; 0.21; 1.34	− 0.05 (− 0.13–0.02); 0.1771	0.95 (0.88–0.98)	0	94.13; 3.3; 0.85
Cardiac complications	0.01 (− 0.08–0.10); 0.7615	1.01(0.92–1.11)	0	94.81; 2.24; 1.79	− 0.02 (− 0.10–0.06); 0.5831	0.98 (0.9–1.06)	0	94.47; 2.35; .1.30

Meta-regression models are based on random effects

* Not enough data to run the analysis

Statistically significant at $p < 0.001$

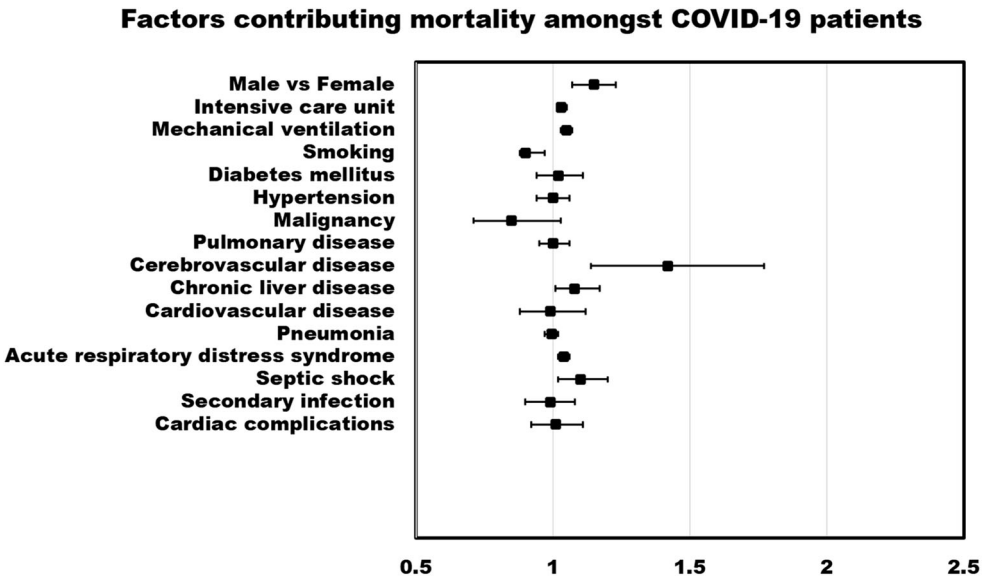

Fig. 1 Forest plot of age-adjusted factors contributing to mortality amongst COVID-19 patients

(28.2%), diabetes (15.4%), cardiovascular disease (12.2%), and cerebrovascular diseases (4.4%) had the highest prevalence in our study cohort. Our results are consistent with other studies from China and outside China [3, 6, 11, 15–18]. Regardless of the variations in the sample size and the geographical locations, cardiovascular disease and hypertension remain the most common comorbidity PM [15, 19–22]. The mortality rate for SARS-CoV was more than 10% and for MERS-CoV was more than 35%, and both are highly pathogenic organisms [23, 24]. The decreased vulnerability of females to viral infections may be assigned to X chromosome and sex hormone protectiveness, both of which play an important role in innate and adaptive immunity [25].

Furthermore, studies have reported that the majority of the COVID-19 patients had coexisting comorbidities, mainly cardiovascular and cerebrovascular diseases [17] and diabetes, similar to MERS-CoV [26] or any type of severe infectious disease that require hospital or ICU admission [27]. In our

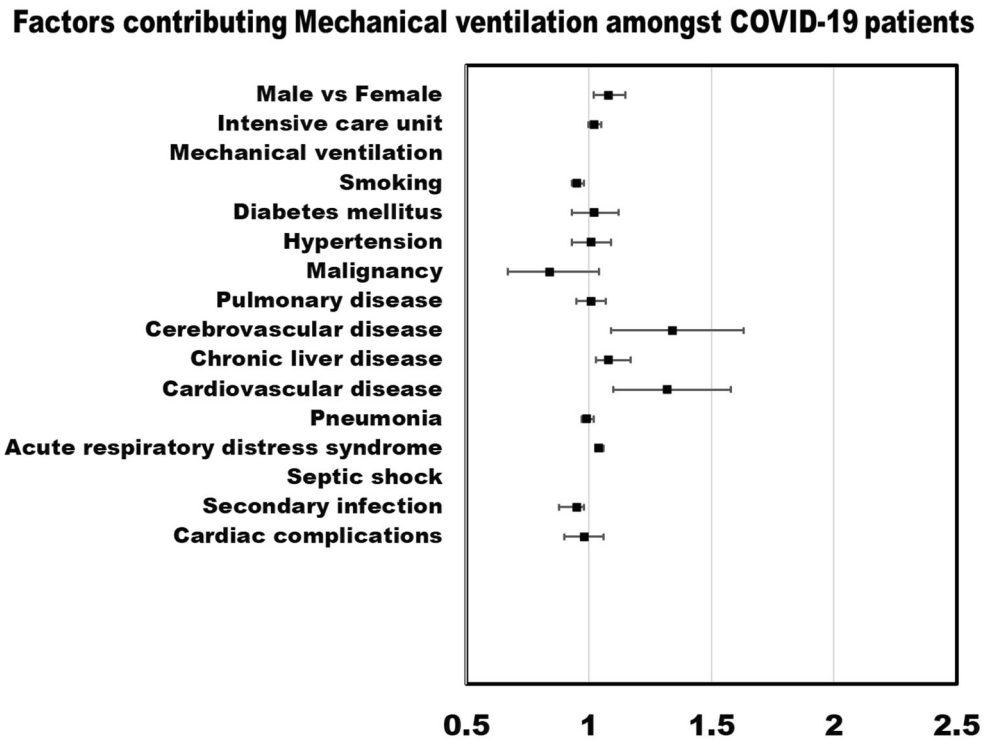

Fig. 2 Forest plot of age-adjusted factors contributing to mechanical ventilation amongst COVID-19 patients

study, comorbidities like pre-existing cerebrovascular disease, cardiovascular disease, and chronic liver disease were significantly associated with increased odds of mortality and IMV utilization in COVID-19 patients. The outcomes in many studies are similar to ours [16, 28]. It is well known that some comorbidities frequently coexist, and such patients are more likely to have poor well-being. A study by Guan et al. has found significantly increased risk of poor outcomes in COVID-19 patients with at least one comorbidity, or even more compared with patients with no comorbidity [29]. They also reported that severe cases were more likely to have hypertension, cardiovascular diseases, cerebrovascular diseases, and diabetes compared with non-severe cases, suggesting that both the category and number of comorbidities should be taken into account when predicting COVID-19 patients' prognosis. There is an assumption that immune dysregulation and prolonged inflammation might be the key drivers of the poor clinical outcomes in COVID-19 but await verification in more mechanistic studies [29].

However, we found no association of hypertension and diabetes with mortality and IMV. To support our findings, a study predicting factors associated with mortality in COVID-19 pneumonia reported that mortality was not associated with malignancy or diabetes [10]. Until now, it is not evident whether the severity or level of control of pre-existing health conditions has affected the risk for severe disease in COVID-19 patients. Additionally, many of these comorbidities have high prevalence in the USA. According to the AHA 2020 report [30], the prevalence of cardiovascular disease (excluding hypertension) was 10.6%. Considering the findings of our study, both highly prevalent comorbidities in COVID-19 patients in the USA and potential risk for more severe COVID-19 disease in patients with these comorbidities highlight the importance of COVID-19 prevention in people with underlying health conditions. Therefore, CDC continues to develop and update resources for persons with underlying health conditions to reduce the risk of acquiring COVID-19 [31].

Interestingly, there has not been published literature on the association of COVID-19 complications with poor outcomes. To our knowledge, this is the first study to report that COVID-19 patients with complications of ARDS have higher odds of mortality and IMV compared with those without ARDS. Hence, our study findings have added to the existing literature of common coexisting comorbidities and complications in patients with COVID-19 and its associated outcomes based on the large sample size and representing global population.

Strength and Limitations

To our knowledge, this is the first large population study that shows association between risk factors and outcomes, using meta-regression of 12,258 RT-PCR confirmed COVID-19 patients. Our findings may provide early insights into designing models for early identification of high-risk patients and prioritizing their treatment based on disease severity, which will help in prudent use of limited healthcare resources during this pandemic. A limitation of this study is missing details on severity of these risk factors. In addition, we have analyzed the group data of COVID-19 hospitalized patients, and individual patient meta-analysis would probably be able to better tease out relationships between multiple factors and reduce the risk of ecological fallacy while attempting to make inferences about individuals using study-level information. Also, since the primary studies are from very different healthcare systems, there may be uncaptured differences in ancillary care, criteria for IMV, ICU care, and etc. Due to non-identical effects being estimated in studies analyzed in our meta-regression, our study has high heterogeneity which we tried to justify using random-effects model and sensitivity analysis.

Conclusion

Our study suggests that COVID-19 patients with coexisting comorbidities such as cardiovascular disease, cerebrovascular disease, and chronic liver disease had poor outcomes of death and IMV compared with those without it. Hence, our study results might be helpful for clinicians in proper triage of patients by watchfully talking about the medical history, as this will help in early identification of high-risk patients who would be more likely to develop serious adverse outcomes of COVID-19 which in turn will be helpful in appropriate allocation of healthcare resources. However, diabetes and hypertension had higher prevalence in the study cohort but no association with mortality and IMV. Future studies should focus specifically on these comorbidities and their associated outcomes.

Authors' Contributions Conceptualization: UP; methodology: UP, PM; acquisition of data: UP, PM; formal analysis and investigation: UP, PM, MSU, TJS; writing—original draft preparation: UP, PM, MSU, DM, AS, FAM, NK; writing—review, critical feedback, and editing: JA, AP, HS; funding acquisition: none; resources: HS; supervision: HS.

Data Availability The data is collected from the studies published online, publicly available, and specific details related to data and/or analysis will be made available upon request.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The data used in this study is deidentified and collected from the studies published online; thus, informed consent or IRB approval was not needed for this study.

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