Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Global Impact of Coronavirus Disease 2019 Infection Requiring Admission to the ICU

A Systematic Review and Meta-analysis

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BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has placed unprecedented burden on the delivery of intensive care services worldwide.

RESEARCH QUESTION: What is the global point estimate of deaths and risk factors for patients who are admitted to ICUs with severe COVID-19?

STUDY DESIGN AND METHODS: In this systematic review and meta-analysis Medline, Embase, and the Cochrane library were searched up to August 1, 2020. Pooled prevalence of participant characteristics, clinical features, and outcome data was calculated with the use of random effects models. Subgroup analyses were based on geographic distribution, study type, quality assessment, sample size, end date, and patient disposition. Studies that reported in-hospital mortality rate of adult patients (age >18 years) with confirmed COVID-19 admitted to an ICU met study eligibility criteria. Critical evaluation was performed with the Newcastle Ottawa Scale for nonrandomized studies.

RESULTS: Forty-five studies with 16,561 patients from 17 countries across four continents were included. Patients with COVID-19 who were admitted to ICUs had a mean age of 62.6 years (95% CI, 60.4-64.7). Common comorbidities included hypertension (49.5%; 95% CI, 44.9-54.0) and diabetes mellitus (26.6%; 95% CI, 22.7-30.8). More than three-quarters of cases experienced the development of ARDS (76.1%; 95% CI, 65.7-85.2). Invasive mechanical ventilation was required in 67.7% (95% CI, 59.1-75.7) of case, vasopressor support in 65.9% (95% CI, 52.4-78.4) of cases, renal replacement therapy in 16.9% (95% CI, 12.1-22.2) of cases, and extracorporeal membrane oxygenation in 6.4% (95% CI, 4.1-9.1) of cases. The duration of ICU and hospital admission was 10.8 days (95% CI, 9.3-18.4) and 19.1 days (95% CI, 16.3-21.9), respectively, with in-hospital mortality rate of 28.1% (95% CI, 23.4-33.0; $I^2 = 96\%$). No significant subgroup effect was observed.

INTERPRETATION: Critically ill patients with COVID-19 who are admitted to the ICU require substantial organ support and prolonged ICU and hospital level care. The pooled estimate of global death from severe COVID-19 is <1 in 3. CHEST 2021; 159(2):524-536

KEY WORDS: coronavirus; critical illness; intensive care; respiratory medicine; SARS-CoV-2

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Since emerging in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed an unprecedented burden on ICUs around the world. SARS-CoV-2 is a highly transmissible upper respiratory tract virus that causes coronavirus disease 2019 (COVID-19). A striking feature of COVID-19 is rapidly progressive respiratory failure, which develops in approximately 5% of infected adults.[1]

At the time of writing (August 28, 2020), there have been >24 million confirmed cases of COVID-19 and more than three-quarters of a million deaths worldwide.[2] In early case series, mortality rates for critically ill patients with COVID-19 were between 40% and 61%, despite advanced ICU supports.[3-5] This mortality rate is substantially greater than in previous viral pneumonitis pandemics, such as the 2009 H1N1 influenza pandemic with morality rates between 10% and 30%.[6,7] Usual provision of ICU level support has also been strained during the current pandemic by the natural history of severe COVID-19 with reports of protracted ICU lengths of stay.[8]

Although COVID-19 is a global pandemic, the burden of disease has not been homogenous, and a number of regions that experienced earlier, rapid community spread reported strained or resource limited health care systems, which may have contributed to the high mortality rates.[3,4,9] More recent ICU series from regions with lesser COVID-19 population prevalence have reported lower ICU mortality rates of approximately 15%.[10] Although there is a need to measure the international burden of critical illness,[11] there is limited understanding of the global impact and outcomes of COVID-19 infection requiring ICU admission.

The objective of this systematic review and meta-analysis was to provide a contemporary and global assessment of the point estimate of death and risk factors for severe disease in patients admitted to an ICU with COVID-19.

Methods

Search Strategy and Selection Criteria

This review was performed in accordance with the Meta-analysis of Observational studies in Epidemiology[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[13] reporting guidelines (e-Appendix 1).

Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from inception to August 1, 2020. Key search terms included "coronavirus," "COVID-19," "SARS-CoV-2" or "severe acute respiratory syndrome," "intensive care," "critically ill," "critical care," "severe." Exact terms used are presented in e-Appendix 2. In addition, reference lists of relevant studies and review articles were searched manually for potentially eligible studies not captured in the primary search. Corresponding authors were contacted for additional data necessary for a meta-analysis. Two reviewers (E. T., J. S.) independently screened titles and abstracts of all identified studies for eligibility. Any discrepancies were resolved by consensus after discussion with a third reviewer (M. P. P.).

The inclusion criteria for studies were (1) design that included randomized controlled trials, nonrandomized controlled trials (case control or controlled cohort), observational studies and case series, (2) study population that included adult patients (≥18 years old) admitted to an ICU or high dependency unit, which included studies that compared ICU and non-ICU cohorts, (3) disease that confirmed COVID-19 or SARS-CoV-2, and (4) outcome that reported in-hospital mortality rates. Exclusion criteria were (1) review articles, opinion articles, case reports, (2) studies that did not define COVID-19 severity or did not include baseline physiologic data, (3) retracted studies, (4) studies that reported probable COVID-19 only, (5) duplicate patient data (from the same source and capture period) with preference given to sample size and quality for inclusion (e-Appendix 3), and (6) studies published in a language other than English.

Data Analysis

Two authors (E. T., J. S.) independently extracted predefined data. Data estimated values of the mean and SD were derived by formulas designed by Wan et al.[14] Extracted information included study characteristics (author, geographic location, design, sample size, and start and end date), participant characteristics (age, sex, smoking status, BMI, comorbidities), presenting symptoms, admission pathologic data, and pulmonary radiologic findings (radiographic and CT imaging, organ system dysfunction, complications, severity of illness scores, treatment and ICU supports, and outcome data (ICU and hospital length of stay and in-hospital mortality rate).

The methodologic quality of included studies was assessed according to the modified versions of the Newcastle-Ottawa scale or the Quality and Synthesis of Case Series and Case Reports Protocol, as appropriate.[15-17] Two reviewers independently assessed each study. Any discrepancies were discussed and resolved by consensus.

The criterion to undertake modelling in the outcome of interest was a minimum of three studies reporting relevant data. The random-effects model (DerSimonian and Laird method) was applied to estimate the pooled prevalence and 95% CIs.[18] To account for extreme prevalence data, prevalence estimates were transformed with the use of the double arcsine method then back-transformed for ease of interpretation.[19] Publication bias was assessed with the use of the funnel plot with asymmetry ascribed to an LFX index greater than ±1. Statistically significant heterogeneity was assessed as a Cochrane's Q test ($P < .10$) and $I^2 > 75\%$. Heterogeneity was further explored through subgroup analyses with the use of the following categoric study characteristics: (1) geographic distribution (North America vs Asia vs Europe vs Middle East), (2) quality assessment - risk of bias (high vs low), (3) sample size (>150 vs ≤150 patients), (4) center type (multicenter vs single center), (5) study type (case series vs retrospective cohort vs case control vs prospective cohort vs prospective cross-sectional vs chart review and national audit), (6) study end date (before April 2020 vs after April), and (7) patient disposition-proportion censored at study end date (<20% in-hospital at time of

publication vs ≥20% in-hospital). Statistical analyses for pooled prevalence were performed with MetaXL (version 5.3; EpiGear International Pty Ltd). For categoric variables (mortality rate by sex), pooled ORs and associated 95% CIs were calculated with the use of a Mantel-Haenszel model; for continuous variables (length of stay), mean differences and associated 95% CIs were calculated with an inverse-variance with the use of Review Manager (RevMan; version 5.3; The Cochrane Collaboration).

Results

A total of 3,873 articles were retrieved with the use of the search strategy. After screening was performed by abstract and title, 191 articles were selected for full-text assessment. Forty-five studies met the inclusion criteria and were included in this review and meta-analysis (Fig 1).

The 45 studies included 16,561 patients from 17 countries from December 29, 2019, to July 30, 2020. There were 16 studies from Europe (n = 13,485),[20-36] 15 studies from China (n = 1,385),[37-51] 11 studies from North America (n = 1,469),[52-62] and three studies from Middle East (n = 222).[63-65] There were 18 case series,[22,24,25,29,31-33,36,38,41,48-50,52,55,60,62,65] nine retrospective cohort studies,[21,23,35,40,45,53,59,61,63] nine case-control studies,[30,37,39,42-44,46,51,58] five prospective cohort studies,[20,26,34,54,56] two chart reviews,[57,64] one cross-sectional study,[47] and one national audit.[27] The main characteristics of the included studies are shown in Table 1 and e-Appendix 4. Sixty variables were analyzed for this meta-analysis (Table 2).

Critically ill patients with COVID-19 had a mean age of 62.6 years (95% CI, 60.4-64.7), a mean BMI of 30.1 kg/m^2 (95% CI, 28.7-31.4) and more than two-thirds were male (65.6%; 95% CI, 62.7-68.5). Mortality rates did not differ between sex (OR [men vs women], 1.20; 95% CI, 0.93-1.55; P = .16) (Table 2; e-Appendixes 5, 6). Common comorbidities included hypertension (49.5%;

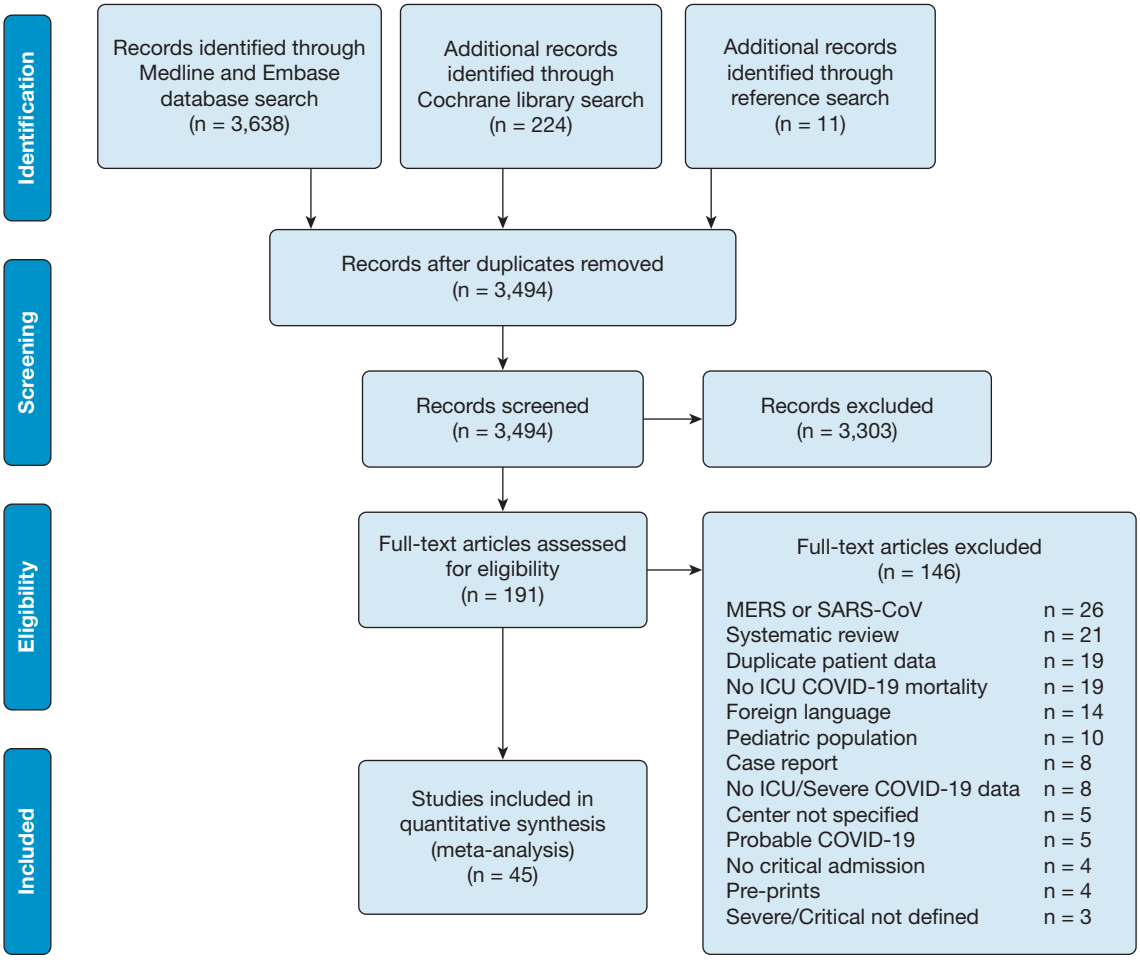

Figure 1 – *Preferred reporting items for systematic reviews and meta-analysis study flow diagram. COVID-19 = coronavirus disease 2019; MERS = Middle East respiratory syndrome; SARS-CoV = severe acute respiratory syndrome coronavirus.*

TABLE 1] Characteristics of Included Studies

Study	Country	Study Design	Sample Size	Dates	Quality
Almazeedi et al[63] (2020)	Kuwait	Retrospective cohort	42	24/02-20/4/2020	Good
Amit et al[64] (2020)	Israel	Chart review	156	05/03-27/04/2020	Good
Arentz et al[52] (2020)	United States	Case series	21	20/02-05/03/2020	Fair
Auld et al[53] (2020)	United States	Retrospective cohort	217	06/03-17/04/2020	Poor
Barrasa et al[20] (2020)	Spain	Prospective cohort	48	04/03-24/03/2020	Poor
Bhatla et al[54] (2020)	United States	Prospective cohort	79	06/03-19/05/2020	Good
Bhatraju et al[55] (2020)	United States	Case series	24	24/02-09/03/2020	Fair
Borobia et al[21] (2020)	Spain	Retrospective cohort	75	25/02-19/04/2020	Good
Cardoso et al[22] (2020)	Portugal	Case series	20	10/03/2020	Poor
Chen et al[37] (2020)	China	Retrospective case control subject	51	22/01-25/03/2020	Poor
Cui et al[38] (2020)	China	Case series	81	30/01-22/03/2020	Poor
Cummings et al[56] (2020)	United States	Prospective cohort	257	02/03-01/04/2020	Good
Ferguson et al[57] (2020)	United States	Chart review	21	13/03-11/04/2020	Poor
Grasselli et al[23] (2020)	Italy	Retrospective cohort	1715	20/02-22/04/2020	Poor
Halasz et al[24] (2020)	Italy	Case series	242	02-04/2020	Fair
Halvatsiotis et al[25] (2020)	Greece	Case series	90	10/03-13/04/2020	Fair
Helms et al[26] (2020)	France	Prospective cohort	150	03/03-31/03/2020	Good
Hur et al[58] (2020)	United States	Retrospective case control subject	138	01/03-08/04/2020	Good
ICNARC et al[27] (2020)	England	National clinical audit	10624	01/03-30/07/2020	…
Khamis et al[65] (2020)	Oman	Case series	24	24/02-24/04/2020	Poor
Klok et al[28,29] (2020)	Netherlands	Case series	184	07/03-05/04/2020	Poor
Li J et al[39] (2020)	China	Retrospective case control subject	74	25/01-26/02/2020	Poor
Ling et al[40] (2020)	China	Retrospective cohort	8	22/01-11/02/2020	Poor
Llitjos et al[30] (2020)	France	Retrospective case control subject	26	19/03-11/04/2020	Poor
Longchamp et al[31] (2020)	Switzerland	Case series	25	08/03-04/04/2020	Poor
Maatman et al[59] (2020)	United States	Retrospective cohort	109	12/03-31/03/2020	Poor
Mitra et al[60] (2020)	Canada	Case series	117	21/02-14/04/2020	Fair

(Continued)

TABLE 1] *(Continued)*

Study	Country	Study Design	Sample Size	Dates	Quality
Myers et al[61] (2020)	United States	Retrospective cohort	113	01/03-31/03/2020	Poor
Pavoni et al[32] (2020)	Italy	Case series	40	28/02-10/04/2020	Fair
Pedersen et al[33] (2020)	Denmark	Case series	16	11/03-01/04/2020	Poor
Richardson et al[62] (2020)	United States	Case series	373	01/03-04/04/2020	Fair
Rodriguez et al[34] (2020)	Spain	Prospective cohort	43	14/03-16/04/2020	Poor
Simonnet et al[35] (2020)	France	Retrospective cohort	124	27/02-05/04/2020	Good
Thomas et al[36] (2020)	United Kingdom	Case series	63	15/03-14/04/2020	Poor
Wang Y et al[41] (2020)	China	Case series	344	25/01-25/02/2020	Good
Wei et al[42] (2020)	China	Retrospective case control subject	14	27/01-11/03/2020	Poor
Wu et al[43] (2020)	China	Retrospective case control subject	83	20/01-19/02/2020	Good
Xu B et al[44] (2020)	China	Retrospective case control subject	107	26/12-01/03/2020	Good
Xu J et al[45] (2020)	China	Retrospective cohort	239	12/01-03/02/2020	Good
Yang L et al[46] (2020)	China	Retrospective case control subject	29	30/01-08/02/2020	Good
Yu et al[47] (2020)	China	Prospective cross-sectional	226	26/02-26/02/2020	Poor
Zhang G et al[48] (2020)	China	Case series	55	02/01-10/02/2020	Fair
Zhang J et al[49] (2020)	China	Case series	19	16/01-20/02/2020	Poor
Zheng et al[50] (2020)	China	Case series	34	22/01-05/03/2020	Fair
Zhou Y et al[51] (2020)	China	Retrospective case control subject	21	28/01-02/03/2020	Poor

95% CI, 44.9-54.0), diabetes mellitus (26.6%; 95% CI, 22.7-30.8), and cardiovascular disease (22.2%; 95% CI, 13.9-31.8). Nearly one-fifth of patients were current smokers (17.4%; 95% CI, 11.8-23.8). The most frequent symptoms on presentation were fever (78.9%), dyspnea (70.0%), cough (68.1%), and anorexia (46.8%). The median time from onset of symptoms to ICU admission was 9.0 days (95% CI, 7.9-10.0) (Table 2; e-Appendix 7).

On admission, inflammatory markers were elevated: C-reactive protein 170.0 mg/L (95% CI, 113.6-226.3), ferritin 1968.3 μg/mL (95% CI, 660.4-3276.1), procalcitonin 1.5 ng/L (95% CI, 1.0-2.0), and D-Dimer 3.1 mg/L (95% CI, 2.0-4.1). Lactate 1.3 mmol/L (95% CI, 1.1-1.6) was not raised markedly. In ten studies that reported chest radiography findings, bilateral infiltrates were seen in 72% (95% CI, 48.1-90.7) of patients.[40,41,43,48,52,55,57,61,63,65] In five studies that reported CT findings, ground glass opacities were reported in 66% (95% CI, 23.7-97.7) of patients[39,41,42,52,63] (Table 2; e-Appendix 8).

More than three-quarters of patients were diagnosed with ARDS during their ICU admission (76.1%; 95% CI, 65.7-85.2) (Fig 2). Approximately one-quarter of patients were reported to have acute kidney injury (27.1%; 95% CI, 20.6-34.2), shock (25.3%; 95% CI, 16.7-35.0), acute cardiac injury (24.2%; 95% CI, 13.5-36.7),

TABLE 2] Pooled Prevalence of Patient Characteristics, Presenting Symptoms, Interventions, Treatment, and Disposition

Variable	Studies	Total Sample Size	Patients	Crude Prevalence (%)	Pooled Prevalence (%), or Pooled Mean, Unit	95% CI (Upper-Lower)	Heterogeneity	
							I^2 (%)	*P* Value
Demographics								
Age	38	15,654	...	...	62.6 y	(60.4-64.7)	98	<.01
BMI	12	1,391	...	...	30.1 kg/m^2	(28.7-31.4)	93	<.01
Male	41	14,431	9,925	68.8%	65.6%	(62.7-68.5)	80	<.01
Current smoker	19	1,321	218	16.5%	17.4%	(11.8-23.8)	87	<.01
Comorbidities								
Hypertension	34	3,283	1,631	49.7%	49.5%	(44.9-54.0)	84	<.01
Diabetes mellitus	35	3,345	907	27.1%	26.6%	(22.7-30.8)	84	<.01
Cardiovascular disease	31	13,604	766	5.6%	22.2%	(13.9-31.8)	98	<.01
OSA	5	287	54	18.8%	20.0%	(12.0-29.5)	64	.03
Chronic kidney disease	25	12,786	431	3.4%	10.0%	6.2-14.6)	95	<.01
COPD	21	2,053	183	8.9%	9.4%	(7.3-11.8)	59	<.01
Asthma	11	985	89	9.0%	9.2%	(7.0-11.6)	27	.18
Malignancy	21	1,925	125	6.5%	6.5%	(5.0-8.1)	42	.02
Chronic liver disease	17	1,744	78	4.5%	4.7%	(2.9-6.8)	69	<.01
Organ transplantation	4	499	21	4.2%	4.4%	(2.7-6.3)	0	.51
Immunosuppressed	10	11,437	402	3.5%	4.1%	(2.5-6.0)	60	<.01
Presenting symptoms								
Fever	17	1,377	1,071	77.8%	78.9%	(68.6-87.6)	94	<.01
Dyspnea	19	1,386	935	67.5%	70.0%	(59.7-79.4)	93	<.01
Cough	20	1,503	1,001	66.6%	68.1%	(58.5-77.0)	93	<.01
Anorexia	3	473	166	35.1%	46.8%	(21.7-72.8)	95	<.01
Fatigue	10	794	364	45.8%	37.6%	(24.3-51.8)	92	<.01
Sputum	10	633	221	34.9%	34.2%	(24.9-44.1)	77	<.01
Myalgia	12	781	192	24.6%	23.2%	(14.4-33.4)	87	<.01
Diarrhea	15	1,278	236	18.5%	15.5%	(10.9-20.7)	79	<.01
Rhinorrhea	5	393	38	9.7%	11.2%	(6.3-17.1)	42	.14
Sore throat	11	701	71	10.1%	10.9%	(5.5-17.7)	82	<.01
Nausea	8	455	42	9.2%	9.5%	(6.1-13.6)	35	.16
Chest pain	3	211	19	9.0%	9.3%	(5.7-13.6)	0	.70
Headache	12	663	38	5.7%	6.5%	(4.2-9.1)	24	.21
Hemoptysis	4	151	8	5.3%	4.5%	(0.6-11.2)	49	.12
Symptoms onset to ICU admission	8	2,030	...	...	9.0 d	(7.9-10.0)	91	<.01
Laboratory results on hospital admission								
C-Reactive Protein	7	732	...	...	170.0 mg/L	(113.6-226.3)	99	<.01
D-Dimer	8	929	...	...	3.1 mg/L	(2.0-4.1)	95	<.01
Ferritin	2	37	...	...	1,968.3 μg/mL	(660.4-3276.1)	91	.02
Lactate	4	377	...	...	1.3 mmol/L	(1.1-1.6)	88	<.01
Lymphocyte count	9	745	...	...	0.8 × 10^9/L	(0.8-0.9)	54	.03
Procalcitonin	3	448	...	...	1.5 ng/L	(1.0-2.0)	72	.03

(Continued)

TABLE 2] *(Continued)*

Variable	Studies	Total Sample Size	Patients	Crude Prevalence (%)	Pooled Prevalence (%), or Pooled Mean, Unit	95% CI (Upper-Lower)	Heterogeneity	
							I^2 (%)	*P* Value
Imaging								
Chest radiography: bilateral chest infiltrates	10	735	381	51.8%	71.7%	(48.1-90.7)	97	<.01
CT chest: ground glass opacity	5	495	267	53.9%	65.5%	(23.7-97.7)	98	<.01
Disease severity on ICU admission								
Sequential Organ Failure Assessment score	12	1,391	...	...	6.3%	(5.1-7.6)	99	<.01
Acute Physiology and Chronic Health Evaluation II score	7	11,099	...	...	16.8%	(14.9-18.8)	98	<.01
Organ dysfunction								
ARDS	13	1,260	819	65.0%	76.1%	(65.7-85.2)	93	<.01
Acute kidney injury	13	1,287	380	30.2%	27.1%	(20.6-34.2)	84	<.01
Acute liver injury	6	715	270	37.8%	25.8%	(1.3-61.6)	98	<.01
Shock	7	895	230	25.7%	25.3%	(16.7-35.0)	88	<.01
Acute cardiac injury	11	1,326	357	26.9%	24.2%	(13.5-36.7)	95	<.01
Arrhythmia	3	302	49	16.2%	22.7%	(3.1-50.5)	93	<.01
Thrombotic event	7	852	195	22.9%	22.6%	(16.3-29.5)	76	<.01
Secondary infection	9	873	159	18.2%	18.4%	(14.0-23.2)	60	<.01
Interventions								
Invasive mechanical ventilation	28	13,543	9,247	68.3%	67.7%	(59.1-75.7)	98	<.01
Vasopressors	12	1,052	581	55.2%	65.9%	(52.4-78.4)	94	<.01
Renal replacement therapy	18	12,276	3,017	24.6%	16.9%	(12.1-22.2)	92	<.01
Noninvasive mechanical ventilation	15	1,519	276	18.2%	16.6%	(9.4-25.3)	93	<.01
Extracorporeal membrane oxygenation	18	1,828	103	5.6%	6.4%	(4.1-9.1)	76	<.01
Treatment								
Antimicrobial therapy	18	1,677	1,526	91.0%	94.6%	(90.6-97.6)	88	<.01
Antiviral therapy	18	1,580	791	50.1%	74.3%	(51.9-91.9)	99	<.01
Intravenous immunoglobulin	8	917	365	39.8%	50.1%	(17.8-82.3)	99	<.01
Glucocorticoid	17	1,617	704	43.5%	43.2%	(24.8-62.5)	98	<.01
Disposition								
ICU length of stay	11	2,484	...	...	10.8 d	(9.3-18.4)	94	<.01
Hospital length of stay	10	2,518	...	...	19.1 d	(16.3-21.9)	95	<.01
In-hospital deaths	45	16,561	6,783	41.0%	28.1%	(23.4-33.0)	96	<.01
Remain in hospital	32	15,842	1,590	10.0%	22.6%	(16.8-28.9)	98	<.01
Discharged from hospital	33	15,896	7,689	48.4%	43.9%	(38.9-48.9)	95	<.01

arrhythmia (22.7%; 95% CI, 3.1-50.5), and/or a thrombotic event (22.6%; 95% CI, 16.3-29.5). The pooled initial Sequential Organ Failure Assessment (SOFA) score was 6.3 (95% CI, 5.1-7.6) and Acute Physiology and Chronic Health Evaluation (APACHE) II score was 16.8 (95% CI, 14.9-18.8) (Table 2; e-Appendix 9). Invasive

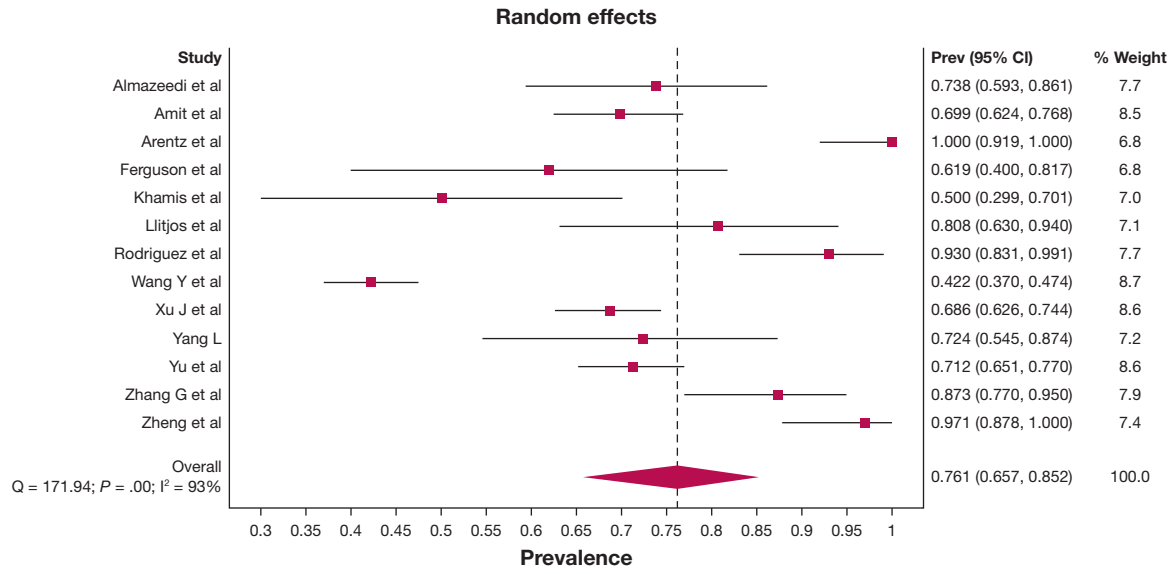

Figure 2 – *Forest plot of prevalence of ARDS. Prev = Prevalence.*

mechanical ventilation was required in 67.7% (95% CI, 59.1-75.7) of patients; 65.9% (95% CI, 52.4-78.2) of patients required vasopressor support; 16.9% (95% CI, 12.1-22.2) of patients received renal replacement therapy; 16.6% (95% CI, 9.4-25.3) of patients received noninvasive ventilation, and 6.4% (95% CI, 4.1-9.1) of patients received extracorporeal membrane oxygenation (Table 2, e-Appendix 10).

Antimicrobial therapy was administered to 94.6% (95% CI, 90.6-97.6) of patients with severe-to-critical COVID-19 infection. Antiviral therapy use was reported in 18 studies, with a pooled prevalence of 74.3% (95% CI, 51.9-91.9). Ten studies reported using lopinavir/rotinavir,[20,37,39,43,45-47,50,64,65] and five studies reported using remdesivir[54-57,64] (Table 2, e-Appendix 10). Glucocorticoid was prescribed to 43.2% (95% CI, 24.8-62.5) of patients.

The pooled mean duration of ICU admission was 10.8 days (95% CI, 9.3-18.4), and the pooled mean hospital duration of admission was 19.1 days (95% CI, 16.3-21.9). The pooled estimate for patients who remained in hospital with uncertain outcomes at the study end point was 22.6% (95% CI, 16.8-28.9). The pooled estimate for in-hospital mortality rate was 28.1% (95% CI, 23.4-33.0) (Fig 3), and discharge from hospital alive was 43.9% (95% CI, 38.9-48.9), albeit with considerable statistical heterogeneity (I^2 96%, $P < .01$; I^2 95%, $P < .01$, respectively). The funnel plot of all 45 studies was asymmetric, which suggests possible publication bias (Table 2; e-Appendixes 11-13).

Subgroup analyses revealed that mortality rate did not differ by geographic distribution, study type or quality, sample size, center type, end of study date, or patient disposition. There is no evidence of substantial difference in the mortality rates across the prespecified subgroups. (e-Appendix 14).

Discussion

This systematic review and meta-analysis of 45 studies includes 16,561 patients from 17 countries across four continents. The main findings are that patients who were admitted to ICU with COVID-19 required considerable organ support, with point estimates that more than three-quarters were diagnosed with ARDS and one-quarter were recorded as having shock and/or acute kidney injury. Invasive mechanical ventilation and vasopressor support were required in more than two-thirds of patients; renal replacement therapy was required in one-fifth of patients, and more than one in 20 of the patients received extracorporeal membrane oxygenation. The in-hospital mortality rate was between 23.4% and 33.0%.

More than 80% of coronavirus cases experience mild-to-moderate symptoms; approximately 15% have severe disease that requires hospitalization, and around 5% require intensive care support.[66,67] Previous meta-analyses have examined risk factors for mortality rates in COVID-19 infections; however, these studies included a majority of data within a certain region[68-72] or included patients with COVID-19 infections but less severe

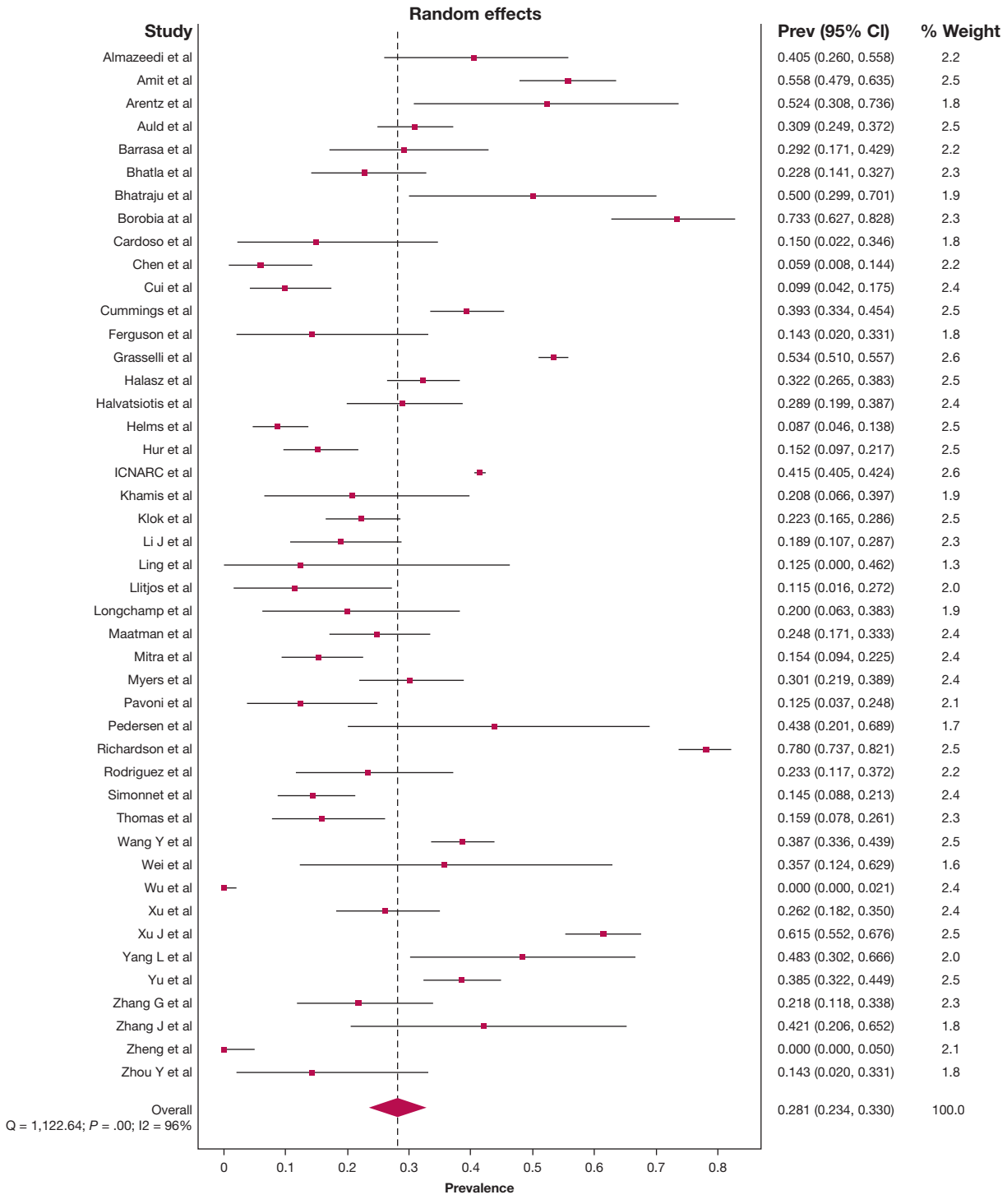

Figure 3 – *Forest plot of prevalence of in-hospital death. Prev = Prevalence.*

symptoms.[73-79] To address this limitation, the current systematic review and meta-analysis provides a comprehensive global overview of patient demographic, comorbidities, signs and symptoms, initial laboratory and imaging results, treatment, organ dysfunction, and outcomes in adults with severe and critical COVID-19. More than two-thirds of patients with severe COVID-19 were men, with a mean age of 62.6 years and a mean BMI of 30.1 kg/m^2, which confirms previous reports that there is a preponderance to severe disease with male sex, older age, and obesity.[69,73] In keeping with an older overweight population, we describe a comorbid

demographic that progress to severe COVID-19, with one-half of patients having arterial hypertension and approximately one-quarter having diabetes mellitus and cardiovascular disease.

This analysis confirms that, across the globe, once admitted to ICU with COVID-19 infection, the duration of admission to ICU and hospital is protracted. The mean ICU length of stay of 10.8 days was approximately double the duration of admission for severe community-acquired pneumonia[80] and longer than observed with H1N1 influenza pneumonia.[81] However, the upper 95% CI for in-hospital mortality rates was only 33.0%. Given that both the duration of admission and the intensity of ICU-level supports have led to enormous strain on critical care provision, particularly in geographic areas that experienced rapid community transmission,[82-84] this may have contributed to the heterogeneity of mortality data.

These estimates of global death for severe COVID-19 (in-hospital mortality rate between 23.4% and 33.0%) may impact the interpretation of existing trial data. For example, data from the RECOVERY trial indicated that dexamethasone caused a marked reduction in deaths (in-hospital censored at day 28) in patients with COVID-19 whose condition required mechanical ventilation (dexamethasone 29.3% vs usual care 41.4%).[85] However, the current meta-analysis of 16,561 patients with severe COVID-19 infection suggests that the magnitude of benefit observed with dexamethasone during the RECOVERY trial may not be reproducible across all settings.

Furthermore, given that global data suggest that less than one-third of patients die once admitted to ICU, the implication of this meta-analysis is that provision of sufficient ICU level service capacity is a global health priority to prevent inequalities in outcomes from this disease.

With 16,561 critically ill patients across 17 countries and four continents, this review is the largest and most granular assessment of outcomes of severe COVID-19 to date. Limitations of this systematic review include the presence of publication bias and that most included studies were case series and retrospective in design. There is a risk of survivor bias, with nearly one-quarter of patients remaining in hospital. The pooled prevalence for patients discharged alive was only 43.9% (95% CI, 38.9-48.9). Studies varied with the censor date for the identification of death. We specified the outcome measure as "death," "remained in hospital," and "discharged alive," and it is possible that all-cause death that is censored at some later landmark (eg, day 90) may be greater than reported in this meta-analysis. There was considerable statistical heterogeneity found for many results. However, despite exploring the cause of heterogeneity through extensive subgroup analyses, there was no singular cause identified. Finally, studies were excluded that were not written in English. Although the risk of bias from excluding studies not published in English is considered low,[86] it is uncertain how the additional patients would have affected the 95% CIs.

This systematic review provides the most expansive snapshot to date of the international experience of COVID-19 that requires critical care support. Advanced age, male sex, obesity, smoking, hypertension, diabetes mellitus, and cardiovascular disease are major risk factors for severe COVID-19. More than two-thirds of patients require invasive mechanical ventilation; approximately 20% of patients require renal replacement therapy, and the mean duration of ICU admission was 11 days. There was marked heterogeneity in mortality rate; however, the global mortality rate point estimate for patients with COVID-19 who are admitted to an ICU was 28%.

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