ORIGINAL ARTICLE

Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation

A Meta-analysis

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Abstract

Rationale: Initial reports of case fatality rates (CFRs) among adults with coronavirus disease (COVID-19) receiving invasive mechanical ventilation (IMV) are highly variable.

Objectives: To examine the CFR of patients with COVID-19 receiving IMV.

Methods: Two authors independently searched PubMed, Embase, medRxiv, bioRxiv, the COVID-19 living systematic review, and national registry databases. The primary outcome was the "reported CFR" for patients with confirmed COVID-19 requiring IMV. "Definitive hospital CFR" for patients with outcomes at hospital discharge was also investigated. Finally, CFR was analyzed by patient age, geographic region, and study quality on the basis of the Newcastle-Ottawa Scale.

Measurements and Results: Sixty-nine studies were included, describing 57,420 adult patients with COVID-19 who received IMV. Overall reported CFR was estimated as 45% (95% confidence interval [CI], 39–52%). Fifty-four of 69 studies stated whether hospital outcomes were available but provided a definitive hospital outcome on only 13,120 (22.8%) of the total IMV patient population. Among studies in which age-stratified CFR was available, pooled CFR estimates ranged from 47.9% (95% CI, 46.4–49.4%) in younger patients (age $\leq$40 yr) to 84.4% (95% CI, 83.3–85.4%) in older patients (age $>$80 yr). CFR was also higher in early COVID-19 epicenters. Overall heterogeneity is high (I^2 $>$90%), with nonsignificant Egger's regression test suggesting no publication bias.

Conclusions: Almost half of patients with COVID-19 receiving IMV died based on the reported CFR, but variable CFR reporting methods resulted in a wide range of CFRs between studies. The reported CFR was higher in older patients and in early pandemic epicenters, which may be influenced by limited ICU resources. Reporting of definitive outcomes on all patients would facilitate comparisons between studies.

Systematic review registered with PROSPERO (CRD42020186997).

Keywords: COVID-19; SARS-CoV-2; case fatality rate; mortality; invasive mechanical ventilation

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At a Glance Commentary

Scientific Knowledge on the Subject: Outcome data for patients with severe coronavirus disease (COVID-19) receiving invasive mechanical ventilation have varied substantially. Globally, the case fatality rate (CFR) for patients with COVID-19 admitted to the ICU and receiving invasive mechanical ventilation is high, but overall estimates informed by available studies are lacking.

What this Study Adds to the Field: Of 57,420 adult patients in 69 studies who met the inclusion criteria for this systematic review and meta-analysis of patients with severe COVID-19, the overall estimate for the reported CFR was 45% (95% confidence interval, 38–52%). Definitive hospital outcomes were only available for 13,120 (36.6%) patients. Significant variability in CFR was also present by age of patients and geographic location of the study.

The novel coronavirus disease (COVID-19) pandemic, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has severely burdened healthcare system capacities in many parts of the world (1). The World Health Organization reports the global crude mortality rate to be 3.9% (2).

The care of critically ill patients with COVID-19 has been rapidly evolving (3). Although there have been promising therapies such as remdesivir (4) and dexamethasone (5), mechanical ventilation continues to be the mainstay of management of severe COVID-19 (6). Hypoxemia (Pa_{O_2} <60 mm Hg) has been commonly reported in hospitalized patients with COVID-19 (7). Early invasive mechanical ventilation (IMV) was promoted early in the pandemic because of concerns of aerosol generation from noninvasive oxygenation therapies facilitating nosocomial viral transmission (8–10).

The case fatality rate (CFR) is defined as the proportion of a population with a disease that dies during a specific period (11). The reported CFRs of critically ill patients with COVID-19 receiving IMV have been observed to be highly variable (12). Causes of this inconsistency likely include the heterogeneity in the management of these patients and in the presentation of outcome data (12, 13). Addressing this knowledge gap will assist in intensive care resource planning and public health strategies.

The aim of this systematic review and meta-analysis was to report the CFR of critically ill adult patients with COVID-19 who received IMV based on the available evidence. The variability in CFR by patient age, geographic region, and study quality was also analyzed in this study.

Methods

This systematic review and meta-analysis was reported using the preferred reporting items for systematic reviews and meta-analyses framework (14) and has been registered on PROSPERO (CRD42020186997). The majority of patients receiving IMV are admitted to the ICU; however, not all ICU patients receive IMV. We therefore included studies explicitly reporting on patients receiving IMV to limit heterogeneity in illness severity. The review process is illustrated in a flow diagram (Figure 1).

Eligibility Criteria

Only studies reporting on consecutive adult patients (≥18 yr of age) with laboratory-confirmed COVID-19 receiving IMV were included. Studies were excluded if *1*) the sample size of the cohort was less than 10, *2*) they did not report the results of original research, or *3*) the cohort consisted only of deceased patients. Studies were also excluded if a significant overlap in patient cohorts was identified.

Search Strategy, Information Sources, and Study Selection

Two authors (Z.J.L. and A.S.) independently searched on the publicly available COVID-19 living systematic review. This dynamic systematic review contains a daily updated list of preprint and published articles relating to COVID-19 obtained from PubMed, EMBASE, medRxiv, and bioRxiv (15). The workflow for obtaining these articles is freely available and has been used previously during the Zika virus epidemic (16). This living platform has been recently validated against an Ovid search relating to COVID-19 (17). Two authors (Z.J.L. and M.P.R.) independently extracted the content of this living systematic review and national registry databases between January 1, 2020, and July 8, 2020. Conflicts in data extraction were resolved by discussion between the reviewers or adjudication by a third author (A.S.). Corresponding authors for all the selected papers were contacted by e-mail for outcome data for patients who were still in the hospital at the time the manuscript was published. The search terms "mortality," "fatality," "ICU," "characteristic," "invasive," "mechanical," "ventilation," "death," and "died" were used within the title and abstract columns of the systematic review list. The searching criteria were combined with the Boolean operator "OR." All studies, including preprint and non-English language articles, were considered. A separate search for COVID-19 national registries was also conducted. Study period and location were analyzed as part of the data collection process.

Definitions

Reported CFR. "Reported CFR" was defined as the CFR among all patients who received IMV, before accounting for patients who were still receiving care in hospital.

Author Contributions: Z.J.L. conceived the project idea, conducted the systematic review and statistical analysis, assisted with data analysis, wrote the initial drafts of the manuscript, created tables and figures, and finalized the manuscript. A.S. conceived the project idea, conducted the systematic review, assisted with data analysis, wrote the initial drafts of the manuscript, and finalized the manuscript. M.P.R. conducted the systematic review, assisted with data analysis, wrote the initial drafts of the manuscript, and finalized the manuscript. G.B. analyzed the data, wrote the initial drafts of the manuscript, and finalized the manuscript. U.K. conducted the systematic review, assisted with data analysis, wrote the initial drafts of the manuscript, and finalized the manuscript. A.A. conducted the statistical analysis and created the tables and figures. B.B. conducted the statistical analysis and wrote the statistical section in the METHODS. S.A. assisted with data collection and analysis and finalized the manuscript. M.K. analyzed the data, wrote the initial drafts of the manuscript, and finalized the manuscript. F.B. analyzed the data and finalized the manuscript. J.R.C. provided oversight for analysis of the data and edited the manuscript. F.R. analyzed the data and edited the manuscript. All authors critically reviewed the manuscript and approved the final version before submission.

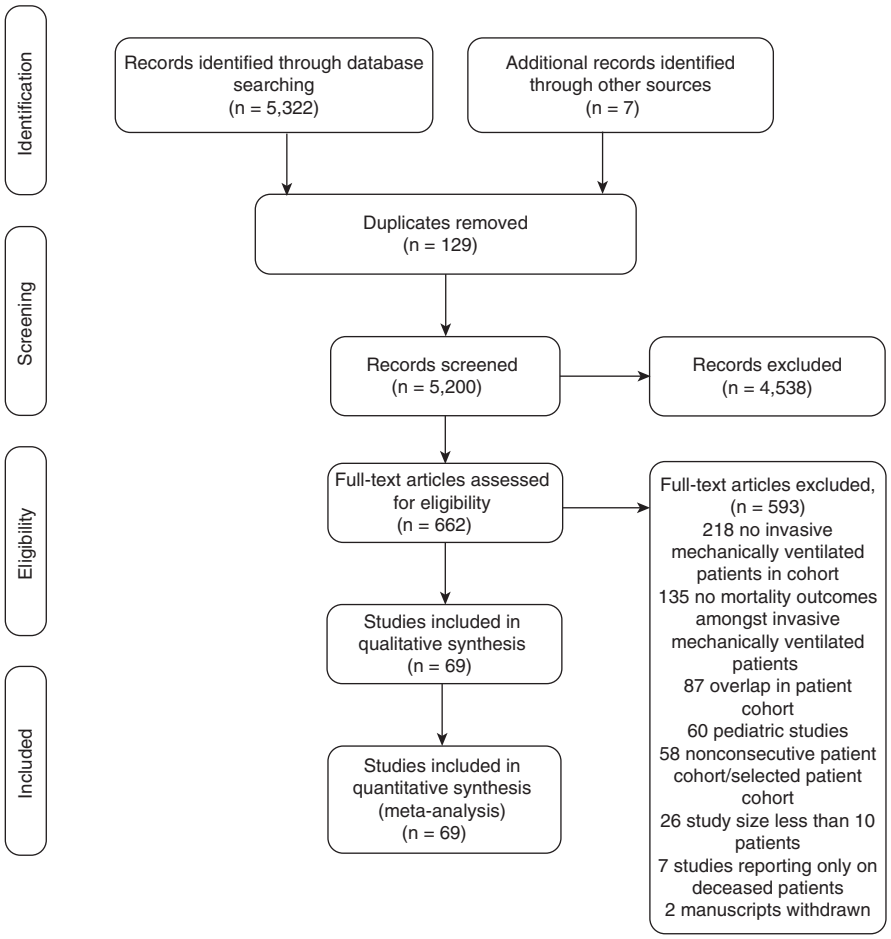


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study inclusions and exclusions. Adapted from Reference 14.

Range of estimates for CFR. We also provided a sensitivity analysis of the best possible and worse possible CFRs, assuming all remaining hospitalized patients either lived (lowest possible) or died (highest possible) in the subset of studies that reported the number of patients who received IMV who were still hospitalized at the time of study conclusion.

Definitive CFR. We examined the number of patients receiving IMV who died divided by the number of patients with a known hospital outcome (died or discharged alive) to calculate the definitive CFR.

Quality Assessment and Risk of Bias in Individual Studies

The Newcastle-Ottawa Scale (NOS) is a quality assessment tool used to evaluate nonrandomized studies on the basis of an eight-item score divided into three domains. The NOS has been selected for the purpose of this study because these domains assess selection, comparability, and ascertainment of the outcome of interest. The NOS is the most suitable for the purpose of comparing both reported and definitive CFR values. The NOS was used by the two reviewers (Z.J.L. and U.K.) to independently evaluate the quality of included studies and assess for risk of bias (18). The same set of decision rules was used by each reviewer to score the studies. Any discrepancies from the NOS were reviewed and resolved by two additional authors (A.S. and M.P.R.).

Study Outcomes

The primary outcome was the reported CFR for patients with COVID-19 receiving IMV based on the published studies. However, multiple methods of reporting CFR existed across different studies. Studies have reported the CFR of patients receiving IMV out of all patients receiving IMV, including those still hospitalized, whereas other studies have reported the CFR among patients who have completed their hospital course. This variance in reporting methods therefore resulted in variance in the CFRs reported by authors. As a secondary outcome, we examined the "definitive hospital CFR" for the subgroup of studies for whom we were able to ascertain hospital discharge outcomes. For all studies, we also present a sensitivity analysis that includes all patients showing "lowest possible" CFR for each study (assuming all patients still hospitalized lived) and a "highest possible" CFR (assuming all patients still hospitalized died). Within the appendix, the definitive hospital CFR is calculated by excluding patients who were still hospitalized to report the CFR only among patients with a known hospital outcome. Studies were also stratified based on geographical location (continent), economy (based on United Nations classification 2020), mean age, and study quality.

Data Analysis and Data Collection Process

Statistical analyzes were performed using the statistical software package Stata, version 16.1 (StataCorp). Mean and SD were used for numerical data and proportion was used for categorical data. The random-effects model and the Hartung-Knapp-Sidik-Jonkman method for meta-analysis (19) were used for the pooled prevalence of CFR because these demonstrate better properties in the presence of heterogeneity, accounting for both within-study and between-study variances (20). Results were presented in forest plots. Heterogeneity was tested by using the χ^2 test on Cochran's Q statistic, which was calculated by means of H and I^2 indices. The I^2 index estimates the percentage of total variation across studies on the basis of true between-study differences rather than on chance. Conventionally, I^2 values of 0–25% indicate low heterogeneity, values of 26–75% indicate moderate heterogeneity, and values of 76–100% indicate substantial heterogeneity. Authors conducted subgroup analyzes to identify the possible causes of substantial heterogeneity (21). Univariable metaregression was used, symmetry of the funnel plots was evaluated, and the Egger's regression test was used to examine for publication bias (22). Confidence interval (CI) was used to evaluate whether differences in CFRs were statistically significant. The 95% CI of prevalence

including 0.0% and 100% were calculated using the standard equation (23). As prevalence cannot fall below 0% or above 100%, the CI is trimmed at 0% and 100% (20).

Additional Analyses

We also examined the reported CFR based on age stratification for the subset of studies that reported outcomes by patient age. In addition, we compared the CFRs in studies from different geographic regions and examined difference between reports from cities with an early and dramatic pandemic outbreak, such as Hubei, China, and New York, United States, compared with studies from other cities in the same country.

Results

A total of 5,322 studies were obtained from the living systematic review with 662 unique studies assessed for eligibility via full-text screening (Figure 1). Sixty-nine studies across 23 countries with reported CFRs were included in the final analysis (13, 24–91), including publicly available national registry data from seven countries (29, 56, 59, 65, 66, 80, 90). A summary of the reported CFRs for adult patients receiving IMV is outlined in Table 1. A total of 121,009 patients with confirmed COVID-19 were reported across 69 studies, with 89,405 patients (73.9%) from national registry data. Across 69 studies, 66,900 patients were male (55.3%). The patients' mean age, as derived by the estimation formula to convert median to mean values (92), was 59.9 years. IMV was administered to 57,420 patients. Fifty-four of the 69 studies reported on the number of patients receiving IMV still hospitalized at the time of study conclusion.

Primary Outcome: Reported CFR of Patients with Severe COVID-19 Receiving IMV

The reported CFR across these studies was calculated at 45% (95% CI, 39–52%). Although a high heterogeneity was observed across all studies ($I^2 = 99.52\%$), our Egger's regression test for publication bias was 0.43 (nonsignificant). High heterogeneity was observed when studies were analyzed by continent ($I^2 > 90\%$). The reported CFRs varied between 36% (95% CI, 24–48%) and 52% (95% CI, 19–85%) among different continents, with no significant difference in CFRs. The forest plot is illustrated in Figure 2. Individual study NOS score is illustrated in Table E1 in the online supplement. There was no significant difference in CFR when studies were analyzed based on NOS score (Figure E1).

Range of Estimates for CFR

Fifty-four studies reported on the number of patients who were still hospitalized at the time of publication. Across these 54 studies, 15,064 of 35,880 patients (42.0%) received IMV. The sensitivity analysis comparing the "lowest possible" CFR (assuming all patients still hospitalized lived) with the "highest possible" CFR (assuming all patients still hospitalized died) ranged from 43% (95% CI, 36–51%) to 64% (95% CI, 56–72%) (Table E2).

Definitive CFR

A total of 13,120 of 15,064 (87.1%) patients (22.8% of the total IMV cohort) completed their hospital stay. Among these patients, 6,463 of 13,120 patients died (49.5%). The adjusted CFR among these patients was 56% (95% CI, 47–65%) (Figure E2). Within this subset of patients, no statistically significant differences in definitive hospital CFRs were observed when analyzing studies by geographical location (continent), economy, mean age (studies with main age >70 yr had a statistically lower CFR; however, the number of patients who received IMV was small [$N = 10$]), or study quality (Figures E2–E5). Heterogeneity continued to remain high ($I^2 > 90\%$) across all analyses.

Analysis of CFR Based on Patient Age and Studies from Early COVID-19 Epicenters

Three studies and three national registries (39, 44, 58, 59, 80, 90) reported on 42,618 IMV patients, of whom 28,547 (67.0%) died, and stratified CFR by age. CFR was >70% among patients aged more than 60 years of age. CFR increased exponentially ($y = 0.429e^{0.1162x}$) with increasing age (Figure 3).

The analysis comparing CFR in Wuhan with that of studies from other regions of China, as well as New York versus other regions in the United States, is illustrated in Figures E6 and E7. The reported CFR across 17 studies (encompassing 640 patients receiving IMV) from China reported an overall CFR of 56% (95% CI, 39–74%). Studies from Wuhan reported a significantly higher CFR of 75% (95% CI, 63–87%) compared with studies from other regions of China (20%; 95% CI 0–45%). Among patients with a known hospital outcome ($N = 11$ studies), the CFR reported from Wuhan (87%; 95% CI 77–97%) was lower than the CFR reported from other regions in China (33%; 95% CI, 0–82%).

An overall reported CFR of 47% (95% CI, 36–57%) was reported across 21 studies encompassing 3,811 patients with COVID-19 receiving IMV in the United States. Studies from New York reported a CFR of 54% (95% CI, 36–72%) whereas other regions in the United States reported a CFR of 41% (95% CI, 30–53%). When considering definitive outcomes, the overall CFR across 21 studies from the United States was 61% (95% CI 50–72%), with eight studies from New York reporting a significantly higher CFR of 78% (95% CI, 68–88%) compared with other regions in United States (49%; 95% CI, 35–63%).

Univariate and Multivariate Analysis

A simple regression (univariate) analysis and multivariate regression analysis were conducted across the 46 studies with definitive hospital outcome (Table E3). Studies were analyzed by common variables, including geographical location (continent), study quality (NOS score), mean age, and economic status. Poor-quality studies reported significantly lower CFRs compared with good-quality studies ($P = 0.035$). Multivariate regression did not yield any further statistical significance in study quality. A univariate analysis of studies from earlier epicenters (Wuhan and New York) showed significantly higher CFRs within these epicenters compared with nonepicenter studies in the same country ($P = 0.010$ for Wuhan vs. other studies in China and $P = 0.002$ for New York vs. other studies in the United States).

Discussion

This is a large international systematic review and meta-analysis to examine global reports of CFRs for adult patients with COVID-19 receiving IMV. The reported CFR was 45% across all 69 studies, but this included patients still in the hospital. Among all 54 studies, lowest possible to best possible hospital CFR ranged from 43% to

Table 1. The 69 Studies Selected for the Systematic Review and Meta-analysis

Study	Location of Study	Sample Size (*N*)	Mean Age (*yr*)	Sex, M (*n*)	Received IMV (*n*)	IMV Patients Still Receiving Care (*n*)	Died after IMV (*n*)	IMV Patients with Definitive Hospital Outcome [*n (%)*]	Primary Outcome: CFR of Patients Requiring IMV by Reported Outcome [*% (95% CI)*]
Chen *et al.*, May 2020 (24)	Hubei, China	135	NR	78	9	0	6	9 (100)	67 (40–93)
Hu *et al.*, May 2020 (25)	Hubei, China	323	59.0	166	34	NR	31	NR	91 (80–100)
Hu and Li, May 2020 (26)	Hubei, China	105	58.2	66	67	NR	39	NR	58 (47–70)
Hua *et al.*, June 2020 (27)	Hubei, China	469	68.0	76	113	0	104	113 (100)	92 (87–97)
Huang *et al.*, June 2020 (28)	Changsha, China	238	45.0	117	4	NR	2	NR	50 (15–85)
Japan registry, July 2020 (29)	Japan	575	NR	NR	575	67	133	508 (88)	23 (20–27)
Jung *et al.*, May 2020 (30)	South Korea	5,179	44.6	2,295	36	NR	21	NR	58 (43–74)
Liao *et al.*, April 2020 (31)	Sichuan, China	81	51.3	66	10	7	3	3 (30)	30 (5–55)
Nasir *et al.*, June 2020 (32)	Karachi, Pakistan	30	62.5	25	10	0	5	10 (100)	50 (24–76)
Ratanarat *et al.*, July 2020 (33)	Bangkok, Thailand	13	58.0	8	5	0	0	5 (100)	0 (0–27)
Ruan *et al.*, March 2020 (34)	Hubei, China	150	NR	102	25	0	25	25 (100)	100 (91–100)
Shi *et al.*, June 2020 (35)	Hubei, China	671	61.7	322	36	NR	29	NR	81 (68–93)
Sirivongrangson *et al.*, June 2020 (36)	Bangkok, Thailand	19	52.0	15	10	2	0	8 (80)	0 (0–18)
Wang *et al.*, April 2020 (37)	Anhui, China	125	38.8	71	4	3	0	1 (25)	0 (0–30)
Wang, June 2020 (38)	Nationwide, China	141	63.0	99	50	25	25	25 (50)	50 (37–63)
Wang, March 2020 (39)	Hubei, China	18	70.4	10	18	12	5	6 (33)	28 (8–47)
Yang *et al.*, May 2020 (40)	Hubei, China	59	66.1	40	59	NR	36	NR	61 (49–73)
Yang *et al.*, May 2020 (41)	Hubei, China	52	59.7	35	22	3	19	19 (86)	86 (71–100)
Ye *et al.*, June 2020 (42)	Zhejiang, China	856	46.0	439	29	NR	1	NR	3 (0–13)
Young *et al.*, March 2020 (43)	Singapore	18	49.5	9	1	0	0	1 (100)	0 (0–44)
Yu *et al.*, May 2020 (44)	Hubei, China	226	63.0	139	121	6	79	115 (95)	65 (57–74)
Zhao *et al.*, June 2020 (45)	Henan, China	29	51.2	14	5	0	1	5 (100)	20 (0–51)
Zheng *et al.*, May 2020 (46)	Hangzhou, China	34	66.7	23	15	13	0	2 (13)	0 (0–14)

(Continued)

Table 1. (*Continued*)

Study	Location of Study	Sample Size (*N*)	Mean Age (*yr*)	Sex, M (*n*)	Received IMV (*n*)	IMV Patients Still Receiving Care (*n*)	Died after IMV (*n*)	IMV Patients with Definitive Hospital Outcome [*n (%)*]	Primary Outcome: CFR of Patients Requiring IMV by Reported Outcome [*% (95% CI)*]
Zhu *et al.*, June 2020 (47)	Hubei, China	102	65.2	59	29	0	25	29 (100)	86 (73–99)
Almazeedi *et al.*, May 2020 (48)	South Surra, Kuwait	1,096	41	888	31	16	13	15 (48)	42 (26–58)
Goshayeshi *et al.*, May 2020 (49)	Mashhad, Iran	1,067	56.9	663	231	32	81	199 (86)	35 (29–41)
Khamis *et al.*, July 2020 (50)	Oman	63	48.0	53	16	NR	5	NR	31 (10–52)
Rinott *et al.*, June 2020 (51)	Israel	403	44.0	220	17	NR	12	NR	71 (50–91)
Shahriarirad *et al.*, June 2020 (52)	South Iran, Iran	113	53.8	71	2	0	2	2 (100)	100 (62–100)
Alfano *et al.*, June 2020 (53)	Modena, Italy	307	65.2	219	53	14	17	39 (74)	32 (20–44)
Busetto *et al.*, May 2020 (54)	Veneto, Italy	92	70.5	57	9	0	0	9 (100)	0 (0–20)
Ceruti *et al.*, May 2020 (55)	Lugano, Switzerland	41	64.0	35	34	4	7	30 (88)	21 (7–34)
France registry, June 2020 (56)	France	4,007	65.0	2,925	2,357	NR	480	NR	20 (19–22)
Giacomelli *et al.*, May 2020 (57)	Lombardy, Italy	233	61.0	72	8	0	7	8 (100)	88 (63–100)
Grasselli *et al.*, April 2020 (58)	Lombardy, Italy	1,591	63.0	1,304	1,150	NR	329	NR	29 (26–31)
ICNARC, 10 July 2020 (59)	United Kingdom	10,421	58.8	320	7,185	426	3,479	6,759 (94)	48 (47–50)
Israelsen *et al.*, May 2020 (60)	Hvidovre, Denmark	175	69.0	85	27	8	17	19 (70)	63 (46–80)
Pavoni *et al.*, May, 2020 (61)	Tuscany, Italy	40	61.0	24	4	1	3	3 (75)	75 (41–100)
Pedersen *et al.*, April 2020 (62)	Zealand, Denmark	17	69.8	12	17	6	7	11 (65)	41 (20–62)
Piano *et al.*, June 2020 (63)	Northern Italy, Italy	584	66.0	357	62	10	18	52 (84)	29 (18–40)
Regina *et al.*, May 2020 (64)	Lausanne, Switzerland	200	66.0	120	38	NR	11	NR	29 (15–43)
Spain registry, July 2020 (65)	Spain	7,695	60.3	5,344	3,867	NR	1,943	NR	50 (49–52)
Sweden registry July, 2020 (66)	Sweden	3,437	59.2	2,530	2,412	58	455	2,354 (98)	19 (17–20)
Zangrillo *et al.*, April 2020 (67)	Lombardy, Italy	73	61.3	61	73	33	17	40 (55)	23 (14–33)
Aggarwal *et al.*, May 2020 (68)	Iowa, United States	16	65.5	12	5	0	0	5 (100)	0 (0–27)
Arentz *et al.*, March 2020 (69)	Washington/Seattle, United States	21	70	11	15	3	10	12 (80)	67 (45–88)
Argenziano *et al.*, May 2020 (70)	New York, United States	1,000	62.7	596	233	86	111	147 (63)	48 (41–54)

(Continued)

Table 1. (*Continued*)

Study	Location of Study	Sample Size (*N*)	Mean Age (*yr*)	Sex, M (*n*)	Received IMV (*n*)	IMV Patients Still Receiving Care (*n*)	Died after IMV (*n*)	IMV Patients with Definitive Hospital Outcome [*n (%)*]	Primary Outcome: CFR of Patients Requiring IMV by Reported Outcome [*% (95% CI)*]
Auld *et al.*, May 2,020 (71)	Georgia, United States	217	63.7	119	165	11	56	154 (93)	34 (27–41)
Bhatraju *et al.*, March 2020 (72)	Washington/Seattle, United States	24	64.0	15	18	3	9	15 (83)	50 (29–71)
Buckner *et al.*, May 2020 (73)	Washington/Seattle, United States	105	64.5	53	19	0	10	19 (100)	53 (32–73)
Ferguson *et al.*, July 2020 (74)	California, United States	72	58.1	38	13	4	3	9 (69)	23 (1–45)
Garibaldi *et al.*, May 2020 (75)	Maryland, United States	832	60.4	443	70	24	24	46 (66)	34 (23–45)
Gold *et al.*, May 2020 (76)	Georgia, United States	305	58.8	151	92	6	38	86 (93)	41 (31–51)
Goyal *et al.*, April 2020 (77)	New York, United States	393	61.5	238	130	88	19	42 (32)	15 (8–21)
Klang *et al.*, May 2020 (78)	New York, United States	3,406	NR	1,961	809	0	682	809 (100)	84 (82–87)
Mani *et al.*, June 2020 (79)	New York, United States	184	64.7	111	30	17	13	13 (43)	43 (27–60)
Mexico registry, July 2020 (80)	Mexico	6,898	57.3	4,665	6,898	NR	4,724	NR	68 (67–70)
Mitra *et al.*, June 2020 (81)	Vancouver, Canada	117	68.0	79	74	25	15	49 (66)	20 (11–29)
Palaiodimos *et al.*, July 2020 (82)	New York, United States	200	62.5	98	42	0	32	42 (100)	76 (63–89)
Petrilli *et al.*, May 2020 (83)	New York, United States	2,721	62.7	1,678	647	86	391	561 (87)	60 (57–64)
Reyes Gil *et al.*, May 2020 (84)	New York, United States	217	NR	126	55	0	45	55 (100)	82 (72–92)
Richardson *et al.*, April 2020 (85)	New York, United States	5,700	60.9	3,437	*1,151*	831	*282*	320 (28)	25 (22–27)
Salacup *et al.*, July 2020 (86)	Philadelphia, United States	242	66.0	123	54	0	38	54 (100)	70 (58–82)
Shekhar *et al.*, May 2020 (87)	New Mexico, United States	50	54.0	23	22	6	12	16 (73)	55 (35–74)
Shi *et al.*, July 2020 (88)	Michigan, United States	172	61.5	97	61	2	16	59 (97)	26 (15–37)
Suleyman *et al.*, June 2020 (89)	Michigan, United States	355	57.5	204	114	6	91	108 (95)	80 (45–100)
Ziehr *et al.*, June 2020 (13)	Massachusetts, United States	66	56.5	43	66	0	11	66 (100)	17 (8–26)
Brazil registry, July 2020 (90)	Brazil	56,372	68.2	32,940	27,748	NR	19,935	NR	72 (71–72)
Olivares *et al.*, June 2020 (91)	Valdivia, Chile	21	58.9	5	9	0	2	9 (100)	22 (0–47)

Definition of abbreviations: CFR = case fatality rate; CI = confidence interval; ICNARC = Intensive Care National Audit and Research Centre; IMV = invasive mechanical ventilation; NR = not reported.

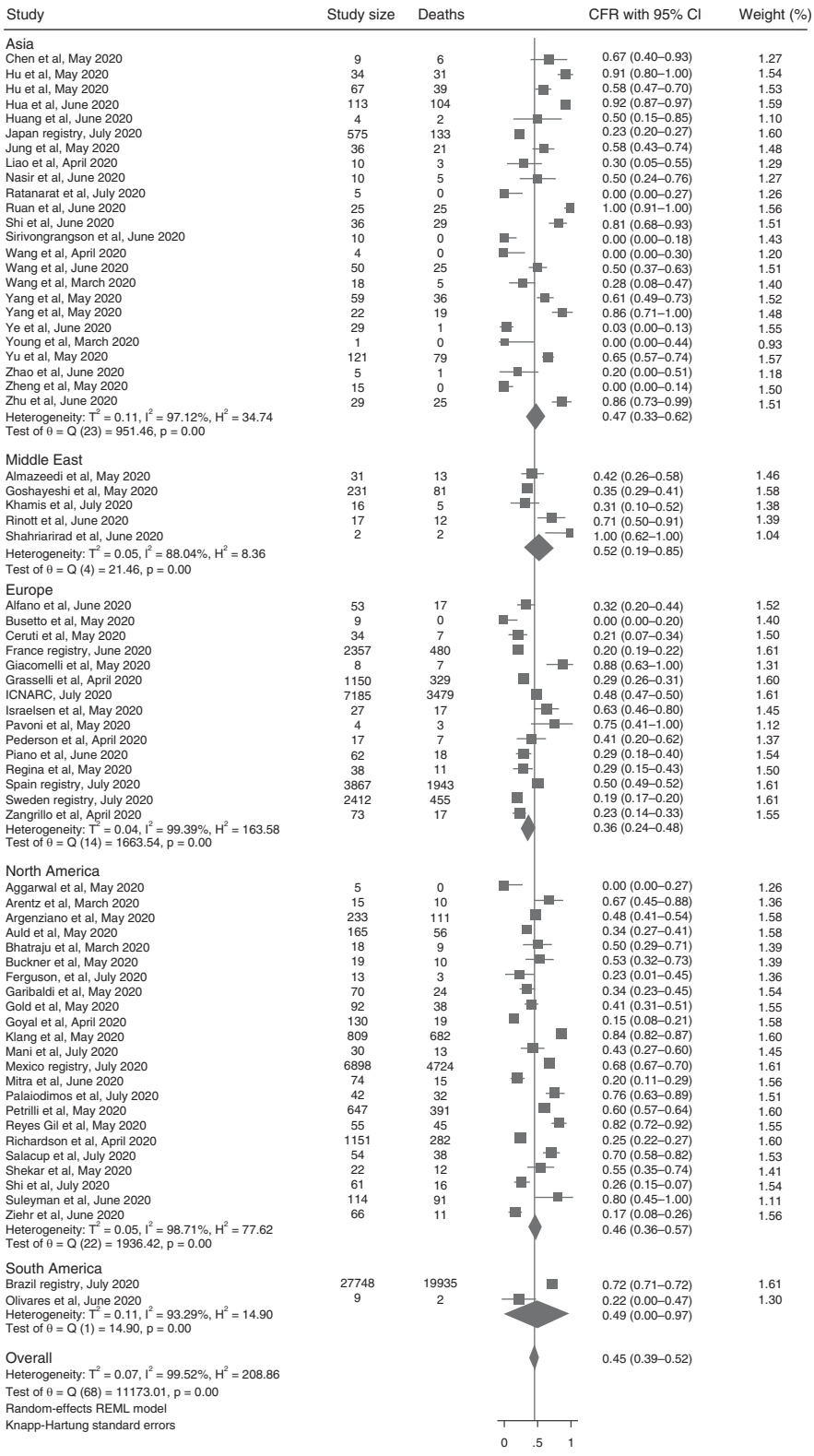


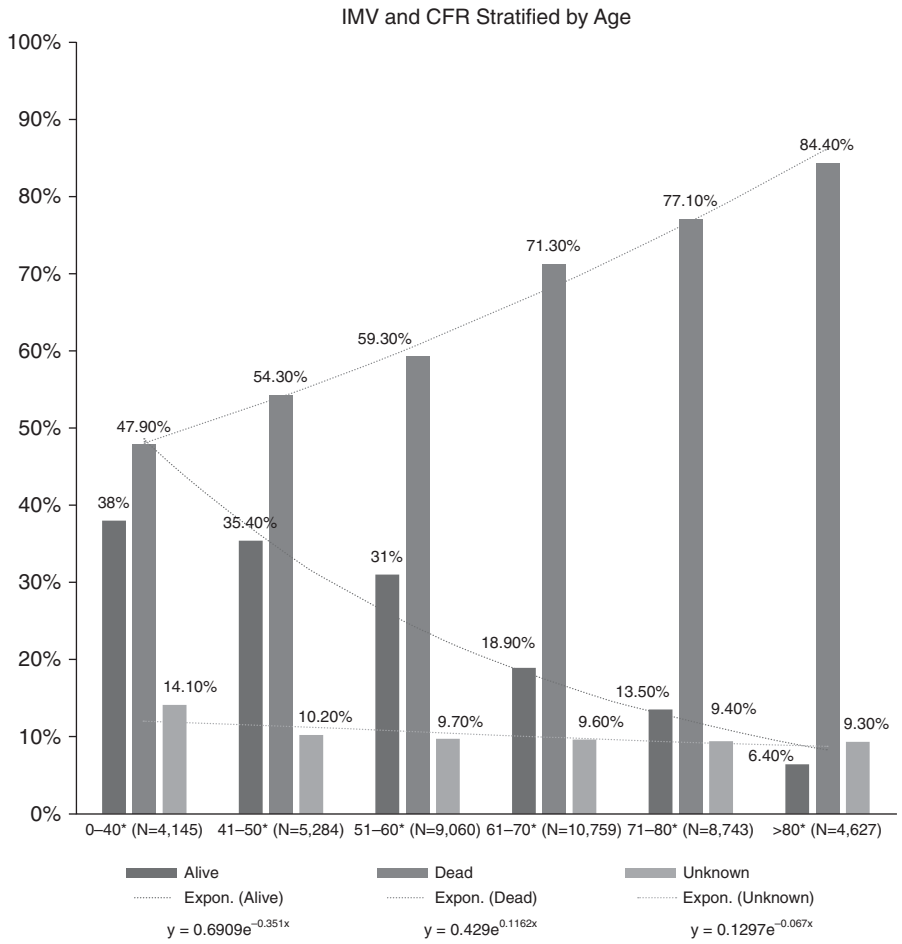
Figure 2. Forest plot of the reported case fatality rates ($N = 69$ studies) for patients receiving invasive mechanical ventilation stratified by continent. CFR = case fatality rate; CI = confidence interval; ICNARC = Intensive Care National Audit and Research Centre; REML = restricted maximum likelihood.

67%. Among patients with a known hospital outcome, the definitive hospital CFR was 56%. We observed no statistical difference between continents. Older patients had a higher CFR, and the CFR was higher in the early COVID-19 epicenters of Wuhan and New York compared with that of other studies from the same country.

The CFR observed in this review of patients with COVID-19 is similar to that of previous outbreaks of severe respiratory infections. Studies from SARS-CoV in 2003 reported a CFR of 45–48% in patients receiving IMV (93, 94), and more recent studies from the Middle East respiratory syndrome reported a 60–74% CFR in critically ill patients (95, 96). In contrast, the CFR is lower in critically ill patients suffering from H1N1 influenza A, in which the CFR of patients receiving IMV was 24.2–26.5% (97). The reported CFR from severe acute respiratory distress syndrome before COVID-19 was lower at 45% (98, 99) when compared with the definitive CFR from COVID-19.

The CFR of patients receiving IMV among studies from Wuhan and New York was significantly higher than that of studies from other regions in China and the United States, respectively. This finding may reflect of the significant challenges faced in the initial stages of the COVID-19 outbreak (100, 101). Reports suggest that prone positioning was infrequent in the initial phase (41), with one Wuhan study reporting only 12% of patients receiving IMV were managed with prone positioning. Variable provider:patient ratios may also have contributed to higher CFR (102–104).

Several factors may account for the large variance in CFRs between studies. ICUs outside of outbreak epicenters may have had the opportunity of time to obtain equipment and consolidate resources before the pandemic (71). This has enabled ICUs to continue at standard patient:provider ratios (71). Closer monitoring and early intensive care for critically ill patients potentially improved patient prognosis (31). Differences in hospital facilities, patient preferences (for which limitations of care may have been in place), and indications for IMV may have also influenced the CFR (12). Finally, the change in triage process considering comorbidities, age, and frailty status in allocating ICU beds and ventilators during the pandemic



Age	Alive n (%, 95% CI)	Dead n (%, 95% CI)	Unknown n (%, 95% CI)
≤40* (N=4,145)	1,575 (38.0, 36.5–39.5)	1,985 (47.9, 46.4–49.4)	585 (14.1, 13.1–15.2)
41–50* (N=5,284)	1,872 (35.4, 34.1–36.7)	2,870 (54.3, 53.0–55.7)	542 (10.2, 9.5–11.1)
51–60* (N=9,060)	2,809 (31.0, 30.1–32.0)	5,373 (59.3, 58.3–60.3)	878 (9.7, 9.1–10.3)
61–70* (N=10,759)	2,033 (18.9, 18.2–19.6)	7,676 (71.3, 70.5–72.2)	1,050 (9.6, 9.2–10.3)
71–80* (N=8,743)	1,180 (13.5, 12.8–14.2)	6,740 (77.1, 76.2–78.0)	823 (9.4, 8.8–10.0)
>80* (N=4,627)	295 (6.4, 5.7–7.1)	3,903 (84.4, 83.3–85.4)	429 (9.3, 8.5–10.1)

Figure 3. Reported case fatality rates for patients receiving invasive mechanical ventilation stratified by age, reported in six studies. *Age stratification for ICNARC was 16–39, 40–49, 50–59, 60–69, 70–79, and ⩾80. CFR = case fatality rate; CI = confidence interval; Expon. = exponential; ICNARC = Intensive Care National Audit and Research Centre; IMV = invasive mechanical ventilation.

may have contributed to a lower CFR among patients receiving IMV, in which younger and less frail patients were prioritized for IMV and ICU care (105–108), whereas older and frailer patients were less likely to receive ventilatory support. These older patients potentially died without IMV support, which is not captured in our findings. If significant numbers of older patients died without receiving IMV support that was indicated and desired, this would suggest our CFR estimates for older patients may be low.

Despite stratifying studies on the basis of location and NOS score, high heterogeneity continued to exist across our meta-analysis. This has been reported in other meta-analyzes studying COVID-19 mortality (109–113). Heterogeneity was the lowest at 83.4% among definitive outcomes from Wuhan (Figure E6). Although the reasons for this are not clear, we believe that studies originating from the same geographical location may provide a less heterogeneous cohort, and hence, the I^2 value was lower. Other potential factors influencing heterogeneity could be differences in illness severity, thresholds for IMV, admission criteria to the ICU, and regional differences in ICU care.

As demonstrated in a recent editorial, the CFR is substantially higher among older patients, with more than 70% of patients over 60 years of age receiving IMV dying (12). It has also been reported that the CFR for patients in their 80s and 90s receiving IMV with comorbidities has been higher (114). Our findings also suggest that older patients receiving IMV had significantly higher mortality.

There are several limitations to this systematic review. First, most of the included studies had very small numbers of patients; only 17 of 69 studies reported on more than 100 patients receiving IMV. Given the available evidence, we conducted a meta-analysis to account for this variability in sample size. Second, multiple studies may have covered similar patient cohorts. However, each study's time period, hospital, and location were considered in the final inclusion of studies to minimize overlap in patient cohorts. Third, 14 studies were not peer reviewed, as they were prepublication articles. However, these studies still provided meaningful data on the CFR of the subgroup of patients with COVID-19 who receive IMV. Fourth, the overall heterogeneity was very high (I^2 >90%), which may preclude a valid conclusion from pooled results. Although we performed various sensitivity and metaregression analyses, the heterogeneity could not be minimized. This is most likely due to the case mix and the structure of age within included populations. Finally, we were unable to examine the influence of timing in the pandemic because timing and region were highly correlated.

Conclusions

The reported CFR for existing studies of adult patients with COVID-19 receiving

IMV was 45%, but many of these reports included patients still in the hospital at the time of publication. Accounting for patients still in the hospital, we found a best possible CFR of 43% and a worst possible CFR of 64%. The CFR increased exponentially in the elderly. Although CFRs did not vary between continents, higher CFRs were noted in early COVID-19 epicenters such as Wuhan and New York compared with other regions in the same country. Additional studies examining long-term CFRs beyond hospital discharge are needed. ■

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References

1. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet* 2020; 395:1225–1228.
2. World Health Organization. Coronavirus disease (COVID-19) situation reports. Geneva, Switzerland: World Health Organization; 2020 [accessed 2020 Jul 30]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
3. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 2020;9: 727–732.
4. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al*.; ACTT-1 Study Group Members. Remdesivir for the treatment of COVID-19: final report. *N Engl J Med* [online ahead of print] 8 Oct 2020; DOI: 10.1056/NEJMoa2007764.
5. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al*.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19: preliminary report. *N Engl J Med* [online ahead of print] 17 Jul 2020; DOI: 10.1056/NEJMoa2021436.
6. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;323:1824–1836.
7. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda, MD: National Institutes of Health; 2020 [accessed 2020 May 28]. Available from: https://www.covid19treatmentguidelines.nih.gov/.
8. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, *et al*.; Asian Critical Care Clinical Trials Group. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med* 2020;8:506–517.
9. McGain F, Humphries RS, Lee JH, Schofield R, French C, Keywood MD, *et al*. Aerosol generation related to respiratory interventions and the effectiveness of a personal ventilation hood. *Crit Care Resusc* 2020; 22:212–220.
10. Rubulotta F, Soliman-Aboumarie H, Filbey K, Geldner G, Kuck K, Ganau M, *et al*. Technologies to optimize the care of severe COVID-19 patients for health care providers challenged by limited resources. *Anesth Analg* 2020;131:351–364.
11. Porta M, editor. *A dictionary of epidemiology.* Oxford, United Kingdom: Oxford University Press; 2014.
12. Wunsch H. Mechanical ventilation in COVID-19: interpreting the current epidemiology. *Am J Respir Crit Care Med* 2020;202:1–4.
13. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, *et al*. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med* 2020;201:1560–1564.
14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
15. Counotte M, Imeri H, Ipekci M, Low N. Living evidence on COVID-19. Berne, Switzerland: Institute of Social and Preventive Medicine:2020; [accessed 2020 Apr 23]. Available from: https://ispmbern.github.io/covid-19/living-review/index.html.
16. Counotte MJ, Egli-Gany D, Riesen M, Abraha M, Porgo TV, Wang J, *et al*. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: from systematic review to living systematic review. *F1000 Res* 2018;7:196.
17. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, *et al*. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. *BMJ* 2020;369: m1328.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Canada: The Ottawa Hospital Research Institute; 2019. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
19. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;14:25.
20. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; 72:39.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315: 629–634.
23. Boyle MH. Guidelines for evaluating prevalence studies. *Evid Based Ment Health* 1998;1:37–39.
24. Chen C, Jiang J, Xu X, Hu Y, Hu Y, Zhao Y. Dynamic liver function indexes monitoring and clinical characteristics in three types of COVID-19 patients [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.13.20099614v2.
25. Hu L, Chen S, Fu Y, Gao Z, Long H, Wang JM, *et al*. Risk factors associated with clinical outcomes in 323 COVID-19 hospitalized patients in Wuhan, China. *Clin Infect Dis* [online ahead of print] 3 May 2020; DOI: 10.1093/cid/ciaa539.
26. Hu K, Li B. Logistic regression analysis of death risk factors of patients with severe and critical coronavirus disease 2019 and their predictive value [in Chinese]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020;32: 544–547.
27. Hua J, Qian C, Luo Z, Li Q, Wang F. Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. *Crit Care* 2020;24:348.
28. Huang Y, Cai C, Zang J, Xie J, Xu D, Zheng F, *et al*. Treatment strategies of hospitalized patients with coronavirus disease-19. *Aging (Albany NY)* 2020;12:11224–11237.
29. Shime N; Japan ECMOnet for COVID-19. Save the ICU and save lives during the COVID-19 pandemic. *J Intensive Care* 2020;8:40.
30. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis* [online ahead of print] 22 May 2020; DOI: 10.1093/cid/ciaa624.
31. Liao X, Chen H, Wang B, Li Z, Zhang Z, Li W, *et al*. Critical care for severe COVID-19: a population-based study from a province with low case-fatality rate in China [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.22.20041277v4.

32. Nasir N, Mahmood SF, Habib K, Khanum I, Jamil B. Treatment of ARDS and hyperinflammation in COVID-19 with IL-6 antagonist Tocilizumab: a tertiary care experience from Pakistan [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.06.23.20134072v1.
33. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical care management of patients with COVID-19: early experience in Thailand. *Am J Trop Med Hyg* 2020;103:48–54.
34. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846–848.
35. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, *et al*. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;41:2070–2079.
36. Sirivongrangson P, Kulvichit W, Payungporn S, Pisitkun T, Chindamporn A, Peerapornratana S, *et al*. Endotoxemia and circulating bacteriome in severe COVID-19 patients [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.29.20109785v1.
37. Wang R, Pan M, Zhang X, Han M, Fan X, Zhao F, *et al*. Epidemiological and clinical features of 125 hospitalized patients with COVID-19 in Fuyang, Anhui, China. *Int J Infect Dis* 2020;95:421–428.
38. Wang T, Tang C, Chen R, Ruan H, Liang W, Guan W, *et al*. Clinical features of coronavirus disease 2019 patients with mechanical ventilation: a nationwide study in China. *Crit Care Med* 2020;48:e809–e812.
39. Wang J, Lu F, Zhou M, Qi Z, Chen Z. Tracheal intubation in patients with severe and critical COVID-19: analysis of 18 cases [in Chinese]. *Nan Fang Yi Ke Da Xue Bao* 2020;40:337–341.
40. Yang X, Cai S, Luo Y, Zhu F, Hu M, Zhao Y, *et al*. Extracorporeal membrane oxygenation for coronavirus disease 2019-induced acute respiratory distress syndrome: a multicenter descriptive study. *Crit Care Med* 2020;48:1289–1295.
41. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–481.
42. Ye C, Zhang S, Zhang X, Cai H, Gu J, Lian J, *et al*. Impact of comorbidities on patients with COVID-19: a large retrospective study in Zhejiang, China. *J Med Virol* [online ahead of print] 16 Jun 2020; DOI: 10.1002/jmv.26183.
43. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, *et al*.; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323:1488–1494.
44. Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, *et al*. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. *Crit Care* 2020;24:219.
45. Zhao J, Gao HY, Feng ZY, Wu QJ. A retrospective analysis of the clinical and epidemiological characteristics of COVID-19 patients in Henan Provincial People's Hospital, Zhengzhou, China. *Front Med (Lausanne)* 2020;7:286.
46. Zheng Y, Sun LJ, Xu M, Pan J, Zhang YT, Fang XL, *et al*. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. *J Zhejiang Univ Sci B* 2020;21:378–387.
47. Zhu Y, Du Z, Zhu Y, Li W, Miao H, Li Z. Evaluation of organ function in patients with severe COVID-19 infections. *Med Clin (Barc)* 2020;155:191–196.
48. Almazeedi S, Al Youha S, Jamal MH, Al-Haddad M, Al-Muhaini A, Al-Ghimlas F, *et al*. Clinical characteristics, risk factors and outcomes among the first consecutive 1,096 patients diagnosed with COVID-19: the Kuwait experience [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.09.20096495v1.
49. Goshayeshi L, Akbari Rad M, Bergquist R, Allahyari A, Hoseini B. Demographic and clinical characteristics of the severe Covid-19 infections: first report from Mashhad University of Medical Sciences, Iran [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.20.20108068v2.
50. Khamis F, Al-Zakwani I, Al Naamani H, Al Lawati S, Pandak N, Omar MB, *et al*. Clinical characteristics and outcomes of the first 63 adult patients hospitalized with COVID-19: an experience from Oman. *J Infect Public Health* 2020;13:906–913.
51. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect* 2020;26:1259.e5–1259.e7.
52. Shahriarirad R, Khodamoradi Z, Erfani A, Hosseinpour H, Ranjbar K, Emami Y, *et al*. Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. *BMC Infect Dis* 2020;20:427.
53. Alfano G, Ferrari A, Fontana F, Mori G, Magistroni R, Marianna M, *et al*. Incidence, risk factors and mortality outcome in patients with acute kidney injury in COVID-19: a single-center observational study [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.06.24.20138230v1.
54. Busetto L, Bettini S, Fabris R, Serra R, Dal Pra C, Maffei P, *et al*. Obesity and COVID-19: an Italian snapshot. *Obesity (Silver Spring)* 2020;28:1600–1605.
55. Ceruti S, Roncador M, Gie O, Bona G, Iattoni M, Biggiogero M, *et al*. Reduced mortality and shorten ICU stay in SARS-COV-2 pneumonia: a low PEEP strategy [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.03.20089318v1.
56. Santé Publique France. COVID-19 Point épidémiologique hebdomadaire du 2 June 2020. France: Santé Publique France; 2020 [accessed 2020 Jul 1]. Available from: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus.
57. Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, *et al*. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. *Pharmacol Res* 2020;158:104931.
58. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al*.; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323:1574–1581.
59. Intensive Care National Audit and Research Centre. ICNARC report on COVID-19 in critical care: 10 July 2020. London, United Kingdom: Intensive Care National Audit and Research Centre; 2020. Available from: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports.
60. Israelsen SB, Kristiansen KT, Hindsberger B, Ulrik CS, Andersen O, Jensen M, *et al*. Characteristics of patients with COVID-19 pneumonia at Hvidovre Hospital, March-April 2020. *Dan Med J* 2020;67:A05200313.
61. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis* 2020;50:281–286.
62. Pedersen HP, Hildebrandt T, Poulsen A, Uslu B, Knudsen HH, Roed J, *et al*. Initial experiences from patients with COVID-19 on ventilatory support in Denmark. *Dan Med J* 2020;67:A04200232.
63. Piano S, Dalbeni A, Vettore E, Benfaremo D, Mattioli M, Gambino CG, *et al*.; COVID-LIVER study group. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. *Liver Int* [online ahead of print] 11 Jun 2020; DOI: 10.1111/liv.14565.
64. Regina J, Papadimitriou-Olivgeris M, Burger R, Filippidis P, Tschopp J, Desgranges F, *et al*. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study [preprint]. *medRxiv* 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.11.20097741v1.
65. Ministerio de Ciencia e Innovacion. Informes COVID-19. Datos.gob.e: Ministerio de Ciencia e Innovación; 2020 [accessed 2020 Jul 1]. Available from: https://datos.gob.es/es.
66. Svenska Intensivvårdsregistret. COVID-19 på svenska intensivvårdsavdelningar. Sweden: Svenska Intensivvårdsregistret; 2020 [accessed 2020 Jul 13]. Available from: https://www.icuregswe.org/data–resultat/covid-19-i-svensk-intensivvard/.

67. Zangrillo A, Beretta L, Scandroglio AM, Monti G, Fominskiy E, Colombo S, *et al*. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc* [online ahead of print] 23 Apr 2020.
68. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. *Diagnosis (Berl)* 2020;7: 91–96.
69. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al*. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA* 2020;323:1612–1614.
70. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, *et al*. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ* 2020;369:m1996.
71. Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, *et al*.; Emory COVID-19 Quality and Clinical Research Collaborative. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020;48:e799–e804.
72. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al*. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382:2012–2022.
73. Buckner FS, McCulloch DJ, Atluri V, Blain M, McGuffin SA, Nalla AK, *et al*. Clinical features and outcomes of 105 hospitalized patients with COVID-19 in Seattle, Washington. *Clin Infect Dis* 2020; ciaa632.
74. Ferguson J, Rosser JI, Quintero O, Scott J, Subramanian A, Gumma M, *et al*. Characteristics and outcomes of coronavirus disease patients under nonsurge conditions, Northern California, USA, March-April 2020. *Emerg Infect Dis* 2020;26:1679–1685.
75. Garibaldi BT, Fiksel J, Muschelli J, Robinson ML, Rouhizadeh M, Nagy P. Patient trajectories and risk factors for severe outcomes among persons hospitalized for COVID-19 in the Maryland/DC region [preprint]. *medRxiv*; 2020 [accessed 2020 May 26]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.24.20111864v1.
76. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, *et al*. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:545–550.
77. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, *et al*. Clinical characteristics of COVID-19 in New York city. *N Engl J Med* 2020;382:2372–2374.
78. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Morbid obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. *Obesity* [online ahead of print] 23 May 2020. DOI: 10.1002/oby.22913.
79. Mani VR, Kalabin A, Valdivieso SC, Murray-Ramcharan M, Donaldson B. New York inner city hospital COVID-19 experience and current data: retrospective analysis at the epicenter of the American coronavirus outbreak. *J Med Internet Res* 2020;22:e20548.
80. La Secretaria de Salud. Informacion referente a casos COVID-19 en Mexico. Gobierno de México: La Secretaría de Salud; 2020 [accessed 2020 Jul 1]. Available from: https://datos.gob.mx/busca/dataset/informacion-referente-a-casos-covid-19-en-mexico.
81. Mitra AR, Fergusson NA, Lloyd-Smith E, Wormsbecker A, Foster D, Karpov A, *et al*. Baseline characteristics and outcomes of patients with COVID-19 admitted to intensive care units in Vancouver, Canada: a case series. *CMAJ* 2020;192:E694–E701.
82. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, *et al*. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism* 2020;108:154262.
83. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966.
84. Reyes Gil M, Gonzalez-Lugo JD, Rahman S, Barouqa M, Szymnaski J, Ikemura K, *et al*. Correlation of coagulation parameters with clinical outcomes in Coronavirus-19 affected minorities in United States: observational cohort [preprint]. *medRxiv*; 2020 [accessed 2020 May 6]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.01.20087932v1.
85. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al*.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA* 2020;323:2052–2059.
86. Salacup G, Lo KB, Gul F, Peterson E, De Joy R, Bhargav R, *et al*. Characteristics and clinical outcomes of COVID-19 patients in an underserved-inner city population: a single tertiary center cohort. *J Med Virol* [online ahead of print] 3 Jul 2020; DOI: 10.1002/jmv.26252.
87. Shekhar R, Upadhyay S, Sheikh A, Atencio J, Kapuria D. Early experience with COVD-19 patients at tertiary care teaching hospital in southwestern United States [preprint]. *medRxiv*; 2020 [accessed 2020 May 18]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.15.20094284v1.
88. Shi H, Zuo Y, Yalavarthi S, Gockman K, Zuo M, Madison JA, *et al*. Neutrophil calprotectin identifies severe pulmonary disease in COVID-19 [preprint]. *medRxiv*; 2020 [accessed 2020 Jul 15]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.06.20093070v3.
89. Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, *et al*. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Netw Open* 2020;3:e2012270.
90. Ministério da Saúde. SRAG 2020 - Banco de Dados de Síndrome Respiratória Aguda Grave - incluindo dados da COVID-19. Datasus: Ministério da Saúde; 2020 [accessed 2020 Jul 7]. Available from: https://opendatasus.saude.gov.br/dataset/bd-srag-2020.
91. Olivares F, Munoz D, Fica A, Delama I, Alvarez I, Navarrete M, *et al*. Covid-19 in Chile: the experience of a regional reference center. Preliminary report. *medRxiv*; 2020 [accessed 2020 Jun 16]. Available from: https://www.medrxiv.org/content/10.1101/2020.06.14.20130898v1.
92. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
93. Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, Slutsky AS, *et al*.; Toronto SARS Critical Care Group. Critically ill patients with severe acute respiratory syndrome. *JAMA* 2003;290: 367–373.
94. Gomersall CD, Joynt GM, Lam P, Li T, Yap F, Lam D, *et al*. Short-term outcome of critically ill patients with severe acute respiratory syndrome. *Intensive Care Med* 2004;30:381–387.
95. Al-Dorzi HM, Aldawood AS, Khan R, Baharoon S, Alchin JD, Matroud AA, *et al*. The critical care response to a hospital outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: an observational study. *Ann Intensive Care* 2016; 6:101.
96. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, *et al*. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014;29:301–306.
97. Masclans JR, Pérez M, Almirall J, Lorente L, Marqués A, Socias L, *et al*. Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect* 2013;19:249–256.
98. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al*.; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307: 2526–2533.
99. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* 2020;323:2329–2330.
100. Du RH, Liu LM, Yin W, Wang W, Guan LL, Yuan ML, *et al*. Hospitalization and critical care of 109 decedents with COVID-19 pneumonia in Wuhan, China. *Ann Am Thorac Soc* 2020;17: 839–846.
101. Zhang H-F, Bo L, Lin Y, Li F-X, Sun S, Lin H-B, *et al*. Response of Chinese anesthesiologists to the COVID-19 outbreak. *Anesthesiology* 2020;132:1333–1338.

102. Wang H, Feng J, Shao L, Wei J, Wang X, Xu X, *et al*. Contingency management strategies of the nursing department in centralized rescue of patients with coronavirus disease 2019. *Int J Nurs Sci* 2020;7:139–142.
103. Lee A, Cheung YSL, Joynt GM, Leung CCH, Wong WT, Gomersall CD. Are high nurse workload/staffing ratios associated with decreased survival in critically ill patients? A cohort study. *Ann Intensive Care* 2017;7:46.
104. European Society of Intensive Care Medicine. COVID-19: ICU nursing capacity and workload. 2020 [accessed 2020 Apr 7]. Available from: https://www.medscape.com/viewarticle/928162.
105. Rosenbaum L. Facing COVID-19 in Italy - ethics, logistics, and therapeutics on the epidemic's front line. *N Engl J Med* 2020;382: 1873–1875.
106. White DB, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. *JAMA* 2020;323: 1773–1774.
107. National Institute for Health and Care Excellence. COVID-19 rapid guideline: critical care in adults. London, United Kingdom: National Institute for Health and Care Excellence; 2020. Available from: https://www.nice.org.uk/guidance/ng159.
108. Sprung CL, Joynt GM, Christian MD, Truog RD, Rello J, Nates JL. Adult ICU triage during the coronavirus disease 2019 pandemic: who will live and who will die? Recommendations to improve survival. *Crit Care Med* 2020;48:1196–1202.
109. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates. *medRxiv*; 2020 [accessed 2020 Jul 7]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.03.20089854v4.
110. Nasiri MJ, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, *et al*. COVID-19 clinical characteristics, and sex-specific risk of mortality: systematic review and meta-analysis. *medRxiv*; 2020 [accessed 2020 Mar 26]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.24.20042903v1.
111. Cohen JF, Korevaar DA, Matczak S, Brice J, Chalumeau M, Toubiana J. COVID-19-related mortality by age groups in Europe: A meta-analysis. *medRxiv*; 2020 [accessed 2020 Apr 16]. Available from: https://www.medrxiv.org/content/10.1101/2020.04.11.20061721v1.
112. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia* 2020;75: 1340–1349.
113. Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. *Crit Care* 2020;24:285.
114. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38:1947–1953.