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COVID-19 in-hospital Mortality: A Concise Worldwide Review

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Abstract:

Background: The global burden of death due to Coronavirus-19 (COVID-19) is considerable. The average mortality for patients hospitalized with COVID-19 has not been reported. This data is important to serve as a benchmark to compare the outcomes of studies across the globe.

Methods: We performed a scoping review of studies across the globe that reported 28-day/hospital mortality. We include studies that enrolled consecutive, unselective patients with COVID-19 and excluded studies with less than 200 participants. Studies were grouped by geographic location, namely Asia, Europe, the USA, and South America. The primary endpoint was the 28-day/ hospital mortality. Comparison across geographic areas and pairwise analysis between groups were performed employing Kruskal-Wallis one-way analysis of variance.

Results: Fifty-three studies met our inclusion criteria, enrolling a total of 767 761 patients. There were 12 studies from Asia with a median mortality of 13 %, 21 studies from Europe with a median mortality of 23 %, 18 studies from the USA with a median mortality of 20 %, and 2studies from South America with a median mortality of 30.0 %. The overall median hospital mortality of all 53 studies was 21 %. The mortality differed significantly between regions ($p < 0.001$). Twenty-four studies reported the percentage of patients remaining in the hospital after 28 days; this averaged 18.5 ± 17.3 percent. The median age was 64 years (IQR 61, 67), with age differing significantly between regions ($p < 0.001$). There was a good correlation between the mean age of the subjects in each study and the hospital mortality (correlation coefficient 0.575, $p=0.000$). Overall, 57 % of patients were male and 21 % of patients were admitted to the ICU.

Conclusion: The median hospital mortality was 21% and this varied significantly across geographic regions. Due to the large percentage of patients still hospitalized at day 28, the real hospital mortality from COVID-19 is likely much higher, reflecting the high death toll of this disease. Coronavirus-19 disease (COVID-19) emerged from China toward the end of 2019 spreading rapidly to reach every nation across the globe. Approximately 20% of patients infected with SARS-CoV-2 require hospitalization with the disease-carrying a high hospital mortality. [1,2] The average mortality burden of hospitalized patients with COVID-19 has not been reported, nor has the variation across geographic areas been studied. This data is important in order to benchmark the outcomes of studies evaluating the hospital mortality of patients with COVID-19 as well as to understand geographic variations in reported hospital mortality.

Keywords: COVID-19; in-hospital mortality, review, age, world.

Introduction

Coronavirus-19 disease (COVID-19) emerged from China toward the end of 2019 spreading rapidly to reach every nation across the globe. Approximately 20 % of patients infected with SARS-CoV-2 require hospitalization with the disease carrying a high hospital mortality. **[1,2]**

The average mortality burden of hospitalized patients with COVID-19 has not been reported, nor has the variation across geographic areas been studied. This data is important in order to benchmark the outcomes of studies evaluating the hospital mortality of patients with COVID-19 as well as to understand geographic variations in reported hospital mortality.

Methods

We performed a comprehensive search of PubMed, Scopus, and Google Scholar for studies published between December 1, 2019, and December 1, 2020, reported in-hospital mortality for patients admitted to hospital with coronavirus-19 (COVID-19) disease. The following keywords were used for the search: ‘‘Coronavirus 2019’’, ‘‘COVID-19’’, ‘‘SARSCoV2’’, “hospital mortality”, “in-hospital mortality”, ‘‘mortality’’ and ‘‘all-cause mortality’’. We included only those studies that enrolled consecutive, non-selective patients admitted to the hospital with COVID-19 that reported 28-day or hospital mortality. We excluded studies that enrolled less than 200 patients and those limited to critically ill patients or any other specific demographic group. The studies were screened to avoid an overlap in patient populations. The following variables were recorded for each study; first author, country, sample size, number of hospitals providing data, date of the first day of enrollment, date of last day of enrollment, mean age, percentage of male patients, percentage of patients admitted to ICU, 28-day/hospital mortality, and percentage of patients still hospitalized at day 28. The countries were grouped as follows: Asia (including India and Iran), Europe, United States of America (USA) and South America.

The primary goal of the study was to compare the 28-day mortality across the four geographic areas; we calculated the median (IQR) 28-day/hospital mortality for each geographic group and for all studies combined. Further, we explored the differences among geographic groups in age, sex, percent of patients in the ICU, percent patients requiring mechanical ventilation (MV), percent of patients in the ICU, percent mortality on MV, percent ICU mortality, and percent of patients remaining in the hospital after 28 days. As most of the variables were not normally distributed, they are reported as the median and inter-quartile range (IQR). Comparison across geographic areas and pairwise analysis between groups were performed employing Kruskal-Wallis one-way analysis of variance. Pearson’s Bivariate analysis was employed to ascertain the possible relationship between 28-day mortality and age, male sex, percent of patients in the ICU, percent patients requiring mechanical ventilation (MV). Statistical analysis was performed using NCSS 2021 (Kaysville, Utah).

Results

After screening 1087 published reports, 53 studies from 11 countries met our inclusion criteria. **[3-55] [3-52] [53-55]** The studies listed by date of enrollment are provided in **Table 1**. Overall, 676 761 patients were enrolled in these studies. A large national database from Brazil contributed 38 % of patients (254 288 patients).**[17]** The hospital mortality and characteristics of the studies grouped by geographic region are provided in Table 2. While the hospital mortality varied from 3.1 % (China) to 43 % (Italy), the median mortality was 13 % for Asia, 23 % for Europe, 20 % for the USA, and 30 % for South America. The overall median hospital mortality of all 53 studies were 21 %. Twenty-four studies reported the percentage of patients remaining in the hospital after 28 days; this averaged 18 %. The median age was 64 years (IQR 61, 67). Overall, 57 % of patients were male and 21 % of patients were admitted to the ICU. There was a statistically significant difference across geographic groups in 28-day mortality, median age, gender, percentage of patients in the ICU, and percentage of patients receiving mechanical ventilation **(Table 2)**. Pairwise analysis of geographic areas demonstrated significant differences in 28-day mortality differing between USA-Europe, USA-Asia, Europe-Asia, and Asia-South America **(Table 2)**. Similarly, the pairwise analysis demonstrated significant differences in age between USA-Europe, USA-Asia, Europe-Asia, and Europe-South America. The utilization of ICU resources and the use of mechanical ventilation differed among geographic areas. Particularly striking is the difference in the use of MV between the USA and Asia. There was a good correlation between the mean age of the subjects in each study and the hospital mortality (correlation coefficient 0.575, p = 0.000; see **Figure 1**). The percentage of males in each study correlated poorly with hospital mortality (r = 0.25, p = 0.06).

Table 1. The studies listed by date of enrollment are:

Author	Country	n	n-hospitals	Date started	Duration Days	Age (yrs.)	Male (%)	ICU (%)	Mortality (%)
Guan [3]	China	1 590	575	12/11/2019	51	48.0	57.2	6.2	3.1
Wu [4]	China	201	1	12/25/2019	32	51.0	63	26.4	21.9
Zhang [5]	China	663	1	1/1/2020	36	55.0	48.0	-	3.8
Liu [6]	China	245	1	1/1/2020	59	53.9	46.5	-	13.8
Liu [7]	China	383	1	1/2/2020	59	46.0	42.3	-	12.9
Luo [8]	China	1 018	2	1/9/2020	82	61.0	51.2	17.0	19.7
Shi [9]	China	416	1	1/20/2020	21	64.0	49.3	-	13.7
Li [10]	China	548	1	1/26/2020	10	60.0	31.0	-	16.5

Cheng [11]	China	701	4	1/28/2020	14	63.0	52.0	10.4	16.1
Sbidian [12]	France	4 642	39	2/1/2020	65	66.1	59.0	2.6	22.5
Knight [13]	UK	35 463	260	2/6/2020	104	73.0	58.3	-	32.2
Docherty [14]	UK	20 133	208	2/6/2020	73	73.0	59.9	17.0	26.0
Lodigiani [15]	Italy	388	1	2/13/2020	57	66.0	68.0	16.0	26.0
Fried [16]	USA	11 721	208	2/15/2020	65	63.8	53.0	20.0	21.4
Ranzani [17]	Brazil	254 288	-	2/16/2020	181	60.0	56.0	39.0	38.0
Nikpouraghdam [18]	Iran	2 968	1	2/19/2020	56	55.0	66.0	-	8.0
Castelnuovo [19]	Italy	3 894	30	2/19/2020	94	67.0	61.7	-	18.2
Yehia [20]	USA	7 139	92	2/19/2020	102	68.0	51.3	40.0	20.3
Jalili [21]	Iran	28 981	1034	2/20/2020	60	57.3	56.0	-	24.4
Fumagalli [22]	Italy	516	2	2/22/2020	48	67.0	66.9	-	23.2
Ciceri [23]	Italy	950	1	2/25/2020	78	65.0	68.0	14.0	17.0
Vena [24]	Italy	317	1	2/25/2020	29	71.0	67.0	20.5	43.0
Karagiannidis [25]	Germany	10 021	920	2/26/2020	53	68.3	51.9	-	22.2
Navaratnam [26]	UK	91 541	500	3/1/2020	91	-	55.3	-	30.8
Byttebier [27]	Belgium	959	4	3/1/2020	152	69.2	54.5	-	15.6
Ahschul [28]	USA	2 355	10	3/1/2020	46	65.3	46.7	-	26.4
Bahl [29]	USA	1 461	8	3/1/2020	30	62.0	53.0	-	22.3
Redd [30]	USA	202	9	3/1/2020	32	63.0	55.0	17.5	15.8
Richardson [31]	USA	5 700	12	3/1/2020	31	63.0	60.3	14.2	21.0
Myers [32]	USA	377	21	3/1/2020	30	61.0	56.0	29.9	15.6
Petrilli [33]	USA	1999	4	3/1/2020	32	62.0	62.0	32.5	14.1
Kim [34]	USA	2491	154	3/1/2020	62	62.0	53.0	32.0	17.0
Nadkarni [35]	USA	4389	9	3/1/2020	60	65.0	56.0	-	24.0
Piroth [36]	France	89 530	-	3/1/2020	60	65.0	53.0	16.3	16.9
Marcolino [37]	Brazil	2054	25	3/1/2020	202	59.0	52.6	41.4	22.0
Ayerbe [38]	Spain	2075	17	3/1/2020	50	67.5	60.0	-	14.5
Goyal [39]	USA	393	2	3/3/2020	28	62.0	60.6	-	10.2
Garibaldi [40]	USA	832	5	3/4/2020	51	63.0	53.0	-	16.0
Berenguer [41]	Spain	4035	127	3/6/2020	11	70.0	61.0	18.5	28.0
Santus [42]	Italy	412	3	3/7/2020	61	66.0	68.0	-	25.5
Palaiodimos [43]	USA	200	-	3/9/2020	13	64.0	49.0	16.0	24.0
Guisado-Vasco [44]	Spain	607	1	3/10/2020	36	69.0	65.0	8.7	23.2
Arshad [45]	USA	2541	6	3/10/2020	53	64.0	51.0	24.2	18.1
Goodall [46]	UK	981	1	3/12/2020	34	69.0	64.0	-	36.0
Mikami [47]	USA	3708	8	3/13/2020	35	66.0	57.0	-	21.7
Catteau [48]	Belgium	8910	109	3/14/2020	48	71.0	54.5		21.6
Rosenberg [49]	USA	1438	25	3/15/2020	40	63.0	59.7	22.8	20.3
Chopra [50]	USA	1648	39	3/16/2020	107	62.0	51.8	13.2	24.2
Horby [51]	UK	6425	176	3/19/2020	81	66.0	64.0	-	24.6
Vizcaychipi [52]	UK	923	2	3/20/2020	33	67.0	61.7	15.0	32.0
Sasas-Rojo [53]	Spain	15 111	150	3/24/2020	98	69.4	57.2	8.3	21.0
Budhiraja [54]	India	976	5	4/1/2020	60	47.5	67.1	29.0	10.5
Rosenthal [55]	USA	35302	592	4/1/2020	60	63.3	53.4	19.4	20.3

Table 2 : Entire Cohort of studies : mortality and characteristics of hospitalized patients §

	USA (n=87660)	Europe(n=294069)	Asia(n=38690)	South America (Brazil) (n=256,312)	p
Age	63 (62,64) [18]	67 (66, 69) [21]	54 (48, 61) [12]	59 (44. 45) [2]	0.00001 ¶
% Male	51 (53, 58) [18]	61 (56,65) [21]	48 (58, 51) [12]	54 (39, 53) [2]	0.001
ICU (%)	20 (16, 32) [12]	16 (14,20) [10]	17 (8,28) [5]	40 (29, 31) [2]	0.043 ¶
MV (%)	18 (12, 22) [15]	15 (10, 17) [11]	8 (3,13) [7]	27 (17, 24) [2]	0.023 ¶
Hospital 28-day mortality (%)	20 (16, 23) [18]	23 (20, 29) [21]	13 (9, 17) [12]	30 (16, 29) [2]	0.00001 ¶
Ventilator Mortality (MV) (%)	46 (36, 71) [8]	40 (35, 59) [5]	*	80 [1]	0.46
ICU Mortality (%)	64 (37, 68) [2]	29 (20, 34) [2]	*	53 (35, 44) [2]	0.19
% Patients remaining in hospital	12 (6, 33) [8]	13 (9, 20) [12]	19 (6, 76) [3]	24 (9,38) [2]	0.22
Number of studies	18	21	12	2	

§ Median (IQR) [number of studies reported] * No data reported

¶ Pairwise differences between groups (p= less than 0.05)

Age: USA-Europe, Europe-Asia, USA-Asia, Europe-South American.

Gender: Europe-Asia; USA-Europe.

% **In ICU**: Europe-South America, Asia-South America.

% **on MV**: USA-Asia, Europe- South America, Asia- South America.

28-day mortality: USA-Europe, USA-Asia, Europe-Asia, Asia-South America

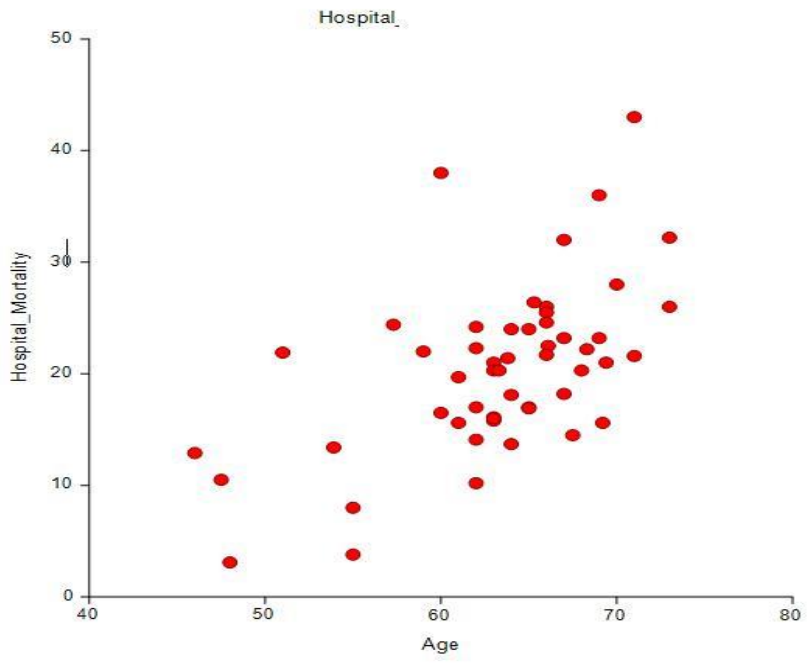

Figure 1. Plot of Age versus Hospital mortality

Discussion

The median in-hospital/28-day mortality for COVID-19 averaged 21 % across the globe. This mortality statistic is useful to compare studies that evaluate the outcomes of patients hospitalized with COVID-19. Due to the high percentage of patients remaining in hospital at day 28, the true hospital mortality is likely much higher and closer to 30%. Furthermore, we noted a marked variation in mortality between geographic regions across the globe. Strikingly, the average mortality was low in China (13 %) while it was high in South America-Brazil (30 %). The low mortality reported in the Chinese studies is likely related to the low median age of the patients (54 years; IQR 48-61) as well as hospital admission criteria (and hospital resources) which likely differed from other parts of the world. As has been demonstrated in previous studies, age is a major determinant of outcome

in patients hospitalized with COVID-19. **[56-58]** Although the incidence of comorbidities increases with aging, this alone does not completely explain the effect of age on mortality. A large meta-analysis that evaluated comorbidities and disease severity across geographic areas demonstrated that the proportion of the three major comorbidities diabetes mellitus, hypertension, and cardiovascular disease was highest in the USA compared to Europe and Asia, with Asia demonstrating the lowest proportional burden of comorbidities.**[59]** Despite this Asia was noted to have a higher degree of severity

of illness when compared with the burden of comorbidities. **[59,60]** One of the potential mechanisms to explain the increased mortality with aging is phenomenon is immunosenescence, whereby a failure to mount an effective adaptive immune response leads to the dysregulated release of cytokines. In addition, inflammation, a chronic low-grade inflammation that develops with advanced age may contribute to immune dysregulation and poorer outcome in elderly patients.**[58]** In the current study, it is noteworthy that the use of MV differed significantly between the USA and Asia. Multiple potential factors may account for this observation including the effect of age, more liberal admission criteria with lower severity of illness, and different approaches to the management of COVID-19 patients. The mortality of 38 % reported in the large national Brazilian study is noteworthy.**[17]** This is likely due to the large disease burden in this lower-middle-income country with regional disparities in the provision and accessibility of health care.

Conclusions

The median hospital mortality for COVID-19 averaged 21 %, however, this statistic varied widely by geographic area, being lowest in Asia and highest in South America. Furthermore, while patient's age and comorbidities as well as admission criteria influence hospital mortality, the accessibility of health care and availability of medical resources likely have a major impact on patient outcomes.

Declarations

Ethics approval: Not relevant

Availability of data: Available on request

Competing interests: None of the authors has any competing interests in the manuscript.

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