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Differential mortality with COVID-19 and invasive mechanical ventilation between high-income and low- and middle-income countries: a systematic review, meta-analysis, and meta-regression

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SUMMARY

The COVID-19 pandemic has markedly affected the health care of patients in low- and middle-income countries (LMICs), but no systematic study to corroborate this effect has been undertaken. In addition, the survival outcomes of patients with COVID-19 who received invasive mechanical ventilation (IMV) have not been well established. We pooled evidence from all available studies and did a systematic review and meta-analysis to assess and compare mortality outcomes between LMICs and high-income countries (HICs). We searched MEDLINE and the University of Michigan Library according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from December 1, 2019, to July 15, 2021, for case-control studies, cohort studies, and brief reports that discussed mortality ratios and survival outcomes among patients with SARS-CoV-2 who received IMV. We excluded studies and case reports without comparison groups, narrative reviews, and preprints. A random-effects estimate of the arcsine square root transformation (PAS) of each outcome was generated with the DerSimonian-Laird method. Seven eligible studies, consisting of 243,835 patients with COVID-19, were included. We identified a significantly higher mortality rate (*i.e.*, a larger PAS) among the patients receiving IMV in LMICs (PAS, 0.754; 95% CI, 0.569-0.900; *P*<.001) compared to patients in HICs (PAS, 0.588; 95% CI, 0.263-0.876; *P*<.001). Considerable heterogeneity was present within the individual subgroups possibly because of the extent of the included studies, which had data from specific countries and states but not from individual hospitals or health care centers. Moreover, the sample population in each study was diverse. Meta-regression showed that a higher mortality rate among patients with COVID-19 who received IMV in both HICs (*P*<.001) and LMICs (*P*=.04) was associated with chronic pulmonary disease. Our study suggests that chronic pulmonary diseases and poor demographics lead to a worse prognosis among patients with COVID-19 who received IMV. Moreover, the survival outcome is worse in LMICs, where health care systems are usually understaffed and poorly financed.

Keywords: COVID-19, invasive mechanical ventilation, invasive respiratory support, meta-analysis, mortality outcome.

INTRODUCTION

The COVID-19 pandemic has had remarkable effects on health care systems and socioeconomic structures. It has greatly increased the number of hospitalizations for pneumonia and multiorgan illnesses worldwide. Approximately 5% of patients with COVID-19 have symptoms that require hospitalization, and 20% of those that are hospitalized have severe symptoms that necessitate intensive care [1].

Although invasive mechanical ventilation (IMV) has been associated with increased mortality events in critically ill patients owing to ventilator-induced lung injury, its outcomes in patients with COVID-19 have not been well established [2]. A published review suggested that mortality rates were higher among patients with COVID-19 who were receiving IMV, but the differences among various health systems were unclear [3].

In most studies the primary outcome has been mortality according to patient demographics with appropriate sample sizes [4-9]. However, the sample sizes were small for measurement of the effect of IMV on dichotomous variables such as mortality. Ranzani et al, in the largest study of the mortality rate among patients with COVID-19 in Brazil, showed that mortality was higher among patients who received IMV [10]. However, it is unclear whether these findings are specific to a particular health system or certain countries. Therefore, we aimed to pool evidence from all the available studies that discussed the survival outcomes of patients infected with COVID-19 who received IMV. We sought a broad view of the outcome by pooling data of entire countries and comparing the results between high-income countries (HICs) and low- and middle-income countries (LMICs).

METHODS

Data sources and search strategy

We performed the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. We electronically searched the MEDLINE and University of Michigan (UoM) Library databases from December 1, 2019, to July 15, 2021, without any language restrictions. The search string for MEDLINE is shown in the Table 1. The search string for the UoM Library was as follows: outcomes and covid-19 and invasive ventilation or respiratory support and low-income countries or middle-income countries and high-income countries. In addition, we manually searched for relevant studies on the internet.

Study selection

Randomized controlled trials, case-control studies, cohort studies, and brief case series were eligible for inclusion. We excluded studies without proper comparison groups, narrative reviews, and preprint papers.

Data extraction and quality assessment of studies

We imported articles retrieved from the systematic search and exported them to EndNote reference library software (Thomson Reuters), where duplicates were identified and removed. Abstracts and likely relevant full texts were screened by 2 coauthors working independently (A.K. and M.K.K.). A third coauthor (H.A.H.) was consulted for decisions about any discrepancies. From the included studies, we extracted the following outcome: prognosis of patients infected with COVID-19 who received IMV. Two coauthors working independently (H.A.H. and M.K.K.) scored each study according to the Newcastle-Ottawa Scale for cohort studies on 3 diverse characteristics: selection of study groups, comparability of groups, and ascertainment of the outcome of interest.

Statistical analysis

OpenMetaAnalyst (MetaMorph, Inc) was used for all statistical analyses [12]. We divided the studies according to World Bank classifications into *high-income* or *low- and middle-income* groups. The World Bank categorizes countries into 2 groups on the basis of gross national income per capita: developing countries and developed countries. A *developing country* is one that has a less developed industrial base and a low Human Development Index. The World Bank classifies LMICs as developing countries and HICs as developed countries [13]. Therefore, we categorized studies that discussed LMICs into only 1 subgroup and studies

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that discussed HICs into a different subgroup (Tables 2 and 3) [4-10].

We performed 1-arm analysis of the pooled studies because all our pooled studies had a cohort design. Moreover, the included studies reported a 1-arm analysis discussing the survival of patients who received IMV. For these reasons, we performed a 1-arm analysis, which helped to minimize confounding bias. The results from the studies were represented as raw data with 95% CIs.

Table 1 - Search String for MEDLINE.

((“outcome”[All Fields] OR “outcomes”[All Fields]) AND (“covid 19”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19 vaccines”[All Fields] OR “covid 19 vaccines”[MeSH Terms] OR “covid 19 serotherapy”[All Fields] OR “covid 19 serotherapy”[Supplementary Concept] OR “covid 19 nucleic acid testing”[All Fields] OR “covid 19 nucleic acid testing”[MeSH Terms] OR “covid 19 serological testing”[All Fields] OR “covid 19 serological testing”[MeSH Terms] OR “covid 19 testing”[All Fields] OR “covid 19 testing”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[MeSH Terms] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR ((“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND (“invasibility”[All Fields] OR “invasible”[All Fields] OR “invasion”[All Fields] OR “invasions”[All Fields] OR “invasive”[All Fields] OR “invasively”[All Fields] OR “invasiveness”[All Fields] OR “invasives”[All Fields] OR “invasivity”[All Fields]) AND (“ventilated”[All Fields] OR “ventilates”[All Fields] OR “ventilating”[All Fields] OR “ventilation”[MeSH Terms] OR “ventilation”[All Fields] OR “ventilate”[All Fields] OR “ventilations”[All Fields] OR “ventilator s”[All Fields] OR “ventilators, mechanical”[MeSH Terms] OR (“ventilators”[All Fields] AND “mechanical”[All Fields]) OR “mechanical ventilators”[All Fields] OR “ventilator”[All Fields] OR “ventilators”[All Fields] OR “ventilation”[All Fields])) OR (“respiratory”[All Fields] AND (“support”[All Fields] OR “support s”[All Fields] OR “supported”[All Fields] OR “supporter”[All Fields] OR “supporter s”[All Fields] OR “supporters”[All Fields] OR “supporting”[All Fields] OR “supportive”[All Fields] OR “supportiveness”[All Fields] OR “supports”[All Fields]) AND (“poverty”[MeSH Terms] OR “poverty”[All Fields] OR (“low”[All Fields] AND “income”[All Fields]) OR “low income”[All Fields]) AND (“countries”[All Fields] OR “country”[All Fields]) OR (“middle-income”[All Fields] AND (“countries”[All Fields] OR “country”[All Fields] OR “country s”[All Fields]) AND “high-income”[All Fields] AND (“countries”[All Fields] OR “country”[All Fields] “[All Fields]) AND (“addition”[All Fields] OR “additional”[All Fields] OR “additions”[All Fields] OR “additive”[All Fields] OR “additively”[All Fields] OR “additives”[All Fields] OR “additivities”[All Fields] OR “additivity”[All Fields]) AND (“manual s”[All Fields] OR “manualization”[All Fields] OR “manualized”[All Fields] OR “manually”[All Fields] OR “manuals as topic”[MeSH Terms] OR (“manuals”[All Fields] AND “topic”[All Fields]) OR “manuals as topic”[All Fields] OR “manual”[All Fields] OR “manuals”[All Fields]) AND (“looked”[All Fields] OR “looking”[All Fields] OR “looks”[All Fields]) AND (“relevance”[All Fields] OR “relevances”[All Fields] OR “relevancies”[All Fields] OR “relevancy”[All Fields] OR “relevant”[All Fields]) AND (“studies”[All Fields] OR “study”[All Fields] OR “study s”[All Fields] OR “studying”[All Fields) AND (“internet”[MeSH Terms] OR “internet”[All Fields] OR “internet s”[All Fields] OR “internets”[All Fields]))

Table 2 - Studies from high-income countries.

		Patients receiving IMV, No.		*Patients not receiving IMV, No.*	
Study, year	*Study type*	*Total*	*Died during IMV*	*Total*	*Died*
Richardson et al., 2020 [6]	Observational study	320	282	2,314	271
Kim et al., 2021 [5]	Surveillance report	462	246	2,028	174
Pouw et al., 2021 [4]	Retrospective cohort	129	39	823	200

Abbreviation: IMV, invasive mechanical ventilation.

Table 3 - Studies from low- and middle-income countries.

		Patients receiving IMV, No		*Patients not receiving IMV, No.*	
Study, year	*Study type*	*Total*	*Died during IMV*	*Total*	*Died*
Baqi et al., 2021 [9]	Observational study	57	53	195	42
Ranzani et al., 2021 [10]	Retrospective cohort	45,205	36,046	186,831	51,469
Surendra et al., 2021 [8]	Retrospective cohort	55	39	4,210	458
Ferreira et al., 2021 [7]	Cohort	1,180	628	16	3

Abbreviation: IMV, invasive mechanical ventilation.

A random-effects estimate of the arcsine square root transformation (PAS) for each outcome was generated with the use of the DerSimonian-Laird method. Given that individual health care systems, demographics, financial backgrounds, and co-morbidities can affect mortality outcomes, we performed sensitivity analysis by removing each study 1 by 1 and then rechecking the precision of the outcome. Heterogeneity across the studies was measured with Higgins I^2, and a value greater than 50% was considered substantial. We could not decrease the heterogeneity in individual subgroups because the sample population was too diverse. To assess the high heterogeneity, meta-regression was performed with use of the PAS for the covariate chronic pulmonary diseases. This variable was specified because it was the most frequently reported comorbidity among the pooled studies. *P* values less than .05 were considered statistically significant.

RESULTS

Literature search

An initial literature search of 2 databases yielded 1,171 studies. After exclusions, 7 studies were included for analysis (Figure 1) [4-10].

Study characteristics and quality assessment

Our studies had a total of 243,835 patients with COVID-19, and 47,408 of these patients were in the IMV group. All studies had considerably high methodological quality. We included only studies published from May 2020 onward because that was when the Centers for Disease Control and Prevention released uniform guidelines to treat patients with COVID-19 [14]. These guidelines provide instructions related to management of COVID-19 patients according to disease severity. We believe that most of the patients included in the studies were treated according to these

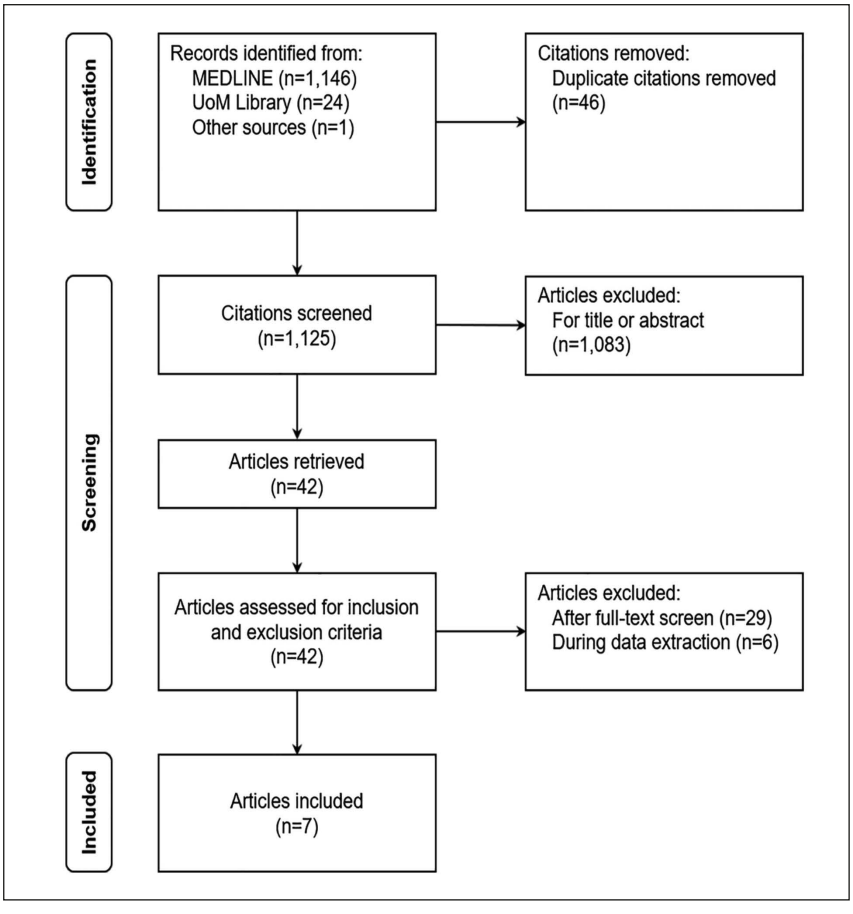

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart of Study Selection. UoM indicates University of Michigan.

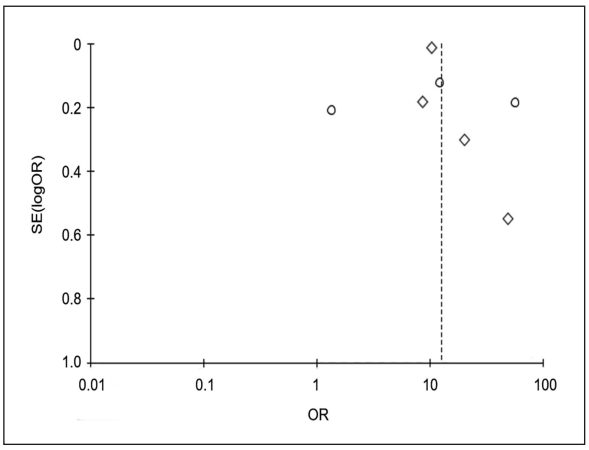

Figure 2 - Funnel Plot. Symmetry indicates an absence of publication bias. Black circles represent high-income countries; red diamonds, low- and middle-income countries. OR indicates odds ratio.

guidelines. This helped to considerably decrease confounding bias. The sample size cutoff for inclusion was set at 100 patients. A symmetric funnel plot indicated an absence of publication bias (Figure 2).

Meta-analysis

The encapsulated results of our meta-analysis are shown in Figure 3 [4-10]. We identified a significantly increased mortality rate (*i.e.*, a larger PAS) among patients receiving IMV in LMICs (PAS, 0.754; 95% CI, 0.569-0.900; *P*<.001) compared to patients in HICs (PAS, 0.588; 95% CI, 0.263-0.876; *P*<.001).

Meta-regression

HIC Subgroup

Meta-regression showed that the poor prognostic effects of IMV among patients with COVID-19 are affected by chronic pulmonary diseases (*P*<.001), such as asthma and chronic obstructive pulmonary disease. The bubble plot for the HIC subgroup is shown in Figure 4.

LMIC Subgroup

Our meta-regression for the studies included in the LMIC subgroup excluded the study by Ranzani et al because it did not report co-morbidities of patients [10]. We found similar results; the survival of patients with COVID-19 who received

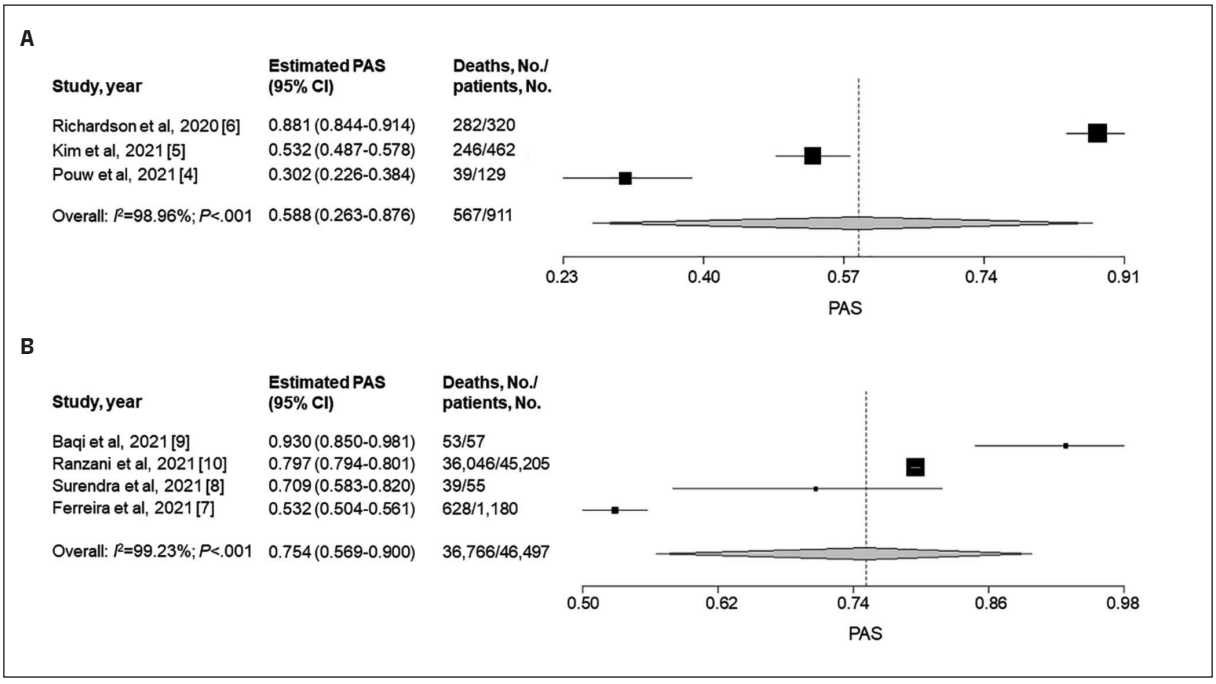

Figure 3 - Results of Meta-analysis. The forest plots represent results of a 1-arm analysis of studies reporting mortality rates among patients with COVID-19 who received invasive mechanical ventilation in high-income countries (A) or in low- and middle-income countries (B). The squares and horizontal lines correspond to the study-specific arcsine square root transformation (PAS) and 95% CIs. The vertical dashed line indicates the overall pooled PAS.

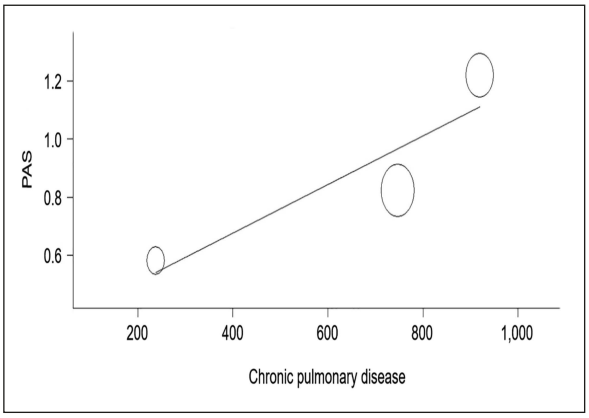

Figure 4 - Bubble plot for patients with COVID-19 who received invasive mechanical ventilation in high-income countries. The covariate was chronic pulmonary disease. PAS indicates arcsine square root transformation.

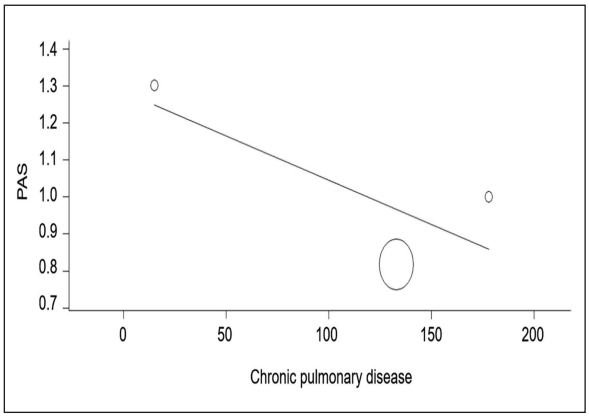

Figure 5 - Bubble plot for patients with COVID-19 who received invasive mechanical ventilation in low- and middle-income countries. The covariate was chronic pulmonary disease. PAS indicates arcsine square root transformation.

IMV was also affected by chronic pulmonary diseases (P=.04). The bubble plot for the LMIC subgroup is shown in Figure 5.

DISCUSSION

This systematic review encapsulates the available global data for HICs and LMICs on the differential mortality of patients with COVID-19 who received IMV. Previous retrospective analyses have demonstrated poor survival among patients receiving IMV [5-11]. Additionally, a previous meta-analysis showed a 43% mortality rate for patients receiving IMV [15]. However, the present study is the first systematic review to compare mortality outcomes between patients in HICs and patients in LMICs. Our study found statistically significant higher mortality rates among patients with COVID-19 who received IMV in the LMIC subgroup than in the HIC subgroup.

Meta-regression showed that the prognostic outcomes are worsened by chronic lung diseases. These diseases are among the most prevalent diseases globally, especially in LMICs where lower respiratory tract infections are quite common, and this appears to be a reason for poorer survival outcomes in LMICs [16, 17].

After meta-analysis, PAS values in the forest plot suggest that mortality is lower in HICs. The most probable reason for that finding is the increased prevalence of co-morbidities in LMICs [18]. We also argue that this finding could have resulted from delayed decision making by the LMIC governments for timely action and handling of the disease and from the sense of disbelief and denial about COVID-19 among the people during the early days of the pandemic. A factor behind this mistrust appears to be that religious organizations in various countries spread misinformation [19]. This is particularly remarkable because no individual study has reported this finding, and it was only divulged on pooling the results. Moreover, delayed vaccine rollout could have been a factor because it has been shown that vaccine efficacy can be markedly affected by the success or failure of quick introduction of a trusted vaccine to the public, which could lead to adverse outcomes in terms of increased rates of infection, hospitalizations, and deaths [20].

The strengths of the study include the extensive search, which was not restricted by language, and the incorporation and synthesis of a broad range of literature.

The major limitations in our study are the retrospective design of the included studies and the heterogeneity of the study populations in terms of physical status, comorbidities, or disease severity in addition to the broad inclusion criteria of our study and the use of studies with pooled data from countries rather than single-center data. Moreover, this systematic review and meta-analysis was not registered in the international prospective register of systematic reviews (PROSPERO).

In conclusion, data from LMICs, in contrast to HICs, showed a significantly increased mortality rate for patients with COVID-19 who received IMV. This result could be attributed to understaffed and poorly funded health care systems in LMICs in addition to delayed vaccine distribution. It is a stark reminder of the differences in quality between health care systems in HICs and LMICs, and these differences should be addressed.

This systematic review also confirms that chronic pulmonary diseases are associated with worse outcomes in patients with COVID-19 who receive IMV.

Author contributions

A.K., H.A.H., M.K.K., and S.A.K. contributed to the concept or design of the manuscript. A.K., H.A.H., and M.K.K. contributed to the extraction of the data. A.K., H.A.H., and M.K.K. contributed to the analysis. A.K., H.A.H., M.K.K., J.P.D.G., N.K.J., T.K., and S.A.K. contributed to the interpretation of the analysis. A.K., H.A.H., I.R., M.K.K., H.A.M., H.S.L., and T.K. drafted the manuscript. All authors critically revised the work and gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REFERENCES

[1] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020; 324 (8), 782-93.

[2] Serpa Neto A, Deliberato RO, Johnson AEW, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med*. 2018; 44 (11), 1914-22.

[3] Tsikala Vafea M, Zhang R, Kalligeros M, Mylona EK, Shehadeh F, Mylonakis E. Mortality in mechanically ventilated patients with COVID-19: a systematic review. *Expert Rev Med Devices*. 2021; 18 (5), 457-71.

[4] Pouw N, van de Maat J, Veerman K, et al. Clinical characteristics and outcomes of 952 hospitalized COVID-19 patients in The Netherlands: A retrospective cohort study. *PLoS One*. 2021; 16 (3), e0248713.

[5] Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis*. 2021; 72 (9), e206-e14.

[6] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020; 323 (20), 2052-9.

[7] Ferreira JC, Ho YL, Besen B, et al. Protective ventilation and outcomes of critically ill patients with COVID-19: a cohort study. *Ann Intensive Care*. 2021; 11 (1), 92.

[8] Surendra H, Elyazar IR, Djaafara BA, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. *Lancet Reg Health West Pac*. 2021; 9, 100108.

[9] Baqi S, Naz A, Sayeed MA, et al. Clinical characteristics and outcome of patients with severe COVID-19 pneumonia at a public sector hospital in Karachi, Pakistan. *Cureus*. 2021; 13 (2), e13107.

[10] Ranzani OT, Bastos LSL, Gelli JGM, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med*. 2021; 9 (4), 407-18.

[11] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009; 339, b2700.

[12] Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *J Stat Softw*. 2012; 49 (5), 1 - 15.

[13] The World Bank. World development indicators. Washington, DC: International Bank for Reconstruction and Development/The World Bank; 2014. Available at: https://openknowledge.worldbank.org/bitstream/handle/10986/18237/9781464801631.pdf?sequence=1&isAllowed=y. [Accessed 1 October 2021].

[14] Centers for Disease Control and Prevention, US Department of Health & Human Services. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Atlanta (GA): Centers for Disease Control and Prevention; 2021. Available at:

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. [Accessed 2022 Jan 14].
[15] Chang R, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes. A systematic review and meta-analysis. *PLoS One*. 2021; 16 (2), e0246318.
[16] Hurd SS, Pauwels R. Global Initiative for Chronic Obstructive Lung Diseases (GOLD). *Pulmonary Pharmacology & Therapeutics*. 2002; 15(4), 353-5.
[17] GBD LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017; 17 (11), 1133-61.
[18] Singh AK, Misra A. Impact of COVID-19 and comorbidities on health and economics: Focus on developing countries and India. *Diabetes Metab Syndr*. 2020; 14 (6), 1625-30.
[19] Bok S, Martin DE, Lee M. Validation of the COVID-19 Disbelief Scale: Conditional indirect effects of religiosity and COVID-19 fear on intent to vaccinate. *Acta Psychol (Amst)*. 2021; 219, 103382.
[20] Paltiel AD, Schwartz JL, Zheng A, Walensky RP. Clinical Outcomes Of A COVID-19 Vaccine: Implementation Over Efficacy. *Health Aff (Millwood)*. 2021; 40 (1), 42-52.