

ORIGINAL RESEARCH



Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis

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ABSTRACT

Objectives: The acute respiratory distress syndrome (ARDS) secondary to viral pneumonitis is one of the main causes of high mortality in patients with COVID-19 (novel coronavirus disease 2019). We systematically reviewed mortality in COVID-19 patients with ARDS and the potential role of systemic corticosteroids in COVID-19 patients.

Methods: Electronic databases and country-specific healthcare databases were searched to identify relevant studies/reports. The quality assessment of individual studies was conducted using the Newcastle–Ottawa Scale. Country-specific proportion of individuals with COVID-19 who developed ARDS and reported death were combined in a random-effect meta-analysis to give a pooled mortality estimate of ARDS.

Results: The overall pooled mortality estimate among 10,815 ARDS cases in COVID-19 patients was 39% (95% CI: 23–56%). The pooled mortality estimate for China was 69% (95% CI: 67–72%). In Europe, the highest mortality estimate among COVID-19 patients with ARDS was reported in Poland (73%; 95% CI: 58–86%) while Germany had the lowest mortality estimate (13%; 95% CI: 2–29%) among COVID-19 patients with ARDS. The median crude mortality rate of COVID-19 patients with reported corticosteroid use was 28.0% (lower quartile: 13.9%; upper quartile: 53.6%).

Conclusions: The high mortality in COVID-19 associated ARDS necessitates a prompt and aggressive treatment strategy which includes corticosteroids. Most of the studies included no information on the dosing regimen of corticosteroid therapy, however, low-dose corticosteroid therapy or pulse corticosteroid therapy appears to have a beneficial role in the management of severely ill COVID-19 patients.

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1. Introduction

A novel coronavirus, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in late 2019 as the causative pathogen for an outbreak of severe pneumonia cases in Wuhan, China, later referred to as novel coronavirus disease 2019 (COVID-19). The unprecedented rate at which COVID-19 is spreading across the globe has perhaps surprised most of the epidemiologists in the world, which may be related to difficulties in the identification of asymptomatic SARS-CoV-2 carrier. While some patients had a relatively mild course of the disease, showing little or no symptoms, it was reported that about 20% of COVID-19 patients required hospitalization, mainly due to severe respiratory manifestations [1–7]. The major morbidity and mortality of hospitalized COVID-19 patients are attributed to acute viral pneumonitis leading to acute respiratory distress syndrome (ARDS) [1,2,8–10]. Based on the previously reported experience with SARS outbreak in 2003, a substantial number of patients (15–49%) developed respiratory failure leading to ARDS, with a mortality rate of 13–64% [11–14]. While SARS-CoV-2 is more contagious

than SARS-CoV, the overall estimated case fatality rate of COVID-19 to date was lower than the SARS (0.82–9.64% versus 11%), and thus it is difficult to predict the fatality rate of COVID-19 patients upon the development of ARDS based on extrapolation from SARS patients [15,16]. Besides, there have been advancements in the management of ARDS since the SARS outbreak which occurred 17 years ago which may lead to more favorable clinical outcomes among COVID-19 patients with ARDS.

Corticosteroids were widely used during the 2002–03 outbreak of SARS in Mainland China and Hong Kong [17]. It was postulated that corticosteroid treatment may improve tissue injury in SARS caused by uncontrolled production of pro-inflammatory cytokines (e.g., interferon-gamma, tumor necrosis factor, interleukins (IL)-1 and IL-6) as an inflammatory response to viral infection [18,19]. A systematic review of 29 studies on corticosteroid use in patients with SARS [20] reported possible harms from corticosteroid use which include delayed virus clearance, increased risk of SARS-related psychosis, diabetes, and avascular necrosis. This has led to the WHO's

Article highlights

- Severe bilateral pneumonia developing into acute respiratory distress syndrome (ARDS) is one of the determinant factors for increased mortality in coronavirus disease 2019 (COVID-19).
- This systematic review and meta-analysis of original studies and country-specific reports assessed the mortality among COVID-19 patients with ARDS and to review the potential role of corticosteroids in COVID-19.
- Relatively high mortality was found with COVID-19 associated ARDS which demands an aggressive therapeutic intervention to prevent deaths.
- Despite the concerns that corticosteroids may hamper virus clearance, the low dose corticosteroids appear to have a role in the management of severely ill COVID-19 patients.

recommendation to avoid the routine use of systemic corticosteroid in COVID-19 beyond clinical trials [21]. However, closer scrutiny of the 2006 systematic review [20] revealed that the findings of most of the included studies reporting the efficacy of corticosteroids use were inconclusive, and thus it may be too early to discard corticosteroid therapy in our armamentarium against COVID-19.

Similar to SARS, it has recently been recognized that the pathophysiology of COVID-19 also involves the overproduction of proinflammatory cytokines, termed cytokine storm, that leads to enhanced vascular hyperpermeability which often triggers ARDS and hence the interest in exploring the role of corticosteroids in mitigating cytokine storm and its associated complications [22]. Specifically, in patients who develop ARDS, stimulation of glucocorticoid receptor with corticosteroids could down-regulate systemic and pulmonary inflammation, which is important to restore tissue homeostasis by accelerating resolution of diffuse alveolar damage and extrapulmonary organ dysfunction [23,24]. It is, therefore, important to revisit the recommendation for corticosteroid use in COVID-19 based on the most recent evidence. This article aimed to estimate the mortality among COVID-19 patients with ARDS and the effects of corticosteroid use on mortality. The article also provides a critical review of the potential roles of systemic corticosteroids in COVID-19, especially in terms of reducing ARDS-associated mortality, based on the currently available evidence to date.

2. Methods

2.1. Search strategy

This systematic review was conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [25]. The following electronic literature databases were searched within March to July 2020 to identify eligible articles published in either English or Chinese languages between 1 December 2019 and 10 July 2020: PubMed (United States National Library of Medicine), Dimensions [26], and Google Scholar. We used the following search terms: ‘acute respiratory distress syndrome OR ARDS OR glucocorticoid* OR corticosteroid* OR methylprednisolone’ AND ‘COVID-19 OR coronavirus disease 2019 OR

novel coronavirus OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2’. We also performed a manual search of the reference list of included studies to avoid the omission of any eligible study. Furthermore, we searched country-specific healthcare databases or public reports to identify original data that met the eligibility criteria.

Two authors (SSH, CSK) independently screened the PubMed and Google Scholar, two authors (SSH & HAM) screened the Dimensions database, and two authors (SSH and FM) screened the country-specific healthcare databases and public reports, to identify relevant articles. CSK assessed all the studies or reports published in the Chinese language (CSK’s native language). At the first stage, we screened the titles and abstracts to filter out the studies that were irrelevant to the aim of the review. In the next stage, potentially relevant articles and reports were accessed for full-text review. In case of any discrepancies and doubts about the relevance of the sources, a third author was involved to resolve by consensus.

2.2. Inclusion and exclusion criteria

Studies or reports eligible for our systematic review included peer-reviewed studies of any design (randomized controlled trial, prospective, retrospective, cohort, case-control, case series, narrative review, country-specific public reports) which reported or consisted of original data on (i) the mortality rate of COVID-19 patients who developed ARDS; or (ii) the mortality rate of COVID-19 patients (with or without ARDS) who reported to have received systemic corticosteroids treatment. We excluded preprints that were yet to complete peer-review process, editorials, correspondences, and commentaries, as well as any overlapping or duplicate studies. Studies involving only pediatric patients or patients with only certain comorbidities (eg, cancer, liver cirrhosis) which may not reflect the true mortality rates were also excluded. We excluded studies which reported inhaled corticosteroids use since they were most likely to be indicated for underlying chronic respiratory diseases instead of indicated for COVID-19 treatment, and the systemic effects of inhaled corticosteroids are limited.

2.3. Quality assessment

The quality assessment of individual studies was conducted using the Newcastle–Ottawa Scale (NOS) for cohort studies because of the unavailability of quality assessment tool for retrospective studies [27]. The NOS is easy to use with its star rating system and considered reliable to measure biases in cohort studies. Each of the selected retrospective cohort studies was evaluated for selection of study group (0–4 stars), comparability or quality of adjustment for confounding factors (0–2 stars), and ascertainment of the outcome of interest (0–3 stars), with a maximum of nine stars representing the highest methodological quality. Pairs of authors independently conducted the quality assessment for each included original study. Any disagreements were discussed between the two authors, and a third author was involved to reach a final judgment where required.

2.4. Data extraction and analysis

The relevant data from all the retrieved studies and reports were extracted, and systematically collected and tabulated using Microsoft Excel and are presented in Table 1. The extracted information included the name of the first author or institutes, country, and region, study type, study site, age, study period, the total number of patients, number of patients with ARDS, number of deaths in patients with ARDS, number of patients receiving corticosteroid therapy, and the number of deaths in patients receiving corticosteroid therapy.

The outcome measure was the pooled mortality estimate among individuals with COVID-19 who developed ARDS. Due to uncertainty and heterogeneity in terms of indications, dosing regimen, disease stage at which corticosteroid was administered, and the type of corticosteroid used, the mortality among individuals with COVID-19 who received corticosteroid therapy could not be pooled in a meta-analysis. Thus, mortality among individuals with COVID-19 who received corticosteroid therapy in each study was presented as descriptive statistics, with critical review and discussion on the role of corticosteroid therapy in COVID-19. All meta-analytical calculations were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia) [28]. The proportion of individuals with COVID-19 who developed ARDS and reported death in each country was first calculated, before combining country-specific proportions to give a pooled mortality estimate of ARDS across all countries. Subgroup analysis of mortality estimate of ARDS was performed by pooling studies from Asia and from Europe only. We employed a random-effects model to estimate the pooled mortality of COVID-19 associated ARDS and to generate a forest plot of the pooled mortality estimate with 95% confidence intervals (CIs) [29]. We examined the heterogeneity between studies using the I^2 statistics with 50% and the χ^2 test with $p < 0.10$, as the thresholds for statistically significant heterogeneity [30].

3. Results

3.1. Search results

Our search yielded 17,046 titles from the selected databases (Figure 1), of which 8,893 titles were duplicates. The remaining 8,153 records were screened as per PRISMA guidelines against the eligibility criteria described in the previous section. A total of 7,808 records were excluded after reading the title and abstract. The full texts of the remaining 345 articles were retrieved for a detailed evaluation. We finally identified 37 articles for the qualitative synthesis [31–67].

Amongst these 37 articles, 26 articles (25 original studies and 1 narrative review) reported mortality in COVID-19 patients with ARDS (with or without corticosteroid use) and were selected for further quantitative analysis [31–36,39–41,43–46,48–50,52–56,58–62]. In addition, we also retrieved two national reports, one each from France [68] and Spain [69] that were also included in the quantitative synthesis of mortality in COVID-19 associated ARDS.

Together, the included articles/reports evaluated 10,815 COVID-19 patients with ARDS for quantitative synthesis of

mortality with ARDS and 2,489 COVID-19 patients (with or without ARDS) for qualitative synthesis of mortality from corticosteroid use.

3.2. Quality assessment

The Newcastle–Ottawa scale was applied for the quality assessment (supplementary data, Table S1) of studies included in the quantitative synthesis of mortality in COVID-19 patients with ARDS. Of the 25 original studies included in the meta-analysis, 16 studies were deemed ‘good’ studies with a score of seven points [31,33–35,40,41,44–46,49,50,52,53,56,58,60] (Table 1). Whereas the remaining 9 studies were regarded as ‘fair’ with a score of 6 points [32,36,39,43,48,54,59,61,62] (Table 1). There was no study categorized as ‘poor’ (i.e., scored less than five points). The quality issue identified in the ‘fair’ studies [32,36,39,43,48,54,59,61,62] was the inadequate follow-up as these studies did not follow all patients from enrollment to discharge (or death) (Table S1). In addition, the comparability item was not assessed due to the absence of control or comparator.

3.3. Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. All of the included original studies were published in 2020 with a wide range of sample sizes from 15 to 1,859. The median/mean ages of subjects were above 40 years old in all original studies.

Among the 26 original articles which reported mortality in COVID-19 patients with ARDS, 25 were original studies [31–36,39–41,43–46,48–50,52–56,58–62], including 19 studies (76%) [31–36,39–41,43–46,48–50,52–54] from China, of which 16 studies (64%) [31–36,39–41,44–46,49,50,52,53] were conducted in the Wuhan city. The remaining 6 studies were from Italy ($n = 3$) [58–60], Germany ($n = 1$) [61], Poland ($n = 1$) [62], and Iran ($n = 1$) [56]. In addition, only 10 out of the 25 original studies are multi-center [34,35,41,44–46,48,49,54,56], while the remaining 15 studies are single-center [31–33,36,39,40,43,50,52,53,58–62]. One of the datasets from Iran on mortality in COVID-19 patients with ARDS was retrieved from a narrative review article [55] which described the Iranian treatment protocol for COVID-19 induced ARDS. The French data on mortality in COVID-19 patients with ARDS (up to 31 May 2020) were retrieved from a weekly report published by the National Public Health Agency of France based on their sentinel surveillance of COVID-19 patients admitted for intensive care [68]. The Spanish data on mortality in COVID-19 patients with ARDS (up to 21 May 2020) were retrieved from a weekly report published by the National Center of Epidemiology of Spain based on their epidemiological survey on COVID-19 patients [69]. Except for two studies [59,60] which included exclusively COVID-19 patients with ARDS, the crude prevalence of ARDS in the remaining 26 articles/reports ranged from 2% to 79%, with a median prevalence of 35% (lower quartile: 18%; upper quartile: 44%).

On the other hand, there are 23 studies [31,33–35,37,38,40–42,44–47,49,51,52,54,57,63–67] included which reported mortality with corticosteroids use in COVID-19 patients (with or without ARDS), in which 17 out of 23 studies (74%) were originated from China [31,33–35,37,38,40–42,44–47,49,51,52,54], where all but

Table 1. Characteristics of included studies presenting proportion of COVID-19 patients with ARDS and COVID-19 patients receiving corticosteroids.

Study	Region, Country	Study Type	Study Site	Age ^a	Study Period	No. of patients	No. of patients with ARDS	No. of deaths in patients with ARDS	Corticosteroids dosing regimen	Mortality in corticosteroids group n/N (%)	NOS Quality Score ^b
Wu et al [31]	Wuhan, China	Retrospective cohort study	Single center	51 (43-60)	25 December 2019-13 February 2020	201	84	44	MTP, dose not mentioned	23/50 (46.0)	7
Chen N et al [32]	Wuhan, China	Retrospective cohort study	Single center	M(SD): 55.5 (13.1)	Jan 1-20 January 2020	99	17	11	-	-	6
Yang et al [33]	Wuhan, China	Retrospective cohort study	Single center	M(SD): 59.7 (13.3)	24 December 2019, to 26 January 2020	52	35	26	No information	16/30 (53.3)	7
Zhou et al [34]	Wuhan, China	Retrospective cohort study	Multicenter	56 (46-67)	29 December 2019-31 January 2020	191	59	50	No information	26/57 (45.6)	7
Deng et al [35]	Wuhan, China	Retrospective cohort study	Multicenter	54 (47-65)	1 January 2020-21 February 2020	225	108	98	No information	88/152 (57.9)	7
Tang et al [36]	Wuhan, China	Retrospective case-control	Single center	62 (47-69)	24 December 2019-7 February 2020	179	73	21	-	-	6
Wang Yin et al [37]	Wuhan, China	Retrospective cohort study	Single center	54(48-64)	Jan 20 - Feb 25, 2020	46	-	-	MTP 1-2 mg/kg/d for 5-7 d	2/26 (7.7)	-
Huang C et al [38]	Wuhan, China	Prospective study	Single center	49 (41-58)	16 December 2019-2 January 2020	41	-	-	MTP 40-120 mg/d	4/9 (44.4)	-
Wang L et al [39]	Wuhan, China	Prospective study	Single center	69 (65-76)	Jan 1 - Mac 5, 2020	339	71	56	-	-	6
Cao et al [40]	Wuhan, China	Cohort study	Single center	54(37-67)	Jan 3-1 February 2020	102	20	15	MTP, dose not mentioned	11/51 (21.6)	7
Wang D et al [41]	Wuhan, China	Retrospective case series	Multicenter	51(36-65)	Jan 1-10 February 2020	107	28	17	No information	18/62 (29.0)	7
Li et al [42]	Wuhan, China	Retrospective cohort study	Single center	M(SD): 51.0 (17.5)	Jan 10-22 February 2020	93	-	-	No information	21/21 (100)	-
Wan et al [43]	Chongqing, China	Retrospective case series	Single center	47(36-55)	Jan 23-8 February 2020	135	21	1	-	-	6
Xu et al [44]	Wuhan, China	Retrospective cohort study	Multicenter	M(SD): 62.5 (13.3)	Jan 12-3 February 2020	239	164	118	MTP 60.9 ± 21.7 mg/d	118/189 (62.4)	7
Chen L et al [45]	Wuhan, China	Retrospective cohort study	Multicenter	59(45-68)	Jan 20-4 April 2020	1859	227	174	No information	165/753 (21.9)	7
Shi Q et al [46]	Wuhan, China	Retrospective cohort study	Multicenter	Diabetes: 64(56-72) Non-diabetes: 65(56-72)	Jan 1 - Mac 8, 2020	306	55	47	No information	30/107 (28.0)	7
Chen F et al [47]	Wuhan, China	Retrospective cohort study	Single center	55(34-68)	Jan 1-15 February 2020	660	-	-	No information	30/184 (16.3)	-
Shi M et al [48]	Hubei, China	Retrospective cohort study	Multicenter	M(SD): 59.4 (16.5)	Jan 1 - Mac 1, 2020	161	69	47	-	-	6
Ruan et al [49]	Wuhan, China	Retrospective cohort study	Multicenter	Died: 67(15-81) Discharged: 50(44-81)	No information	150	62	55	No information	31/53 (58.5)	7
Wang Yang et al [50]	Wuhan, China	Retrospective cohort study	Single center	60(48-69)	Jan 25-25 February 2020	344	145	128	-	-	7
Yan et al [51]	Wuhan, China	Retrospective cohort study	Single center	64(49-73)	Jan 10-24 February 2020	48	-	-	No information	35/39 (89.7)	-
Wang K et al [52]	Wuhan, China	Ambispective cohort study	Single center	Died: 58(46-67) Survived: 67(62-78)	No information	548	207	76	No information	65/341 (19.1)	7

(Continued)

Table 1. (Continued).

Study	Region, Country	Study Type	Study Site	Age ^a	Study Period	No. of patients	No. of patients with ARDS	No. of deaths in patients with ARDS	Corticosteroids dosing regimen	Mortality in corticosteroids group n/N (%)	NOS Quality Score ^b
Pan et al [53]	Wuhan, China	Case-control	Single center	68(61–75)	Jan 27 – Mar 19, 2020	124	91	89	-	-	7
Huang M et al [54]	Jiangsu, China	Retrospective cohort study	Multicenter	57(26–97)	Jan 24–20 April 2020	60	9	0	No mention of agent used; 40 to 80 mg/d	0/34 (0)	6
Jamaati et al [55]	Iran	Descriptive	Single center	-	Up to Mar 3, 2020	231	72	18	-	-	-
Javanian et al [56]	Iran	Retrospective cohort study	Multicenter	M(SD): 60.1 (13.9)	Feb 25 – Mar 17, 2020	100	4	3	-	-	7
Yang et al [57]	Montreal, Canada	Retrospective case series	Single center	-	NC	15	-	-	MTP, HYC, DEX, Dose: 40–160 mg/d	3/15 (20.0)	-
Inciardi et al [58]	Lombardy, Italy	Retrospective cohort study	Single center	M(SD): 67.0 (12.0)	Mar 4 – Mar 25, 2020	99	19	18	-	-	7
Zangrillo et al [59]	Milan, Italy	Retrospective case series	Single center	61(54–69)	Feb 20–2 April 2020	73	73	17	-	-	6
Cavalli et al [60]	Milan, Italy	Retrospective cohort study	Single center	Standard treatment: 70(64–78) Anakinra: 62(55–71)	Mar 2020	45	45	10	-	-	7
Dreher et al [61]	Aachen, Germany	Retrospective cohort study	Single center	65(58–76)	Feb – Mar 2020	50	24	3	-	-	6
Nowak et al [62]	Warsaw, Poland	Retrospective cohort study	Single center	M(SD): 63.7 (19.6)	Mar 16–7 April 2020	169	41	30	-	-	6
National Public Health Agency of France [68]	France	Sentinel surveillance of COVID-19 patients admitted to intensive care	Nationwide	-	Mar 16–31 May 2020	4,007	3,185	593	-	-	-
2,335	-	Epidemiology [69]	Spain	Epidemiological survey	Nationwide	-	Up to 12:00 on	-	21 May 2020	250,287	5,807
Cruz et al [63]	Madrid, Spain	Retrospective cohort study	Single center	Corticosteroids: M(SD): 65.4 (12.9) Non-	corticosteroids: M(SD): 68.1 (15.7)	-	-	-	Mar 4–7 April 2020	463	-
-	No mention of agents used; pulse therapy or 1 mg/kg/d	55/396 (13.9)	-	-	-	92	-	-	Pulse therapy: MTP 2 mg/kg/d for 3 days, 250 mg/d for 3 days, and 500 mg/d for 3 days	6/83 (7.2)	-
Rubio et al [64]	Granada, Spain	Retrospective cohort study	Single center	M(SD): 63.9 (12.9)	-	21	-	-	DEX 4 mg three times daily for two days, followed by 4 mg twice daily for two days and then 4 mg once daily for two days	0/21 (0)	-
Selvaraj et al [65]	Rhode Island, USA	Case series	Single center	M(SD): 60.0 (15.8)	Apr 16–16 May 2020	-	-	-	-	-	-

(Continued)

Table 1. (Continued).

Study	Region, Country	Study Type	Study Site	Age ^a	Study Period	No. of patients	No. of patients with ARDS	No. of deaths in patients with ARDS	Corticosteroids dosing regimen	Mortality in corticosteroids group n/N (%)	NOS Quality Score ^b
So et al [66]	Tokyo, Japan	Case series	Single center	64(47–73)	Mar 2020	7	-	-	Pulse therapy: MTP 1000 or 500 mg/d for three days, followed by 1 mg/kg/d, then tapered off	0/7 (0)	-
Lee et al [67]	Daegu/No information	Gyeongsangbuk-do, Korea 15/28 (53.6)	-	Retrospective cohort study	Multicenter	72	(68–79)	(68–79)	Feb 18–4 March 2020	98	-

ARDS = acute respiratory distress syndrome; DEX = dexamethasone; HYC = hydrocortisone; M = mean; MTP = methylprednisolone; PRED: prednisolone; SD = standard deviation
^aAge was reported as median (lower quartile-upper quartile) unless otherwise indicated.

^bOnly for original studies included in the meta-analysis to determine mortality estimates of ARDS in COVID-19 (7 = good studies; 5–6 = fair studies; 0–4 = poor studies)

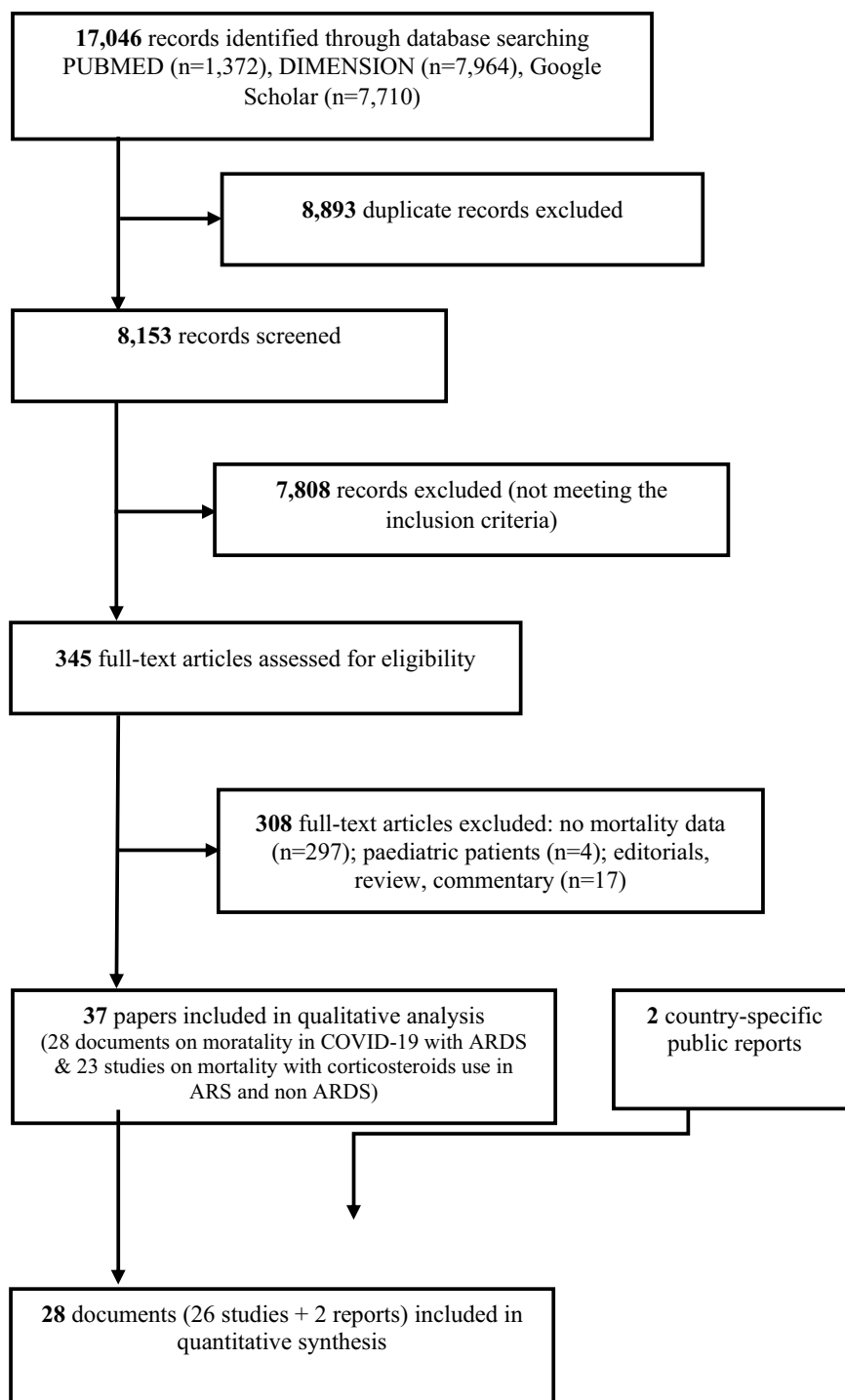


Figure 1. Study selection process (PRISMA).

one [54] were conducted in the Wuhan city of China. The remaining six studies were originated from Spain ($n = 2$) [63,64], Canada ($n = 1$) [57], United States ($n = 1$) [65], Japan ($n = 1$) [66], and Korea ($n = 1$) [67]. Furthermore, 10 out of 23 studies are multi-center [34,35,41,44–47,49,54,67], while the remaining 13 studies are single-center [31,33,37,38,40,42,51,52,57,63–66]. Except for three studies [57,65,66] which included exclusively COVID-19 patients who received corticosteroids, the crude prevalence of corticosteroid use in the remaining 20 studies ranged from 22% to 90%, with a median prevalence of 53% (lower quartile: 29%; upper quartile: 66%).

3.4. Mortality estimate of COVID-19 patients with ARDS

The mortality data in the original articles and national reports [31–36,39–41,43–46,48–50,52–56,58–62,68,69] among COVID-19 patients with ARDS are summarized in Table 1. The pooled mortality estimate among COVID-19 patients with ARDS across all countries was 39% (95% CI: 23–56%; Figure 2). China had the highest mortality estimate among COVID-19 patients with ARDS of 69% (95% CI: 67–72%; Figure 2). In Europe (Figure 2), the highest mortality estimate among COVID-19 patients with ARDS was reported in Poland (73%; 95% CI: 58–86%), followed

by Spain (40%; 95% CI: 39–41%), and France (19%; 95% CI: 17–20%). Germany was found to have the lowest mortality estimate among COVID-19 patients with ARDS (13%; 95% CI: 2–29%). Subgroup analysis which limited only to the studies from Asia (China and Iran) involving COVID-19 patients with ARDS [31–36,39–41,43–46,48–50,52–56] presented a mortality estimate of 65% (95% CI: 53–76%). Subgroup analysis which limited only to the studies/reports involving COVID-19 patients with ARDS from European countries [58–62] reported a mortality estimate of 34% (95% CI: 20–50%).

3.5. Mortality in COVID-19 patients (with or without ARDS) with reported corticosteroid use

The 23 studies [31,33–35,37,38,40–42,44–47,49,51,52,54,57,63–67] that reported on mortality among COVID-19 patients (with or without ARDS) with systemic corticosteroid use are summarized in Table 1. Most of the studies included no information on the dosing regimen of systemic corticosteroid therapy [33–35,41,42,45–47,49,51,52,67]. Studies that included this information [30,37,38,40,43,48,50] reported a range of corticosteroids (methylprednisolone [31,37,38,40,44,57,64,66], prednisolone [66], hydrocortisone [57], and dexamethasone [57,65]) with varying doses and durations of treatment. Four studies reported the use of pulse corticosteroid therapy [63–66]. Only six studies specified explicitly that corticosteroid therapy was intended for COVID-19 [37,51,63–66]. Except for one study [31] that reported mortality from corticosteroid use exclusively in COVID-19 patients with ARDS (46%), the remaining 22 studies reported the use of corticosteroids in COVID-19 patients with or without ARDS. The reported crude mortality rates of COVID-19 patients (with or without ARDS) with corticosteroids use from the included studies were very broad and ranged from as low as 0% to as high as 100%. The median crude mortality rate of COVID-19 patients with reported corticosteroid use was 28.0% (lower quartile: 13.9%; upper quartile: 53.6%).

4. Discussion

This systematic review and meta-analysis present the pooled mortality estimates among COVID-19 patients with ARDS. The overall pooled mortality estimate of COVID-19 associated

ARDS (39%) was comparable to the in-hospital mortality rate of patients with all-cause ARDS (non-COVID-19) managed with currently optimal therapies which include intensive care admission and mechanical ventilation, as reported in a recent systematic review (45%) [70] and the 2016 LUNG SAFE study (40%) [71].

The highest country-specific mortality from COVID-19 associated ARDS was found in China, which may be due to a lack of understanding of the origin and pathophysiology of the infection by SARS-CoV-2, as well as its management during the early outbreak of COVID-19. Of the 19 original Chinese studies included, all but two are originated in Hubei province (Wuhan is the capital city of Hubei province) [31–36,39–41,44–46,48–50,52,53], the epicenter of the COVID-19 outbreak. In fact, the study of Chen N et al. [32] included a cluster of patients (49% of total patients included) who had a history of exposure to the Huanan seafood market, which is referred to as the ‘ground zero’ of the COVID-19. The pooled mortality estimate of ARDS in COVID-19 patients from Chinese studies (69%) was higher than the previously reported mortality rate of Chinese patients with non-COVID-19 related sepsis and ARDS (42%) from a recent single-center prospective study [72]. This coincides with the reason detailed above for high mortality of ARDS in COVID-19 in China where the understanding toward pathophysiology and management of sepsis (non-COVID-19-related) was far more established than COVID-19. In fact, the lower pooled mortality estimate of ARDS in European studies (34%) relative to Chinese studies may be due to a better understanding of the management of COVID-19 when the epicenter of COVID-19 shifted from China to Europe.

The mortality estimate of ARDS in COVID-19 in France (19%) was much lower than the previously reported mortality rate among patients with all-cause ARDS (non-COVID-19) admitted to intensive care units in a French multicenter, prospective cohort study [73] (34%). However, the prospective study [73] included data spanning from the year 1997 to 2014, in which the role of lung-protective mechanical ventilation had yet to be established for most of the study duration (before 2010s) and thus may account for the reported higher mortality rate. On the other hand, a German-wide multi-center prospective cohort study (DACAPO study [74]) which evaluated the influence of quality of intensive care on patients with

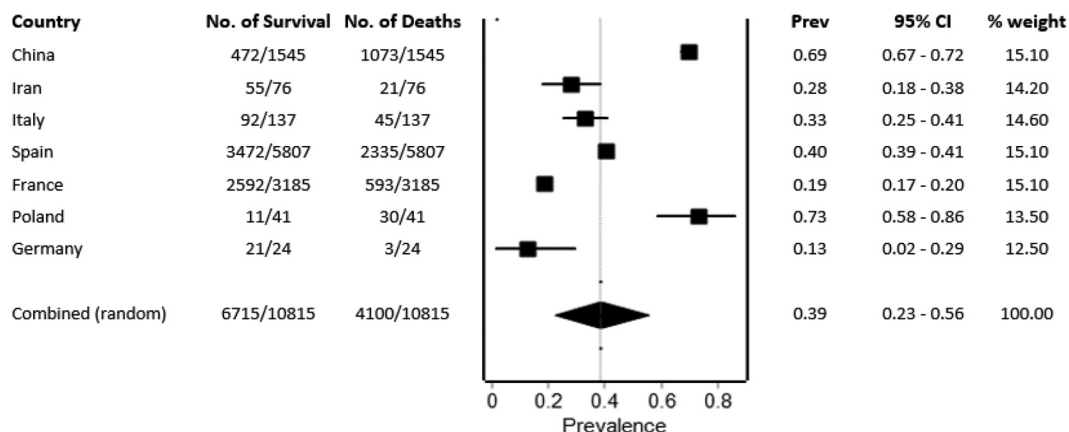


Figure 2. Pooled mortality estimate (%) in COVID-19 patients with ARDS (Heterogeneity: $I^2 = 100\%$; $p = 0.001$).

all-cause ARDS (non-COVID-19) reported a mortality rate of 27% in this cohort of patients, which was higher than the observed mortality estimate of COVID-19 associated ARDS in Germany (13%). Nevertheless, the German mortality estimate of ARDS in COVID-19 was originated from only one study [61], which included only 24 COVID-19 patients with ARDS, and therefore may be subject to high risk of selection biases.

The mortality estimate of COVID-19 associated ARDS in Iran (28%) was comparable to the mortality rate of hospitalized patients with ARDS due to H1N1 influenza (34%) as reported in a single-center, cross-sectional study [75] in Iran.

The difference in mortality estimates of COVID-19 associated ARDS among countries may be explained by the setting where patients with ARDS were receiving care since the management of ARDS requires a well-organized and advanced level of care. The exceptionally high mortality estimate of COVID-19 associated ARDS (73%) in Poland may be due to the small study size, and the fact that not every patient who developed ARDS received intensive care (41 patients with ARDS but only 27 patients were admitted into intensive care units, and hence the remaining 14 patients may have received suboptimal care) [62]. Indeed, the French and German mortality data were derived exclusively from ARDS patients admitted to the intensive care units which may have contributed to the relatively lower mortality estimate of COVID-19 associated ARDS in France (19%) and Germany (13%). A previous study [76] has reported lower death rates from ARDS among patients admitted to high-volume intensive care units than low- and moderate-volume ICUs. Though the study compared among different intensive care units, it did suggest that settings with high case volume may affect the quality of care of patients with ARDS and medical wards typically have higher case volume than intensive care units.

The high mortality rate in COVID-19 associated ARDS necessitates a prompt and aggressive treatment strategy. It has long been our understanding that inflammation is the key factor that drives the pathophysiology of ARDS, irrespective of the etiology [77]. Further examination of the inflammatory cascade reveals that insufficient glucocorticoid receptor-mediated inhibition of proinflammatory NF- κ B may be central to the pathogenesis of ARDS [78]. This necessitates consideration for the administration of corticosteroid therapy to prevent death. The current recommendation by WHO was against the routine use of corticosteroids in COVID-19 associated pneumonia outside of clinical trials [21]. However, such recommendation requires a review especially in a subpopulation of COVID-19 patients with ARDS which may benefit from corticosteroid therapy. A 2018 meta-analysis [79] which included nine randomized trials of corticosteroid therapy (low-dose methylprednisolone) in patients with all-cause ARDS (non-COVID-19) has not only shown a significant reduction in mortality (risk ratio = 0.68; 95% CI: 0.57–0.82) but also improved time to extubation and duration of hospitalization. Treatment was generally well-tolerated except transient hyperglycemia that was the most common adverse effect reported. Similarly, a recent meta-analysis [80] with seven randomized controlled trials in patients with all-cause ARDS (non-COVID-19) reported reduced all-cause mortality (risk ratio = 0.75; 95% CI:

0.59–0.95), duration of mechanical ventilation (mean difference: -4.93 days; 95% CI: -7.81 days to -2.06 days), and increased ventilator-free days (mean difference: 4.28 days; 95% CI: 2.67 days to 5.88 days), with any type of corticosteroid therapy compared to placebo. Nevertheless, it was also observed that corticosteroid therapy slightly increased the risk of hyperglycemia (risk ratio = 1.12%; 95% CI: 1.01 to 1.24). Since a preliminary comparison of plasma cytokine profile found no significant difference between patients with COVID-19 receiving intensive care ($n = 9$; 67% with ARDS) and patients with non-COVID-19 associated sepsis ($n = 28$; 43% with ARDS) [81], the benefits of corticosteroid therapy are likely to extend to patients with COVID-19 associated ARDS. Wu C et al [31] found that methylprednisolone (dose and regimen were not reported) reduced the risk of death in patients with COVID-19-associated ARDS (hazard ratio [HR] = 0.38; 95% CI: 0.20–0.72). However, without adjustment of potential confounders, the findings of the study should be treated with caution.

The recommendation by WHO to avoid the routine use of corticosteroid therapy in COVID-19 was due to a lack of evidence of effectiveness and possible harm [21]. Nevertheless, the systematic review of corticosteroid therapy among SARS patients which formed the basis for the WHO's recommendation included many studies where the findings were inconclusive [20]. In fact, many have ignored the positive findings of a large-scale database study reported by Long et al. [82] in 2016 that evaluated the efficacy of corticosteroid therapy among 5,327 patients with SARS. This study was not included in the 2006 aforementioned systematic review. After adjustment for possible confounders in this study, it was reported that corticosteroid therapy significantly reduced the risk of mortality by 47% (HR = 0.53, 95% CI: 0.35–0.82) in severe cases of SARS, albeit no difference was noted in the risk of mortality in non-severe cases.

Whilst we found a wide range of crude mortality rates in COVID-19 patients receiving corticosteroids (with or without ARDS) in our systematic review, the largest studies from China included in our systematic review reported crude mortality rates of 21.9% [45]. An indirect comparison with the case fatality rate in COVID-19 patients who developed severe illness in China (49.0%) [83] hinted toward possible benefits of corticosteroid therapy since the recommendation by the National Health Commission of China [84] was to consider administration of corticosteroids in COVID-19 patients with rapid deterioration. In fact, Cruz et al. [63] in their retrospective cohort study of 463 COVID-19 patients in Spain reported significantly reduced odds of in-hospital mortality in COVID-19 patients receiving corticosteroid therapy upon adjustment of potential confounders (odds ratio = 0.19; 95% CI: 0.05–0.74), with no difference in mortality between pulse and non-pulse corticosteroid therapy. To the best of our knowledge, this was the only study thus far at the time of writing this article that provided adjusted mortality estimate among COVID-19 patients receiving corticosteroids.

It is likely that corticosteroid therapy was only administered during the very late stages of COVID-19 when other recommended interventions lead to little or no improvement, where

the full potential benefits of corticosteroid therapy may not be demonstratable. This may be due to WHO's recommendations against using corticosteroids in COVID-19 patients. In fact, Zhang et al. [85] in their single-center, retrospective case series study reported that severely ill COVID-19 patients with multi-organ failure who died in intensive care unit had a mean delay of 1.5 days in the initiation of corticosteroid therapy compared to patients who had improved in the intensive care unit and transferred to the general wards. Though the findings from the study should not be treated as conclusive, it did suggest that future studies should compare the clinical outcomes between early and late administration to inform the appropriate timing for administration of corticosteroids in severely ill COVID-19 patients since corticosteroid therapy may not be very effective in the late stages of COVID-19 to contain the overwhelming production of cytokine.

Corticosteroid therapy was also associated with improvement in clinical outcomes other than mortality among severely ill COVID-19 patients with or without ARDS. Zhou et al. [86] reported an improvement in oxygen saturation (SaO_2) and arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) with corticosteroid therapy in 15 patients with COVID-19 complicated by ARDS. So et al. [66] in their case series of 7 mechanically ventilated COVID-19 patients with ARDS reported complete withdrawal of ventilator support in all cases within seven days of treatment with intravenous pulse therapy of methylprednisolone (1000 or 500 mg/day of methylprednisolone for three days intravenously, followed by 1 mg/kg once daily, then tapered by 10 or 20 or 30 mg/day of prednisolone orally, finishing at 10 mg of prednisolone), along with a reduction in median C-reactive protein levels. A retrospective, observational, single-center study by Wang Yin et al. [37] also reported a significantly faster resolution of symptoms (shorter time to normalize body temperature), faster improvement of SaO_2 and better improvement in the absorption degree of the focus in chest computed tomography among 46 severely ill COVID-19 patients receiving methylprednisolone (1–2 mg/kg/day for 5–7 days) compared to the control. Yang et al. [57] in their case series of 15 critically ill patients with COVID-19 noted an improvement in C-reactive protein level and $\text{PaO}_2/\text{FiO}_2$ upon administration of corticosteroid therapy. Selvaraj et al. [65] described a case series of 21 COVID-19 patients with hypoxic respiratory failure and reported a significant reduction in mean C-reactive protein levels compared to baseline with none of the patients required mechanical ventilation upon administration of dexamethasone (4 mg three times daily for two days, followed by 4 mg twice daily for two days and then 4 mg once daily for two days). Nevertheless, these studies [37,57,65,66,86] may be too small and may have potential selection biases therefore the findings cannot be treated as conclusive.

Despite the possible improvement in clinical outcomes, the best dosing regimen of corticosteroid therapy in patients with COVID-19 with severe manifestations of the disease is still not known. Lu et al. [87] in their case-control study which included 62 critically-ill COVID-19 patients (31 pairs with and without corticosteroid therapy matched by propensity score methods) noticed significantly elevated mortality risk ($p = 0.003$) with an

increased dose of corticosteroids after adjustment for administration duration, with every 10 mg increment in equivalent hydrocortisone dose was associated with an additional 4% mortality risk (adjusted hazard ratio: 1.04, 95% confidence interval: 1.01–1.07). However, a case-control study with propensity score matching suffers inherently from the limitation that the analysis does not adjust other potential confounders that may exist, and therefore the findings from Lu et al. may not be conclusive. An ambispective cohort study [88] reported significantly higher risk of mortality in COVID-19 patients receiving high-dose corticosteroid therapy (the maximum dose was equivalent to or more than 1 mg/kg/day of prednisone) compared to no corticosteroid use (adjusted HR = 3.50; 95% CI: 1.79–6.86) in adjusted Cox proportional hazards regression analysis, while no difference in mortality was reported between low-dose corticosteroid therapy (the maximum dose was <1 mg/kg/day of prednisone) relative to no corticosteroid use (HR = 1.26, 95% CI: 0.61–2.58). Cruz et al. [63] who demonstrated a significant reduction in the mortality of COVID-19 patients receiving corticosteroid therapy employed either a regimen of 1 mg/kg/day of methylprednisolone or pulse corticosteroid therapy (unclear regimen). In the aforementioned study by Long et al. [82] on SARS patients, there was a significant reduction in the risk of mortality for both cohorts of SARS patients with severe disease receiving either average daily corticosteroid doses (equivalent methylprednisolone dose) of 80 mg/day or 160 mg/day, compared to no corticosteroid use, respectively, though no difference in the risk of mortality compared to no corticosteroid use beyond average daily corticosteroid doses of 160 mg/day.

Whether corticosteroid therapy is of benefit in COVID-19 patients with only mild-to-moderate manifestations of the disease is uncertain. Zha et al. [89] included 31 patients with mild COVID-19 disease (none reported ARDS) in their observational study, 11 of whom received corticosteroid therapy (methylprednisolone 40 mg once or twice daily) within 24 hours of admission for a median 5 days. There was no statistical difference in terms of viral clearance time, duration of symptoms, and length of hospital stay between corticosteroid arm and non-corticosteroid arm. Yuan et al. [90] included 35 pairs of propensity score-matched mild-to-moderate COVID-19 patients with and without corticosteroid treatment and reported no significant difference between the two groups with regards to progression to severe disease, length of hospital stay, duration of viral shedding, and duration of fever. However, both studies may be too small to conclude the efficacy of corticosteroid in COVID-19 patients with the mild-to-moderate illness. Nevertheless, extrapolation from SARS patients [69] suggested that corticosteroids do not reduce the risk of death in non-severe cases but any improvement in other clinical outcomes is unknown.

One of the concerns by WHO in corticosteroid therapy for COVID-19 patients was a possible delay in viral clearance, extrapolated from a multicenter, retrospective cohort study [91] of patients with the Middle East respiratory syndrome, though a closer examination of this study revealed no delay in viral clearance with corticosteroid therapy of more than 7 days. Nevertheless, mixed findings on viral clearance in

COVID-19 patients receiving corticosteroids had been reported. Ling et al. [92] observed that the duration of viral RNA detection for oropharyngeal swabs and feces in COVID-19 patients treated with a corticosteroid was longer than those without corticosteroid treatment (15 days vs. 8 days, $p = 0.013$ and 20 days vs. 11 days, $p < 0.001$ for oropharyngeal swabs and feces, respectively). However, the regimen of corticosteroid therapy was not mentioned by the authors in this study. Gong et al. [93] reported a significant delay in the negative conversion of viral nucleic acid testing among COVID-19 patients receiving methylprednisolone (1–2 mg/kg/day) than their counterparts without receiving methylprednisolone (29.11 ± 6.61 days versus 24.44 ± 5.21 days; $p < 0.05$). Likewise, Chen X et al. [94] reported that corticosteroid treatment was associated with a significant delay (40%) in the negative conversion of viral nucleic acid testing among COVID-19 patients upon adjustment of co-variables (adjusted HR = 0.60; 95% CI: 0.39–0.94) though the regimen of corticosteroid therapy was not described. In contrast, both Shi et al. [95] and Xu et al. [96] reported no association between corticosteroid treatment (no mention of regimen) and duration of viral nucleic acid detection in their multivariable analysis (adjusted HR = 1.00; 95% CI: 0.53–1.89 and adjusted odds ratio = 1.38; 95% CI: 0.52–3.65, respectively). It is possible that the duration of viral shedding may be influenced by the dose of corticosteroid administered since Li et al. [97] reported that high-dose (80 mg/day, adjusted HR = 0.67, 95%CI: 0.46–0.96) but not low-dose corticosteroids (40 mg/day, adjusted HR = 0.72, 95% CI: 0.48–1.08) delayed viral shedding in patients with COVID-19, which may explain the increased risk of mortality with high-dose corticosteroid therapy as detailed beforehand. Fang et al. [98] compared the viral clearance time of COVID-19 corticosteroid users and non-corticosteroid users and reported no significant difference in both groups, stratified according to non-severe cases (17.6 ± 4.9 days vs. 18.7 ± 7.7 days) and severe cases (18.8 ± 5.3 days vs. 18.3 ± 4.2 days). Notably, non-severe COVID-19 corticosteroid users in the study received a median hydrocortisone-equivalent dose of 237.5 mg/day (interquartile range: 206.3–300.0 mg/day) for a median duration of 7 days (interquartile range: 5.5–8.0 days), while severe COVID-19 corticosteroid users received a median hydrocortisone-equivalent dose of 250.0 mg/day (interquartile range: 250.0–250.0 mg/day) for a median duration of 4.5 days (interquartile range: 3.5–5.8 days).

There are some limitations to this review that should be considered when interpreting the findings of this study. The majority of the original studies (17/23) reporting on mortality in COVID-19 patients with corticosteroid use originated from China [31,33–35,37,38,40–42,44–47,49,51,52,54] and therefore the results related to the use of corticosteroids may need a careful extrapolation to the global population. Nevertheless, we did include a relatively large study from Spain ($n = 396$) [63] which reported significantly reduced risk of mortality in COVID-19 patients upon adjustment of confounders. The results of original studies should be interpreted with caution as the details of corticosteroid therapy were not mentioned in many studies [33–35,41,42,45–47,49,51,52,67] making it difficult to determine the most

appropriate treatment protocol for the corticosteroid therapy. Moreover, the use of the therapeutic intervention in the sickest patient and the small sample size may have also masked the beneficial effect of corticosteroid in some studies. Despite limited data was available, we managed to retrieve mortality data in COVID-19 patients with ARDS from six countries in addition to China and improved the reliability of the analysis presented in this article. Nevertheless, original studies that reported mortality in COVID-19 patients with ARDS with inadequate duration of follow-up [32,36,39,43,48,54,59,61,62] may have underestimated the mortality rate than if followed up until definite outcome (death/discharged).

5. Conclusion

The mortality estimate of COVID-19 patients with ARDS was similar to the present mortality rate of patients with all-cause, non-COVID-19 ARDS. It was still largely unknown whether the corticosteroid therapy could reduce the mortality risk of COVID-19 associated ARDS, albeit one study hinted on such a possibility. Improvement in other clinical outcomes (e.g. oxygenation indices, markers of inflammation, and resolution of signs and symptoms) in COVID-19 patients was also noted though without certainty due to methodological flaws. There is a need for a rigorously designed observational study, accounting for a range of co-variables and confounders, which details the dosing regimen and duration of corticosteroid therapy as well as the stage at which corticosteroid therapy is initiated, to reach firm conclusions. This is also the take-home message from this article.

6. Expert Opinion

The current COVID-19 pandemic adversely impacted upon economy and costed many lives across the world particularly in developed countries. One of the main causes of deaths in severely ill COVID-19 patients was ARDS, a result of uncontrolled inflammatory processes originating from the airways and the SARS-CoV-2 mediated cytokine storm. The mortality rate augmented due to the lack of an effective treatment led researchers to investigate the potential role of systemic corticosteroids to mitigate the cytokine storms in severely ill COVID-19 patients to prevent death. Indeed, this was initially received criticism and became controversial due to the obvious effects on corticosteroids on immunity and the potential for delayed viral clearance. The studies from previous viral outbreaks supported the notion that corticosteroid should not be used in COVID-19 patients due to the risks of delayed viral clearance. However, there was a dearth of high-quality data to evidence that the delayed viral clearance represents a significant prognostic factor of the disease, while patients deteriorated rapidly once cytokine storms developed, leading to ARDS mediated death. Therefore, the benefits of administration of systemic corticosteroids in severely ill COVID-19 patients outweighs the potential risk of delayed viral clearance.

Importantly, the role of systemic corticosteroids has been previously established before COVID-19 for the treatment of all-cause ARDS. Besides, extrapolation of data from patients

with SARS observed the effectiveness of systemic corticosteroids among patients with severe illness. This systematic review provided further evidence of the effectiveness of low-dose corticosteroid therapy in reducing the risk of mortality in COVID-19 patients with severe course of illness including those who develop ARDS. Recently, the release of the results from a randomized controlled trial (RECOVERY [99]) on the use of dexamethasone demonstrated mortality benefits in a subset of COVID-19 patients receiving respiratory support, which supports the findings of this systematic review and meta-analysis, though the data from RECOVERY trial has yet to complete the peer-review process at the time of writing this article. Nevertheless, the current evidence supports the recommendations by the Society of Critical Care Medicine [100] in permitting the use of systemic glucocorticoids in patients with COVID-19 who have moderate-to-severe ARDS (patients with a partial arterial pressure of oxygen/fraction of inspired oxygen [PaO₂: FiO₂] < 100 mmHg).

The worsening glycaemic control is anticipated with the systemic corticosteroids use in both diabetic and non-diabetic COVID-19 patients. Although, it is not in the scope of this systematic review to discuss the management of acute hyperglycaemia induced by systemic corticosteroids, we still foresee that the mortality benefits of corticosteroid therapy outweigh the risks of altered glycaemic control. Nevertheless, hyperglycaemia during hospitalization has been linked to a worse prognosis in COVID-19 patients, therefore, it is imperative that clinicians should be prepared to initiate or adjust insulin therapy based on the type of corticosteroid administered (i.e. either long- or short-acting), in order to maintain optimal glycaemic control during the course of treatment.

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