ORIGINAL ARTICLE

Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin in 1142 patients with coronavirus disease 2019: a systematic review and meta-analysis

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KEY WORDS

coronavirus disease 2019, drug therapy, meta-analysis

EDITORIAL

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ABSTRACT

INTRODUCTION The treatment effects of antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin are controversial in patients with coronavirus disease 2019 (COVID-19).

OBJECTIVES This study aimed to evaluate the impact of drug therapy on the risk of death in patients with COVID-19.

PATIENTS AND METHODS The PubMed, Embase, Web of Science, Cochrane Library, and major preprint platforms were searched to retrieve articles published until April 7, 2020. Subsequently, the effects of specific drug interventions on mortality of patients with COVID-19 were assessed. Odds ratios (ORs) and relative risks (RRs) with corresponding 95% CIs were pooled using random effects models.

RESULTS Of 3421 references, 6 studies were included. Pooled results from retrospective studies revealed that antiviral agents may contribute to survival benefit (OR, 0.42; 95% CI, 0.17–0.99; $P = 0.048$; $I^2 = 82.8\%$), whereas a single randomized controlled trial found no effects of an antiviral agent on mortality (RR, 0.77; 95% CI, 0.45–1.3; $P = 0.33$). Glucocorticoid use led to an increased risk of death (OR, 2.43; 95% CI, 1.44–4.1; $P = 0.001$; $I^2 = 61.9\%$). Antibiotics did not significantly affect mortality (OR, 1.13; 95% CI, 0.67–1.89; $P = 0.64$; $I^2 = 0\%$). Similarly, intravenous immunoglobulin had a nonsignificant effect on mortality (OR, 2.66; 95% CI, 0.72–9.89; $P = 0.14$; $I^2 = 93.1\%$).

CONCLUSIONS With the varied heterogeneities across interventions, the current evidence indicated a probable survival benefit from antiviral agent use and a harmful effect of glucocorticoids in patients with COVID-19. Neither any of antibiotics nor intravenous immunoglobulin were associated with survival benefit in this population.

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INTRODUCTION Since the outbreak of coronavirus disease 2019 (COVID-19) emerged in Wuhan, Hubei, China, in December 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has rapidly spread to 199 countries and territories around the world. As of April 18, 2020, the pandemic of SARS-CoV-2 resulted in 2 160 207 confirmed cases of infection and 146 088 deaths globally.[1] At present, the number of confirmed cases and deaths related to SARS-CoV-2 infection are still rising, posing a big challenge to healthcare professionals.

The management of patients with SARS-CoV-2 infection has raised concerns worldwide. However, there was insufficient evidence to prove that any drug in clinical use had definitive effects on COVID-19. Most published studies on COVID-19 were retrospective and adopted

WHAT'S NEW?

Coronavirus disease 2019 (COVID-19) has become a health crisis worldwide. Until now, there has been no evidence showing that any drug had definite beneficial effects in patients with COVID-19. Although antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin are widely used in clinical practice, their efficacy is still controversial. In this meta-analysis, we evaluated the association between drug therapy (antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin) and the risk of death in patients with COVID-19. We found that current evidence indicated a probable survival benefit of antiviral agent use and a harmful effect of glucocorticoids in this population. Neither any of antibiotics nor intravenous immunoglobulin were associated with survival benefit. Our study provides physicians with evidence-based knowledge on drug therapy in patients with COVID-19.

an observational design with inadequate sample size, making it difficult to evaluate whether a specific intervention was effective or not. Among all the pharmacological interventions for patients with COVID-19, antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin were most controversial drugs. Therefore, we carried out a systematic review and meta-analysis to evaluate the effects of antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin on clinical outcomes of patients with COVID-19, hoping that our study will provide up-to-date information on the treatment of this novel coronavirus.

PATIENTS AND METHODS

Search strategy

We followed a comprehensive search strategy to identify any relevant articles on the topic, mainly from 4 medical databases including PubMed, Cochrane Library, Web of Science, and Embase. We also searched relevant papers using the Google search engine and major preprint platforms including Medrix, bioRxiv, and SSRN. Tailored search terms featured "2019-nCoV," "COVID-19," "Coronavirus," "SARS-CoV-2," and "Wuhan Coronavirus" (Supplementary material, *Table S1*). No language restriction or publication status criteria were set. Reference lists of relevant articles were also screened for eligible studies. The last search was performed on April 7, 2020.

Study selection Two investigators (LP and LH) independently screened the manuscripts of the potentially eligible studies. Another investigator (SH) checked the results, and disagreement was resolved by consensus. Inclusion criteria were as follows: 1) randomized controlled trials (RCTs), cohort studies, case control studies, and cross-sectional studies; 2) study settings and patient characteristics were provided; and 3) detailed data on drug interventions and outcomes were available. Drug interventions included the use of antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin. Outcomes referred to the number of survivors and nonsurvivors at the end of the follow-up of each study. Exclusion criteria were: 1) duplicate reports; 2) preliminary studies that included patient groups overlapping with those presented in most recent reports.

Quality assessment The Newcastle–Ottawa quality assessment scale was used to assess study quality and risk of bias for retrospective studies.[2] The scale consists of 3 elements (selection, comparability, and exposure) and is covered by 8 items. According to this scale, the number of stars was used to evaluate study quality. A total of 4 stars can be awarded for selection, 2 for comparability, and 3 for exposure. Studies with 1 to 3 stars were considered as those of low quality; studies with 4 to 6 stars, of moderate quality; and studies with 7 to 9 stars, of high quality. The modified Jadad score (7 points) was used to assess the quality of RCTs, with classification criteria of high quality (6–7 points), moderate quality (4–5 points), and low quality (1–3 points).[3] Two investigators (LP and LH) independently performed quality assessment, and the third investigator (WL) checked the results and resolved any disagreement.

Definition of interventions and outcomes All-cause mortality at the end of follow-up of each study was regarded as the primary outcome. A pharmacological intervention was defined as a situation in which patients received a specific drug of interest (including antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin). Pooled analyses were performed to evaluate the association of intervention effects and patient outcomes according to the study definitions.

Data extraction We used a standard strategy to extract the following data from each study: study characteristics (authors, date of publication, study design, duration of follow-up, and sample size), participants (age and sex), patients with COVID-19 who received pharmacological interventions (antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin) or not, and outcomes (number of nonsurvivors and survivors). Data were independently extracted by 2 investigators (XG and WJ) and checked by the third investigator (DC). Our protocol was not published or registered owing to the rapid emergence of this infectious disease.

Statistical analysis Statistical analyses were performed using the STATA software, version 14 (StataCorp, College Station, Texas, United States). As most studies were retrospective and expected to be heterogenous, we chose the random effects model for data synthesis.[4] For retrospective studies, we used odds ratios (ORs) and 95% CIs as effect measures. For RCTs, we pooled results using relative risk (RR) and 95% CIs. All the ORs and RR with corresponding 95% CIs were graphically visualized on forest plots. Heterogeneity across studies was evaluated using the Cochrane Q test and the I^2 test (I^2 = 100%

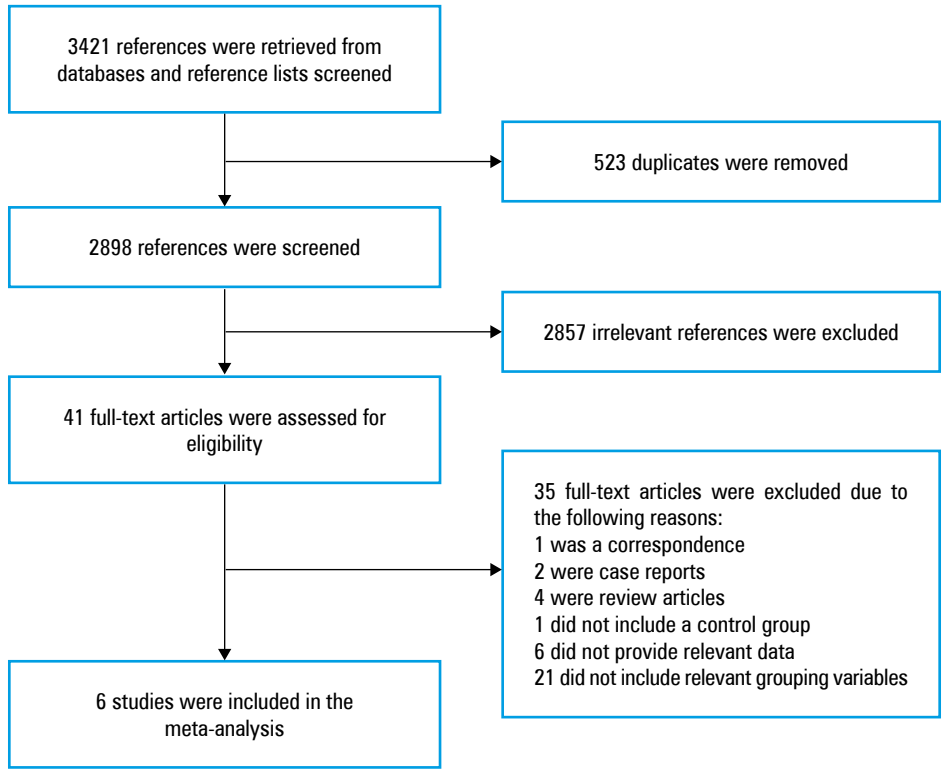

FIGURE 1 Flowchart of literature search and study selection

[(Q – *df*) / Q]). The I^2 value of 0% to 49%, 50% to 74%, and higher than 75% indicated low, moderate, and high heterogeneity, respectively.[5]

Subgroup analyses and sensitivity analysis plans were proposed based on the quality of studies, study design, participants, and types of drugs, as appropriate. Publication bias was assessed by funnel plots if more than 10 studies were included. A 2-sided *P* value less than 0.05 was considered significant.

RESULTS

Search results and study selection

The flowchart of study selection is presented in FIGURE 1. We identified 3421 references by the initial database query and manual search. Among them, 523 were removed as duplicates and 2857 were excluded after title and abstract screening. Eventually, 41 articles were eligible for full-text review. Thirty-five studies were excluded due to the following reasons (Supplementary material, *Table S2*): 21 did not include relevant grouping variables; 6 did not report relevant data on pharmacotherapy; 4 were review articles; 2 were case reports; 1 did not include a control group; and 1 was a correspondence. Six studies presenting patients' pharmacotherapy data and outcomes were included for systematic review and meta-analysis.

Characteristics of the included studies

The main characteristics of the included studies are shown in TABLE 1. A total of 1142 patients were included. Geographically, all studies originated from China, with varied sample sizes ranging from 52 to 274 patients. Of these, 5 were retrospective and observational[6-10] and there was a single RCT.[11] Of the 6 included studies, all except the study by Yang et al[7] received funding. Patients enrolled in these studies were at a median age of 40 to 69 years and predominantly male (55% to 67%).

Study quality and publication bias

The quality assessment of the included studies is summarized in Supplementary material, *Tables S3* and *S4*. According to the Newcastle Ottawa scale, the 5 retrospective studies were graded to be of moderate-to-high quality, with a mean number of 7.6 (range, 6–8) stars awarded. However, none of the retrospective studies specified how the patients were assigned to a drug intervention group or a control group. As a result, all retrospective studies had a high risk of selection bias with regard to receiving a specific drug intervention or not. The quality of the RCT was high, with 6 points according to the Jadad scale. Publication bias assessment was waived, as the number of the studies included was lower than 10.[12]

Main effect

Antiviral agent

Among the 5 retrospective studies, 2[6,8] reported detailed data on antiviral agent use. A single study[6] summarized the proportion of oseltamivir (66.7%), ganciclovir (40.3%), lopinavir / ritonavir (14.9%), and interferon α (10.9%) use among the enrolled patients. Another one[8] reported the proportion of lopinavir / ritonavir use in survivors (21%) and nonsurvivors (22%). Only a single study[8] reported the median (interquartile range [IQR]) time interval between disease onset and initiation of antiviral treatment (14 [10–17] days). None of the retrospective studies reported on the dosing regimen and the duration of antiviral agent treatment. Pooled results from the 5 retrospective studies

TABLE 1 Characteristics of the studies included in the meta-analysis

Study	Country	Design	Time	Follow-up, d	Patients, total n	Male sex, n (%)	Age, y
Yang et al[7]	China	Single-center, retrospective, observational	December 24, 2019 to January 26, 2020	28	52	35 (67)	Mean (SD), 59.7 (13.3)
Zhou et al[8]	China	Multicenter, retrospective, observational	December 29, 2019 to January 31, 2020	22	191	119 (62)	Median (IQR), 56 (46–67)
Wu et al[6]	China	Single-center, retrospective, observational	December 25, 2019 to January 26, 2020	40	201	128 (64)	Median (IQR), 51 (43–60)
Chen et al[9]	China	Single-center, retrospective, observational	January 13, 2020 to February 12, 2020	Until February 28, 2020	274	171 (62)	Median (IQR), 62 (44–70)
Deng et al[10a]	China	Multicenter, retrospective, observational	January 1, 2020 to February 21, 2020	Not available	225	124 (55)	Nonsurvivors: median (IQR), 69 (62–74) Survivors: median (IQR), 40 (33–57)
Cao et al[11]	China	Single-center randomized controlled trial	January 18, 2020 to February 3, 2020	28	199	120 (60)	Median (IQR), 58 (49–68)

a In this study, the age of the whole study cohort was not available.

Abbreviations: IQR, interquartile range

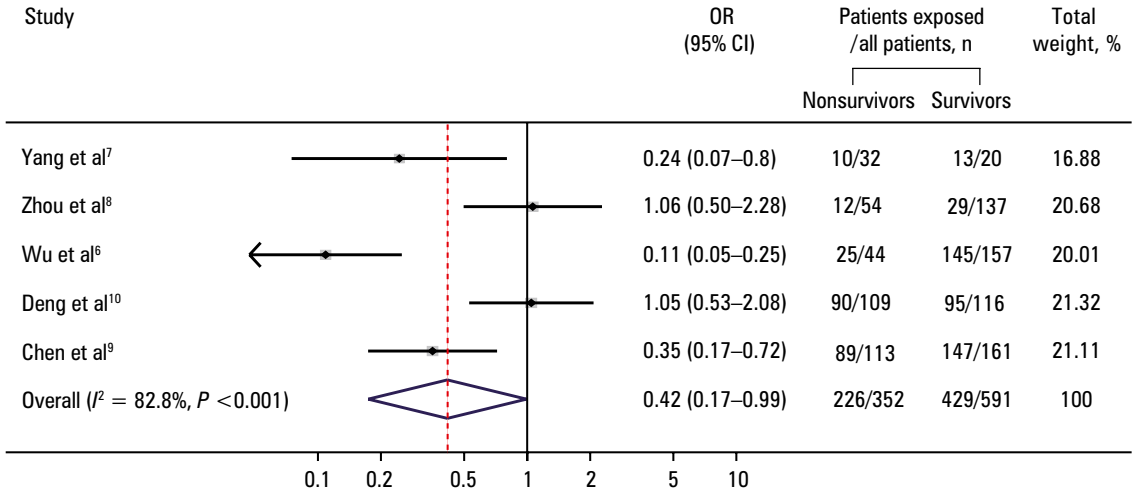

FIGURE 2 Estimates of the effect of antiviral agent use on mortality. Weights are derived from random-effects analysis.
Abbreviations: OR, odds ratio

revealed that antiviral agents may contribute to survival benefit (OR, 0.42; 95% CI, 0.17–0.99; $P = 0.048$; $I^2 = 82.8\%$) (FIGURE 2). The RCT only used lopinavir/ritonavir (400 mg/100 mg, administered orally for 14 days) as the antiviral agent and found no effect of this drug combination on mortality (RR, 0.77; 95% CI, 0.45–1.3; $P = 0.33$).

Glucocorticoids Five retrospective studies reported on the proportion of glucocorticoid use among nonsurvivors and survivors, and a single study[6] focused on the effect of a specific type of glucocorticoid (methylprednisolone) on mortality. Only 1 retrospective study[8] reported the median (IQR) time from disease onset to corticosteroid treatment in nonsurvivors and survivors (13 [10–17] days vs 12 [10–15] days; $P = 0.55$). The dosing and duration of glucocorticoid treatment were not specified in any retrospective study. Pooled results demonstrated that glucocorticoid use was associated with an increased risk of death (OR, 2.43; 95% CI, 1.44–4.1; $P = 0.001$; $I^2 = 61.9\%$) (FIGURE 3). Although the RCT reported on the median (IQR) time from disease onset to glucocorticoid therapy initiation (13 [11–17] days) and the median (IQR) duration of glucocorticoid therapy (6 [3–11] days), it did not show any association between glucocorticoid use and mortality.

Antibiotics Five retrospective studies compared the use of antibiotics between nonsurvivors and survivors, but none reported the types of antibiotics, dosing, time of initiation, and therapy duration. Antibiotics did not significantly affect mortality (OR, 1.13; 95% CI, 0.67–1.89; $P = 0.64$; $I^2 = 0\%$) (FIGURE 4). The RCT did not provide data on the association of antibiotic use and mortality.

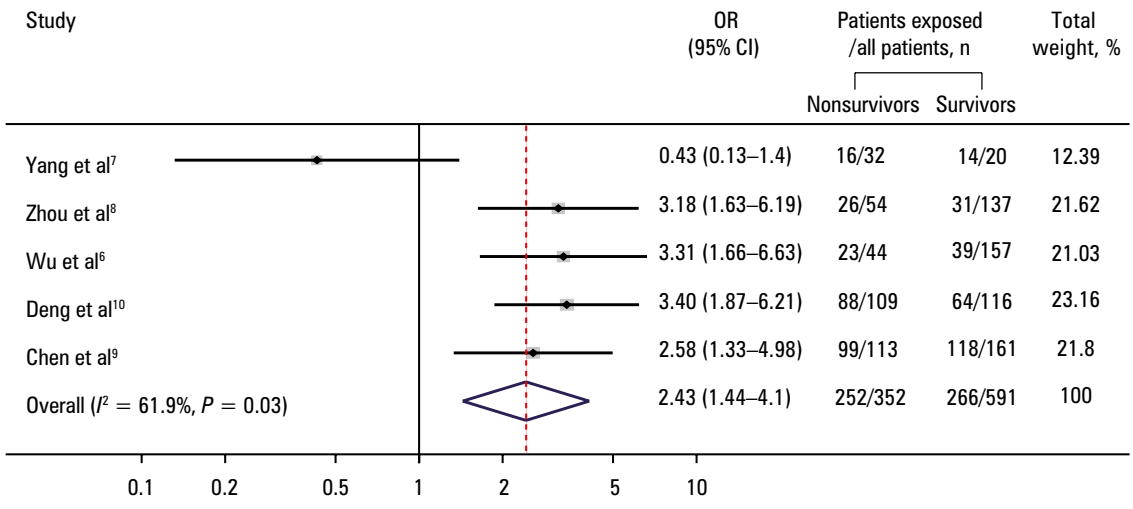

FIGURE 3 Pooled effects from retrospective studies on the impact of glucocorticoid use on mortality. Weights are derived from random-effects analysis.
Abbreviations: see FIGURE 2

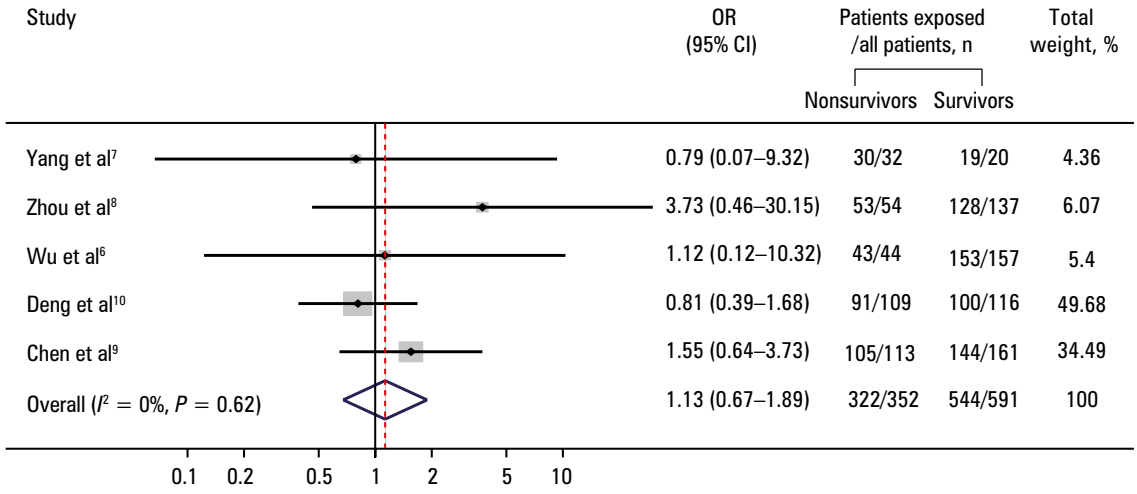

FIGURE 4 Pooled effects from retrospective studies on the impact of antibiotic use on mortality. Weights are derived from random-effects analysis.
Abbreviations: see FIGURE 2

Intravenous immunoglobulin Neither the retrospective studies nor the RCT presented data regarding daily dosing, time of initiation, and duration of intravenous immunoglobulin therapy. Pooled results from 4 retrospective studies[7-10] revealed nonsignificant effects of intravenous immunoglobulin use on mortality. (OR, 2.66; 95% CI, 0.72–9.89; P = 0.14; I^2 = 93.1%) (FIGURE 5).

Subgroup and sensitivity analyses We failed to conduct further subgroup and sensitivity analyses owing to the limited number of included studies at this stage.

DISCUSSION

As COVID-19 is a new, emerging infectious disease, there is currently no effective treatment for this new entity. The combination of supportive care, antiviral therapy, antimicrobial therapy, and immunomodulation has been the main therapeutic strategy for patients with COVID-19. At present, data regarding the treatment efficacy of drug therapy for COVID-19 are limited. In this meta-analysis, we evaluated the association of drug therapy (antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin) and the risk of death in patients with COVID-19. Our main finding was that antiviral agent use may be associated with improved survival, whereas glucocorticoids may increase the risk of death in the analyzed population. Neither any of antibiotics nor intravenous immunoglobulin were associated with survival benefit in patients with COVID-19.

It has been suggested that patients with severe COVID-19 are more likely to have a high viral load and long virus-shedding time.[13] The rationale of using antiviral agents to reduce the viral load and the subsequent immunopathological damage seems reasonable. Oseltamivir, ganciclovir, lopinavir / ritonavir, and interferon α are among the most frequently used antiviral drugs in the treatment of COVID-19 in China. However,

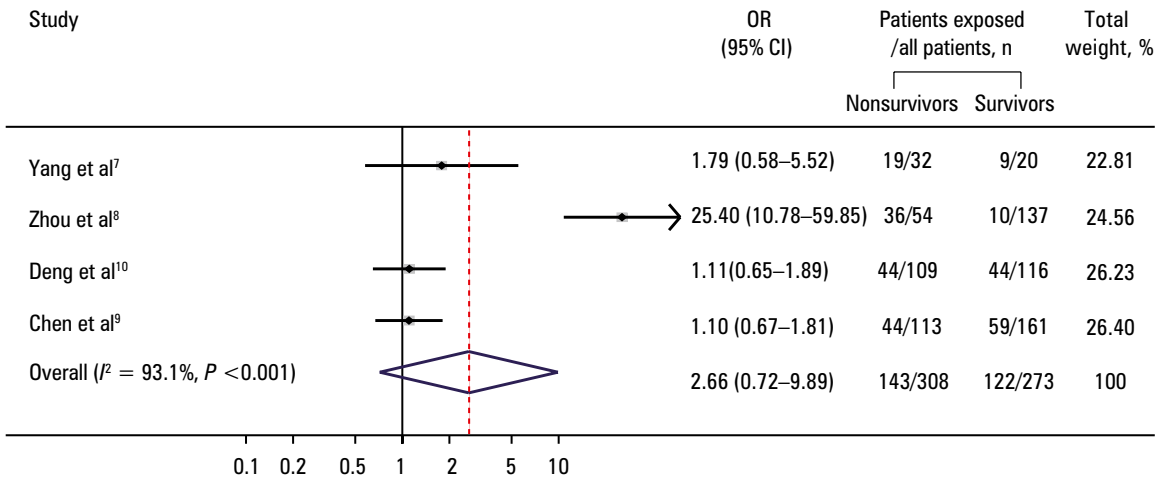

FIGURE 5 Pooled effects from retrospective studies on the impact of intravenous immunoglobulin use on mortality. Weights are derived from random-effects analysis.
Abbreviations: see **FIGURE 2**

none of them has been proven to have a definite effect by now. Lopinavir / ritonavir has been regarded as a promising drug for COVID-19. In a preliminary study, lopinavir / ritonavir was effective in the treatment of patients with SARS-CoV infection.[14] In addition, lopinavir / ritonavir was associated with decreased viral load and improved clinical symptoms in patients with COVID-19.[15] However, results from a recent randomized clinical trial suggested no significant difference between the group receiving lopinavir / ritonavir and the standard-care group regarding time to clinical improvement, 28-day mortality, and viral RNA load in throat swabs.[11] There has been even less evidence regarding the effects of other antiviral agents on clinical outcomes. In our study, pooled results from retrospective studies suggested an association between antiviral agent use and survival benefit, whereas the RCT failed to prove it. We also observed a significant heterogeneity in the treatment effects of antiviral agents across studies. The heterogeneity may be partially explained by varied baseline demographics and disease severity between studies. Also, there were no identical criteria guiding antiviral agent use. Therefore, further research is urgently needed to determine the clinical efficacy of different types of antiviral agents.

Although glucocorticoids were commonly used in SARS and Middle East respiratory syndrome (MERS) and are currently used in patients with COVID-19, their efficacy is still controversial.[16] Glucocorticoids are a double-edged sword for patients with viral pneumonia. On one hand, glucocorticoids appear to attenuate pulmonary inflammation and exudation. On the other hand, they also inhibit immune response and pathogen clearance. In a randomized, double-blind, placebo-controlled trial,[17] SARS-CoV plasma viral load was monitored after fever onset, and corticosteroid use was associated with delayed viral clearance. Similarly, a recent study of patients with MERS indicated that glucocorticoids did not improve survival and resulted in delayed clearance of MERS-CoV.[18] In addition, a systematic review and meta-analysis, which included 6548 patients with influenza, indicated that patients who received glucocorticoid therapy showed increased mortality, longer intensive care unit stay, and a higher risk of secondary bacterial or fungal infection than those who did not receive glucocorticoids. The current World Health Organization interim guidance on the management of severe acute respiratory infection advised against the use of glucocorticoids in patients with suspected SARS-CoV-2 infection unless otherwise indicated.[19] In our study, pooled results suggested that glucocorticoid use was associated with unfavorable outcomes. However, it should be noted that patients who received glucocorticoids were generally more critically ill and more likely to require mechanical ventilation, vasopressors, and renal replacement therapy.[16,20] The significant heterogeneity between studies also undermined the effectiveness of pooled estimates. Therefore, well-designed RCTs with balanced baseline characteristics will be helpful in evaluating the real effects of glucocorticoids on clinical outcomes.

Empiric antimicrobial therapy was also widely used in patients with COVID-19, although there was no evidence from RCTs supporting this recommendation. The rationale for antibiotic use in patients with COVID-19 is partially based on the fact that bacterial coinfection has been found in other types of viral pneumonia, including MERS and influenza, especially in ventilated patients who were at high risk of developing superinfection.[21] In our analysis, all data regarding antibiotic use were from retrospective studies. Pooled results with negligible heterogeneity (I^2 = 0%) suggested that there was no significant impact of antibiotic use on mortality. Due to the retrospective design of the included studies,

with no balanced baseline and lack of a causal link between exposure and outcome, the association between antibiotic use and mortality should be verified in prospective, controlled studies.

There has been limited evidence regarding the use of intravenous immunoglobulin in patients with COVID-19. Two case series have reported that high-dose immunoglobulin alone or combined with a medium dose of glucocorticoids could effectively reverse disease progression in patients with COVID-19 (Zhou et al, 2020, unpublished data).[22] However, intravenous immunoglobulin therapy may result in an increased risk of severe adverse events including anaphylactic reactions, transfusion-related lung injury, renal failure, thromboembolism, and other late reactions.[21,23] As a result, the recent published guidelines on the management of critically ill adults with COVID-19 did not suggest the routine use of standard intravenous immunoglobulin.[21] In our study, pooled analysis showed a high heterogeneity and suggested that intravenous immunoglobulin use was not associated with a low mortality risk.

Limitations This meta-analysis had some limitations. First, a limited number of eligible studies was available owing to the short time scales since the outbreak of SARS-CoV-2 infection. Second, the pooled results in our analyses were mainly derived from retrospective studies, and the heterogeneity for estimates of antiviral agents, glucocorticoids, and intravenous immunoglobulin was high (I^2 >75% in all cases). Third, in contrast to RCTs, all the included retrospective studies did not have predefined interventions and control groups. Also, these studies did not specifically consider confounding effects when presenting data on drug interventions and outcomes. There was a risk that estimates derived from retrospective studies might have been obscured by confounding factors (eg, cointerventions and baseline characteristics) when evaluating the impact of a specific drug intervention on the outcomes. In addition, selection bias may have been present in retrospective studies, as whether a patient received a specific drug intervention or not largely depended on the physician's decision. Therefore, pooled results from retrospective studies should be interpreted with caution owing to unadjusted confounding and a high risk of selection bias. Fourth, as the epidemic emerged in China first, all the included studies were from China. Conclusions derived from this study should be treated cautiously when extrapolated to other races and regions.

Conclusions With the varied heterogeneities across interventions, the current evidence indicated a probable survival benefit related to antiviral agent use and a harmful effect of glucocorticoids in patients with COVID-19. Neither any of antibiotic treatments nor intravenous immunoglobulin use were associated with survival benefit in this population.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT WL and DC conceived the concept of the study. LP and SZ contributed to the study design. All authors were involved in data collection. LP and SZ analyzed the data. LP, SZ, LH, and XG wrote the first draft of the manuscript. WL and DC supervised the design, data collection, and writing of the paper. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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