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. 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). 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. 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 I² test (I² = 100%...
Yang et al 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.

Main effect Antiviral agent Among the 5 retrospective studies, 26,8 reported detailed data on antiviral agent use. A single study5 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 one8 reported the proportion of lopinavir/ritonavir use in survivors (21%) and non-survivors (22%). Only a single study6 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

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\frac{(Q - df)}{Q}\]. The \(P\) 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 observational6-10 and there was a single RCT.11 Of the 6 included studies, all except the study by

![Flowchart of literature search and study selection](image-url)
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\(^8\) focused on the effect of a specific type of glucocorticoid (methylprednisolone) on mortality. Only 1 retrospective study\(^6\) 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.
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 of any 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. 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,
Drug therapy in COVID ‑19 indicated that glucocorticoids did not improve survival and resulted in delayed clearance of MERS ‑CoV. 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.

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. 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. In a recent randomized clinical trial, 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. 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. 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.

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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). 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 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 (I² > 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/pam.

ARTICLE INFORMATION
CONTRIBUTION STATEMENT WL and DC conceived the concept of the study. LP and S2 contributed to the study design. All authors were involved in data collection. LP and S2 analyzed the data. LP, S2, UH, 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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