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Review Article

Efficacy of intravenous immunoglobulins (IVIG) in COVID-19 patients: a systematic review and meta-analysis

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Abstract

Background and purpose: Though controversial, many clinical trials have been conducted to evaluate the efficacy of intravenous immunoglobulins **(**IVIG) in COVID-19 cases. Therefore, a systematic review and meta-analysis have been performed to evaluate the efficacy of IVIG in the treatment of COVID-19 patients.
Experimental approach: A systematic search was performed in electronic databases and preprint servers up to November 20, 2021. Since substantial heterogeneity was expected, a random-effects model was applied to pool effect size from included studies to calculate the standardized mean differences (SMDs) for the continuous variables and relative risks (RRs) for the dichotomous variable with 95% confidence intervals (CIs).
Findings/Results: Five randomized clinical trials and seven cohort studies were analyzed among the 12 eligible studies with a total of 2,156 patients. The pooled RR of mortality was 0.77 (CI 0.59-1.01, *P*-value = 0.06), and of mechanical ventilation was 1.50 (CI 0.29-7.83; *P*-value = 0.63) in the IVIG group compared with the standard care group. The pooled SMD of hospital length of stay was 0.84 (CI -0.43-2.11; *P*-value = 0.20) and of ICU length of stay was -0.07 (CI -0.92-0.78; *P*-value = 0.86) in the IVIG group compared with the standard care group.
Conclusion and implications: This meta-analysis found that the IVIG therapy was not statistically different from the standard care group. Mortality, ICU admission, mechanical ventilation, length of hospital stay, and length of ICU stay were not significantly improved among IVIG recipients. However, statistical indifference is not equal to clinical indifference.

Keywords: Clinical efficacy; Intravenous immunoglobulin; Meta-analysis; Mortality rate; SARS-CoV-2 infection; Systematic review.

INTRODUCTION

By November 2021, more than 245 million cases of coronavirus disease 2019 (COVID-19) had been confirmed worldwide. COVID-19 has caused approximately four million deaths worldwide (1). The mortality rate and severity of the disease have also increased over time. To control this catastrophic pandemic, considerable efforts have been made (2). While many therapeutic strategies, vaccines, and drugs have been developed to combat SARS-CoV-2 infection (3), each with its advantages and limitations (4), no specific therapy has yet been developed for COVID-19. In this regard, clinicians have used several antiviral or anti-inflammatory agents to control the SARS-CoV-2 infection, but none has been proven fully effective (5,6). Among these agents, intravenous immunoglobulin (IVIG) has been used to treat COVID-19 cases (7).

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Traditionally, IVIG has been used to treat patients with autoimmune diseases, chronic inflammatory diseases, dermatomyositis, systemic lupus erythematosus, Kawasaki disease, multiple sclerosis, idiopathic thrombocytopenic purpura, and chronic lymphocytic leukemia. This agent has immunomodulatory properties and consists of human immunoglobulins and neutralizing antibodies against microbial infections derived from patients who have recovered from various infections (8). All IgG subclasses, including IgG1-4, are present in IVIG and resemble normal human plasma (9). Previous studies with viral infections such as SARS, Middle East respiratory syndrome (MERS), Ebola, and Influenza H1N1 have shown that administration of IVIG can effectively curb inflammation and is associated with a good prognosis in patients with viral infections (10). Though controversial, many clinical trials have been conducted worldwide to evaluate the efficacy of IVIG in COVID-19 cases. This expensive agent, whose efficacy is uncertain, is a major burden on healthcare systems. Therefore, a summary of previous studies seems helpful to provide a comprehensive insight into IVIG therapy in COVID-19 cases. Here, a systematic review and meta-analysis have been performed to evaluate the efficacy of IVIG in the treatment of COVID-19 patients.

METHODS

Protocol and registration

This systematic review and meta-analysis was conducted and reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklists. The study protocol was prospectively registered in the PROSPERO database (CRD42021251113) and can be accessed at https://www.crd.york.ac.uk/prospero/.

Eligibility criteria

For this systematic review and meta-analysis, studies were selected using the following criteria: population (P), intervention (I), comparison (C), and outcomes (O) (PICO); P, hospitalized patients with a confirmed diagnosis of COVID-19; I, IVIG; C, any comparator provided as the standard of care (SOC) or placebo; and O, mortality rate as the primary outcome. We included comparative studies, randomized controlled trials (RCTs), case-control studies, and cohort studies. Other published literature was excluded, such as editorials, letters to the editor, commentaries, case series, case reports, and reviews (of any type).

Patients with an oxygen saturation of 93% or less, while breathing room air, a respiratory rate of 30 breaths/min or more, a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2) less than 300 mmHg, or lung infiltrates greater than 50% were considered severe (11). Patients with shock, organ failure, or acute respiratory distress syndrome requiring mechanical ventilation and all patients requiring ICU admission were also considered critical (12).

Information sources

Potential studies were identified through a systematic search of online databases, including PubMed, Embase, CENTRAL, ClinicalTrials.gov, Scopus, and preprint servers (medRxiv, bioRxiv, and SSRN) up to November 20, 2021. No time or language filters were applied.

Search

In general, the following search keywords were used: “covid19,” “covid-19,” “SARS-CoV-2,” “severe acute respiratory syndrome coronavirus type 2,” “Coronavirus disease 2019,” “2019-nCoV,” “novel coronavirus,” “emerging coronavirus,” “Wuhan coronavirus,” “IVIG,” “immunoglobulin, IV,” “IV immunoglobulin,” “human intravenous immunoglobulins,” “intravenous immunoglobulin,” “intravenous immunoglobulins,” “intravenous IG,” and “immunoglobulin, intravenous”. The search strategies used in the databases can be accessed by contacting the corresponding author.

Data collection process

Three reviewers (S. Rezaei, B. Fatemi, and M. Peikanpour) independently selected eligible studies and collected the following data when available: study design, patient demographics, disease characteristics, and outcomes of interest (mortality, ICU admission, mechanical ventilation, length of hospital stay, and ICU

length of stay). Reviewers extracted data from the included studies' texts, tables, and graphs. Any discrepancies were resolved by the two lead reviewers (S. Rezaei and B. Fatemi).

Risk of bias in individual studies

Three reviewers (S. Rezaei, B. Fatemi, and M. Peikanpour) independently assessed all included studies for risk of bias (RoB). Disagreements regarding RoB were resolved by discussion and consensus. We used version 2 of the Cochrane Risk-of-Bias Tool (RoB 2) to assess RoB in the RCTs. In addition, the Newcastle Ottawa scale (NOS) tool was used to assess RoB in cohort studies.

Summary measures

In the meta-analysis phase, we calculated standardized mean differences (SMDs) and relative risks (RRs) based on the type of study outcomes.

Synthesis of results

The heterogeneity of the included studies was assessed using the inconsistency index I^2. Because of significant heterogeneity among studies, we used the DerSimonian and Laird random-effects model (13-15). The combined effect size and its 95% confidence interval (CI) for each outcome of interest were calculated using the number of events in both IVIG cases (IVIG plus SOC) and controls (SOC). The subgroup meta-analysis of study outcomes based on the study design was also performed (RCT and cohort).

RoB across studies

The potential risk of publication bias was assessed by visual inspection of the funnel plots for each study outcome. In this approach, we plotted effect sizes against their standard errors.

Additional analyses

Using STATA software, meta-regression analyses were performed to assess the effects of sex, age, study design, and baseline disease stage on the primary outcome. Meta-analyses were performed using RevMan 5.4.1. Differences were considered significant if the $P < 0.05$.

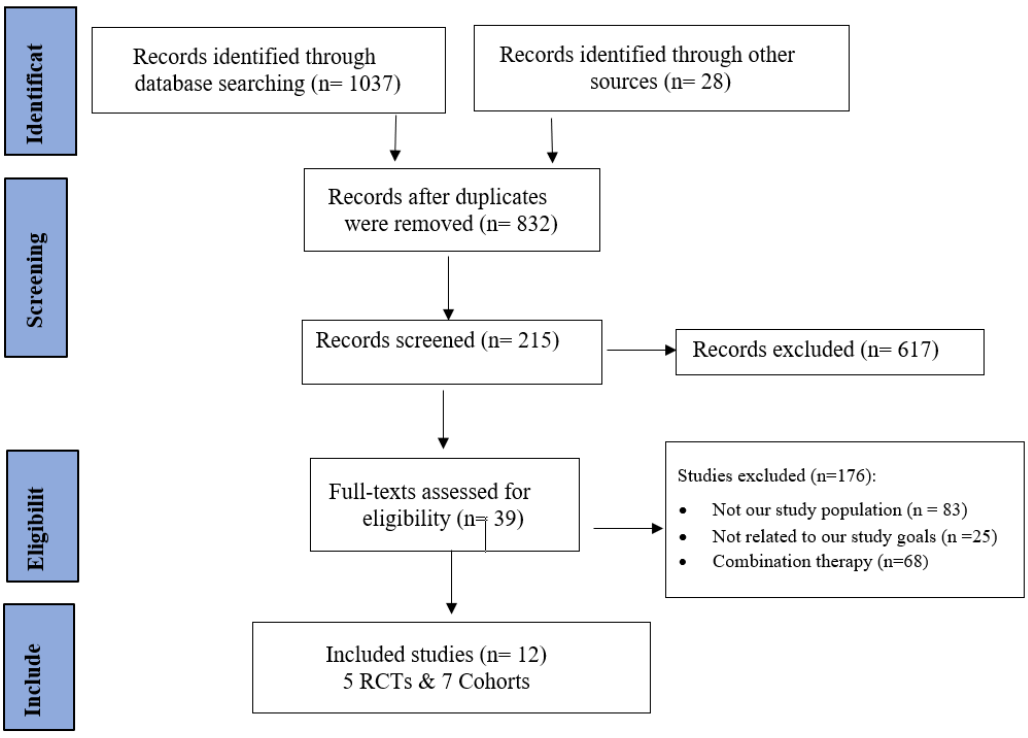

Fig. 1. Flow diagram of the systematic review.

RESULTS

Study selection

Figure 1 illustrates the results of our search strategy (PRISMA flow diagram). A systematic search of online databases yielded 1037 citations, and 28 were found in the manual search. After removing duplicates, 832 articles remained. Twelve articles, including five RCTs and seven cohorts, were finally included in our systematic review and meta-analysis based on the eligibility criteria.

Characteristics of the studies

Of the 12 included articles, five were RCT (16-20), and seven were cohort studies (21-27). In addition, Shao *et al.* considered two separate studies in this meta-analysis because of the inclusion of severe and critical patients. A total of 2,156 patients were included in these studies, of which 995 received IVIG plus SOC and 1,161 received only SOC. These studies evaluated the effect of IVIG administration in patients with moderate, severe, and critical COVID-19.

The mean age of the patients in the IVIG group was 57.72 ± 9.69 years compared with 58.50 ± 11.03 years in the SOC group. In addition, nearly 49% of the patients in the IVIG group and 53% in the SOC group were males. The median follow-up time was 28 (range 20 to 100) days. Table 1 illustrates the baseline characteristics of the patients in the included studies.

Mortality was reported as the primary outcome in all 13 included studies. Moreover, length of hospital stay, ICU length of stay, and mechanical ventilation were reported in 10, 4, and 3 studies, respectively.

RoB within studies

Based on the RoB tool, all included RCTs had a high risk of bias (high risk of bias in at least one domain). Based on the NOS risk of bias tool, four of the seven cohort studies were of good quality, and the other three studies were of fair quality (Table 2). None of the included cohorts reported "loss to follow-up" and "patient withdrawals" as a domain of the NOS tool, and this was the main source of existing bias among the included cohorts.

Results of individual studies and synthesis of results

Mortality

Pooling all 13 studies (five RCTs and eight cohorts) with 2156 patients, the RR of mortality was 0.77 (95% CI 0.59 to 1.01, $P = 0.06$; Fig. 2). The I^2 statistic of 59% showed substantial heterogeneity between studies assessing mortality.

In addition, the symmetry of the funnel plot suggests against publication bias (Fig. 3A).

To perform a sensitivity analysis, we repeated the meta-analysis for the RR of mortality based on the classification of studies into two subgroups: severe and critical.

Three studies, two cohorts, and one RCT, with 588 critical patients, yielded a RR of mortality equal to 0.73 (95% CI 0.54 to 0.97, $P = 0.03$). In contrast, eight studies (five cohorts and three RCTs) with 2002 severe patients yielded an RR of mortality of 0.78 (95% CI 0.49 to 1.24, $P = 0.29$). There was also less heterogeneity in calculating the RR of mortality among critically ill patients than in severely ill patients; I^2 statistics of 42% in critical patients were compared to 66% in severe patients (Fig. 4).

In addition, the asymmetry of the resulting funnel plot suggests the possibility of publication bias (Fig. 3B).

Hospital length of stay

A total of 10 studies (four RCTs and six cohorts) with 1030 patients reported hospital length of stay as a secondary outcome. The pooled SMD of hospital length of stay was 0.84 (95% CI -0.43 to 2.11; $P = 0.20$; Fig. 5). The I^2 statistic equal to 98% indicates a critical level of heterogeneity between included studies in measuring the length of stay outcome.

In addition, the funnel plot asymmetry suggests publication bias for the pooled SMD of hospital length of stay (Fig. 3C).

ICU length of stay

Only four RCTs with 276 patients reported ICU length of stay as a secondary outcome. The pooled SMD of ICU length of stay was -0.07 (95% CI -0.92 to 0.78; $P = 0.86$; Fig. 6). The I^2 statistics of 91% suggest considerable heterogeneity between included studies. Moreover, the resulting funnel plot asymmetry suggests probable publication bias (Fig. 3D).

Table 1. Baseline characters of included studies.

Study (References)	Study type	Country	Duration of administration (day)	SOC	Follow-up (day)	Age mean ± SD		Male n (%)		Stage of disease
						IVIG	SOC	IVIG	SOC	
Cao (22)	Cohort	China	5	Oxygen therapy, antivirals,	28	56.84 ± 5.81	59 ± 4.48	19 (73)	57 (64)	Severe
Esen (21)	Cohort	Turkey	5	Hydroxychloroquine, antivirals, azithromycin, tocilizumab or anakinra, methylprednisolone	40	65.3 ± 15.49	71.3 ± 15.26	37 (72)	31 (73)	Critical
Farrokhpour (23)	Cohort	Iran	5	Antivirals, hydroxychloroquine	20	64.52 ± 12.97	72.42 ± 16.6	16 (69)	26 (60)	Severe
Gharebaghi (17)	RCT	Iran	3	Antiviral and one chloroquine-class drug	28	54.79 ± 3.68	56.12 ± 4.69	21 (70)	20 (68)	Severe
Huang (24)	Cohort	China	3	Corticosteroids, Chinese medicine, hydroxychloroquine, thymosin α, antivirals	100	55.72 ± 5.68	54.82 ± 4.67	23 (51)	50 (55)	Moderate
Gonzalez (18)	RCT	Mexico	5	Convalescent plasma	28	56.24 ± 15.57	60.7 ± 19.49	39 (65)	80 (61)	Critical
Raman (16)	RCT	India	5	Azithromycin, antivirals, piperacillin + tazobactam,	28	48.4 ± 11.6	49 ± 13.5	14 (28)	19 (38)	Moderate
Sakoulas (20)	RCT	USA	3	Antiviral, convalescent plasma, glucocorticoid		54 ± 9.32	54 ± 8.82	10 (62)	10 (58)	Severe
Liu (27)	Cohort	China	9	Antiviral, Glucocorticoid	28	63.67 ± 13.39	64 ± 14.88	243 (57)	258 (61)	Severe
Shao (25)	Cohort	China		NA	28	60.88 ± 3.53	55.7 ± 5.49			Critical, Severe
Tabarsi (19)	RCT	Iran	3	Oxygen and fluid support, antivirals, hydroxychloroquine	28	54.29 ± 12.89	52.47 ± 14.49	40 (76)	25 (78)	Severe
Hou (26)	Cohort	China		Antiviral, Glucocorticoid	28	54.8 ± 12.4	55.3 ± 15.5	27 (57)	34 (51)	Severe

SOC, Standard of care; RCT, randomized controlled trials; IVIG, intravenous immunoglobulin; SOC, standard of care; NA, not applicable.

Table 2. Risk of bias in cohort studies based on the Newcastle-Ottawa scale tool.

Study	Selection				Comparability		Outcome			Total quality score	Quality
Cao (22)	1	1	1	1	1	0	1	0	0	6	Fair quality
Esen (21)	1	1	1	1	1	0	1	1	0	7	Good quality
Farrokhpour (23)	1	1	1	1	1	0	1	0	0	6	Fair quality
Huang (24)	1	1	1	1	1	1	1	1	0	8	Good quality
Liu (27)	1	1	1	1	1	1	1	0	0	7	Good quality
Shao (25)	1	1	1	1	0	0	1	1	0	6	Fair quality
Hou (26)	1	1	1	1	1	1	1	0	0	7	Good quality

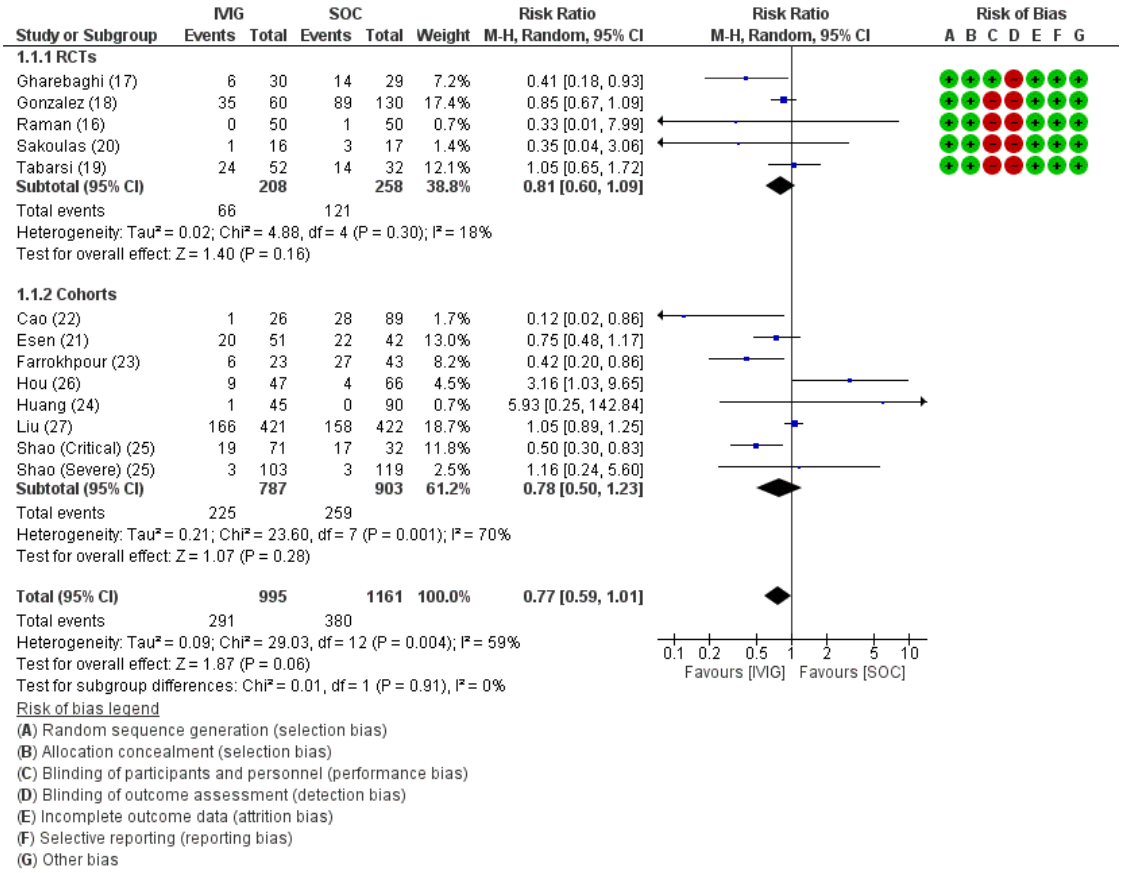

Fig. 2. Forest plot of the pooled risk ratio of mortality. CI, Confidence interval; IVIG, intravenous immunoglobulin; M-H, Mantel-Haenszel method; SOC, the standard of care.

Mechanical ventilation

Only three of the 13 studies (two RCTs and one cohort) with 230 patients reported mechanical ventilation as a secondary outcome. The pooled RR of mechanical ventilation was 1.50 (95% CI 0.29 to 7.83; P = 0.63; Fig. 7). The I^2 statistic of 80% also indicates substantial heterogeneity among the included studies. In addition, the small number of included studies makes it difficult to assess whether publication bias exists based on the funnel.

Risk of bias across studies

In the mortality assessment, the funnel plot's symmetry indicated no publication bias (Fig. 3A). In addition, the asymmetry of the funnel plot in assessing the hospital length of stay suggests publication bias (Fig. 3C). However, due to the small number of studies in the pooled ICU and the need for mechanical ventilation, it was difficult to assess publication bias using the funnel plots (Fig. 3D).

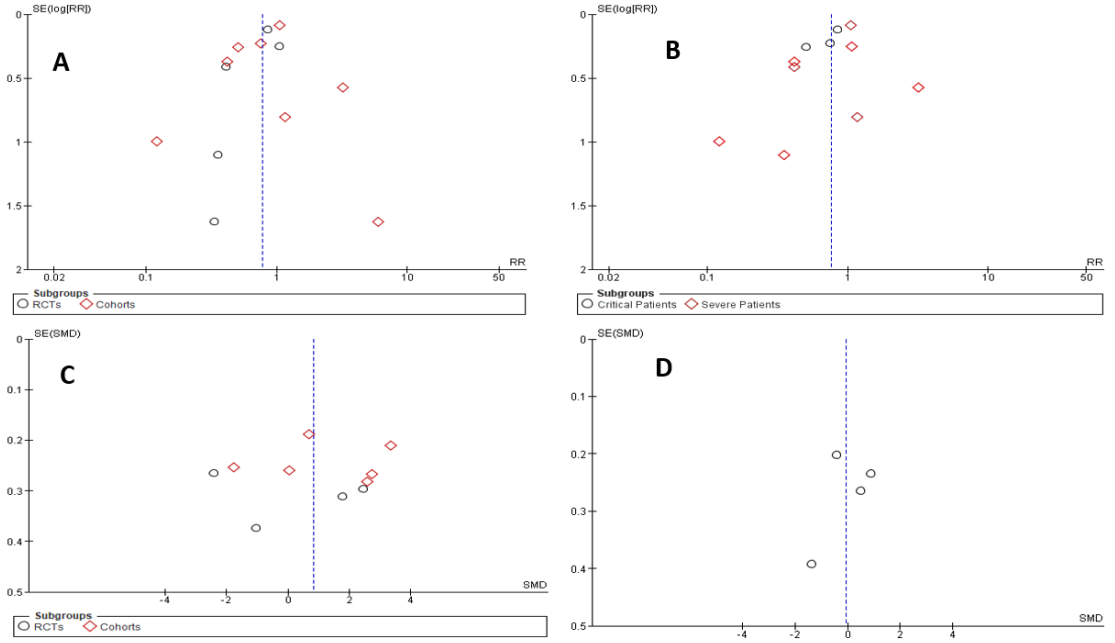

Fig. 3. Funnel plots. (A) Funnel plot of mortality assessment; (B) funnel plot of the RR of mortality in severe and critically ill patients; (C) funnel plot of hospital length of stay assessment; (D) funnel plot of ICU LOS. RR, Risk ratio; SE, standard error; SMD, standardized mean difference.

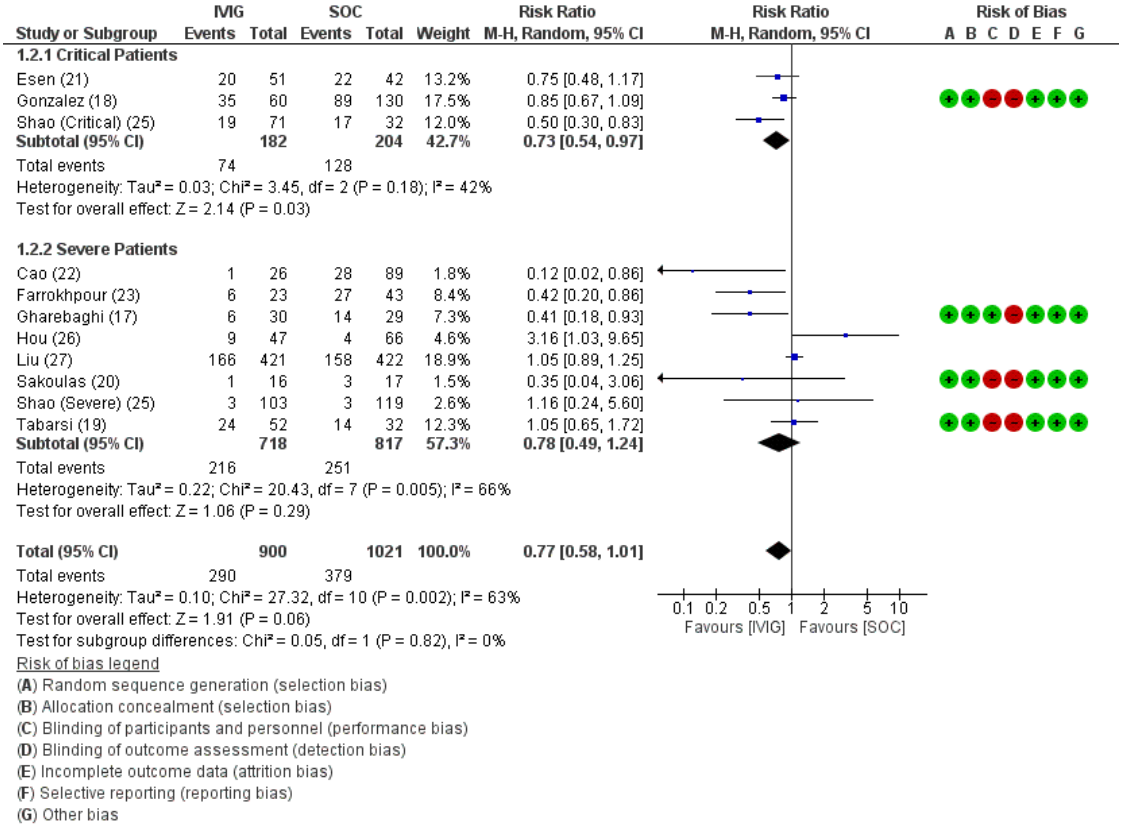

Fig. 4. Forest plot of the pooled risk ratio of mortality in critical and severe patients. CI, Confidence interval; IVIG, intravenous immunoglobulin; M-H, Mantel-Haenszel method; SOC, the standard of care.

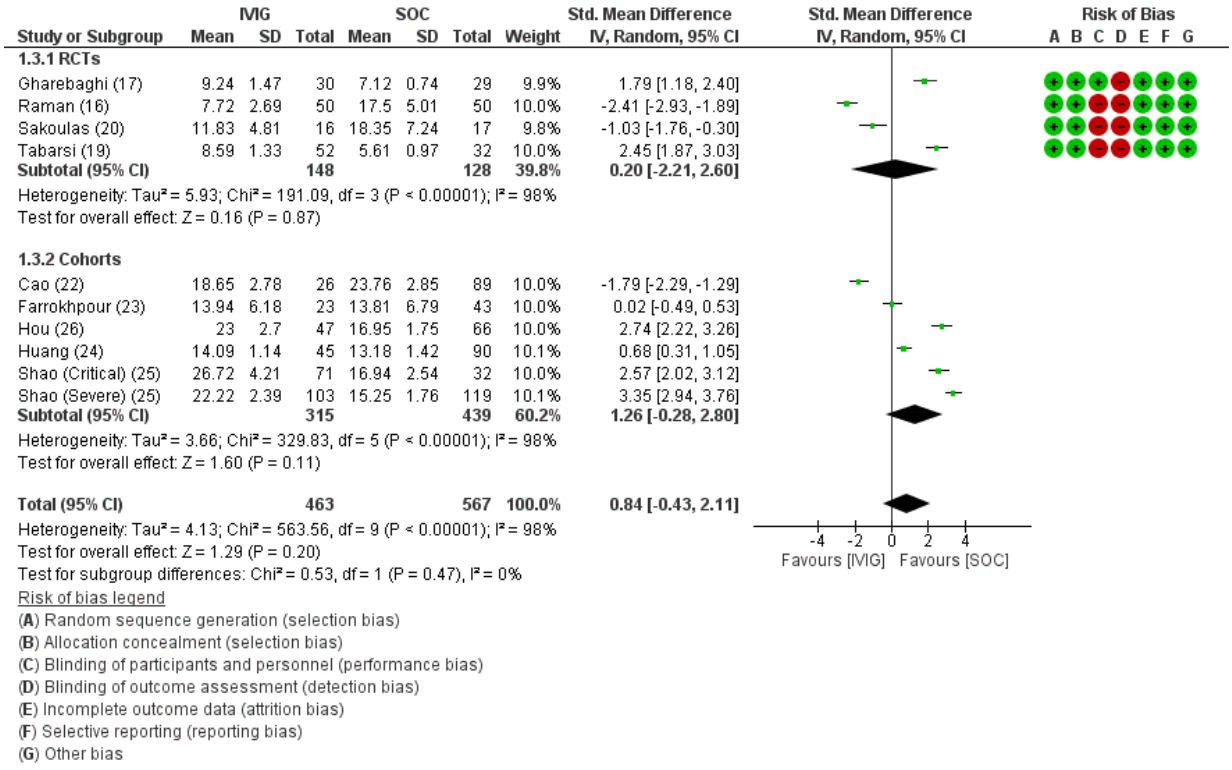

Fig. 5. Forest plot of pooled standardized mean difference of hospital length of stay. CI, Confidence interval; IVIG, intravenous immunoglobulin; SOC, the standard of care; Std, standardized.

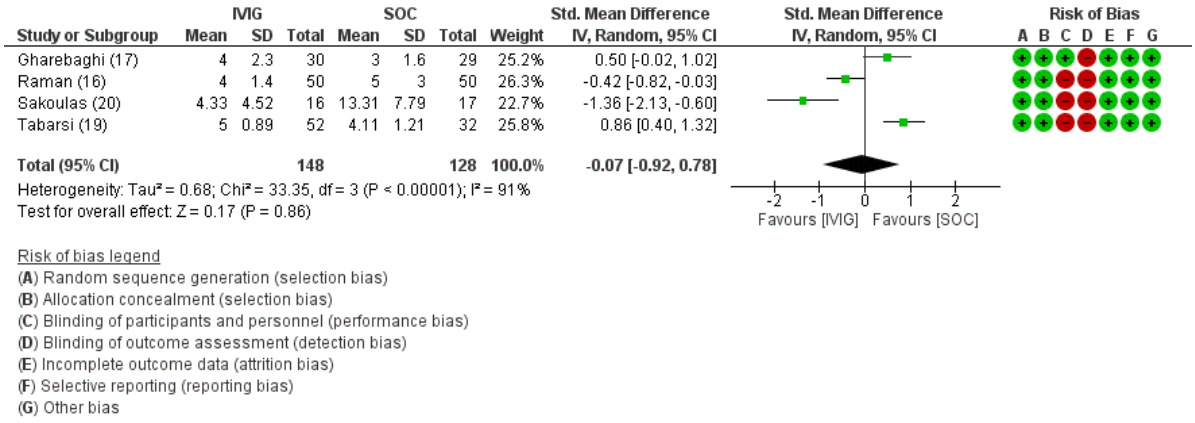

Fig. 6. Forest plot of pooled standardized mean difference of ICU length of stay. CI, Confidence interval; IVIG, intravenous immunoglobulin; SOC, Standard Of care; Std, Standardized.

Additional analysis

A subgroup analysis was performed based on the type of study. The cohort studies' results confirmed RCT results for all outcomes except the need for mechanical ventilation.

In meta-regression, we found no association between the RR of mortality between IVIG and SOC groups and the independent variables of sex, age, study design, and stage of disease, with a significant level of $P < 0.05$.

After excluding the outlier study (24) as a sensitivity analysis of our result, the RR of mortality did not change significantly (RR = 0.76; 95% CI 0.58 to 1.00, $P = 0.05$, $I^2 = 60\%$).

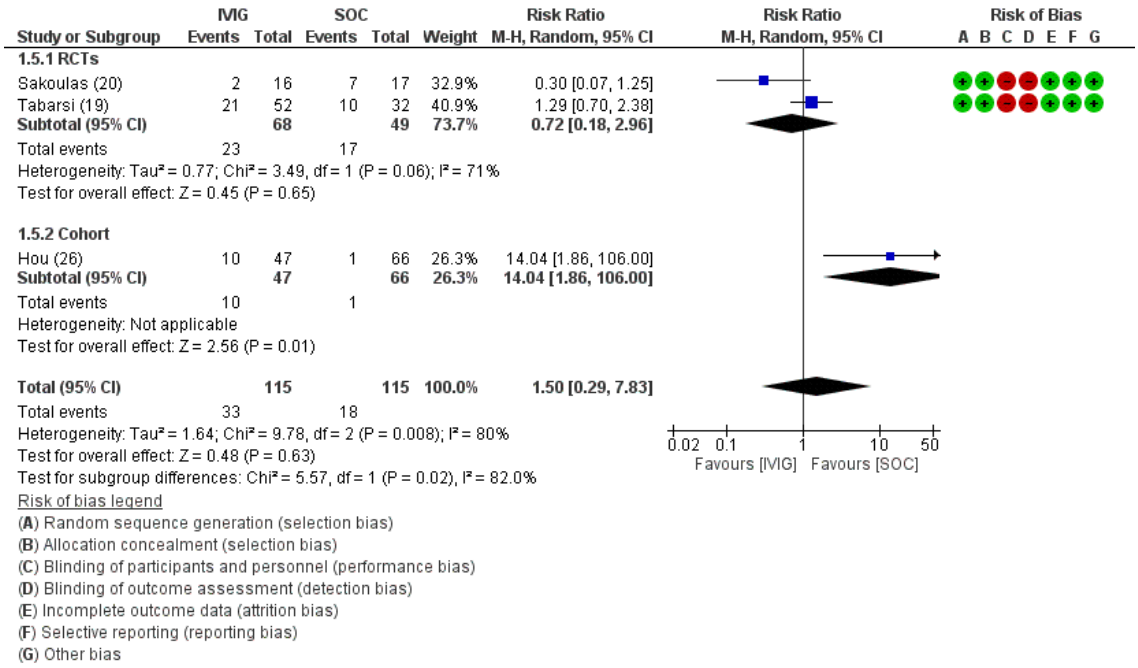

Fig. 7. Forest plot of the pooled risk ratio of need for mechanical ventilation. CI, Confidence interval; IVIG, intravenous immunoglobulin; M-H, Mantel-Haenszel method; SOC, the standard of care.

DISCUSSION

Summary of evidence

This systematic review and meta-analysis aimed to evaluate the clinical efficacy of IVIG in hospitalized patients with COVID-19. Although there are several studies on the clinical use of IVIG in COVID-19 patients (28), there is much controversy with no clinical consensus in this regard (29). IVIG therapy can cause severe adverse events, including hypersensitivity reactions, transfusion-related lung injury, renal injury, thromboembolism, and other delayed adverse events (30). In this systematic review, the relevant articles were selected and carefully evaluated. Finally, 12 studies were selected for further analysis, and the corresponding data were extracted. The risk of bias in these studies was also assessed. The data on clinical parameters such as mortality, ICU admission, mechanical ventilation, length of hospital stay, and length of ICU stay were extracted from the abovementioned studies. The data were extracted and pooled for meta-analysis. The SMD and 95% confidence interval were calculated for each parameter. The result showed that the IVIG therapy, at $P < 0.05$, was not statistically associated with lower mortality compared to the standard care therapy group.

This study also examined the effects of IVIG therapy in severe and critical populations. Huang *et al.* (24) and Raman et al. (16) studied patients in the moderate phase, whereas Esen *et al*. (21), Gonzalez *et al*. (18), and Shao *et al*. (25) studied critical patients. The results of this sub-analysis showed that critical patients benefited more than severe patients. This result differs from Xiang's study. Like the current study, Xiang *et al.* conducted a meta-analysis to evaluate the efficacy of IVIG therapy for COVID-19. They reported no significant difference between severe and critical patients in point of clinical efficacy. IVIG has anti-inflammatory properties that could lower the level of inflammatory cytokines and stop the cytokine release syndrome. However, the effect of IVIG on clinical efficacy was not statistically significant in Xiang *et al.* meta-analysis (28).

The results of our study showed that there is no statistically significant difference between IVIG therapy and SOC in terms of mortality reduction in severe patients. However, those critical cases benefited from IVIG therapy in terms of mortality reduction. Furthermore, the heterogeneity of the studies was high, which

might affect the results. ICU admission, mechanical ventilation, length of hospital stay, and length of ICU stay are dependent variables. Intubated patients need to be treated in the ICU, which increases the length of ICU stay. These parameters are related to other variables such as the severity of illness, patients' underlying diseases, days between symptom onset and admission, nursing care, and other therapeutic interventions (31). Previous studies have shown that the SARS-CoV-2 virus reaches its peak replication in the first seven days after exposure and that most patients form antibodies to SARS-CoV-2 in the following days (32). This pathophysiology indicates that IVIG should be administered promptly.

The results showed that the IVIG therapy did not statistically improve the above variables. However, the population studied was very heterogeneous, and the results should be interpreted cautiously. Pei *et al*. (33) and Xiang *et al*. (28) performed two meta-analyses on the clinical efficacy of IVIG therapy in COVID-19 cases. They included six and seven studies, respectively. More recent articles were included in the current study for a comprehensive evaluation. No statistically significant differences were found between the IVIG therapy and standard care group in either of the above meta-analyses. However, Pei *et al*. (33) found that IVIG therapy reduced mortality in critical patients. However, Pei *et al*. study faced some limitations, including a small sample size and low analysis quality with high heterogeneity.

Limitations

The current meta-analysis has some limitations. The articles studied did not measure the immunity panel with humoral and cellular responses. Therefore, the effects of IVIG therapy on immune system induction in COVID-19 patients remain unresolved. Another limitation is the pure effects of IVIG therapy. Due to the nature of the COVID-19 disease, holding other treatments from patients was difficult and unethical. For example, the administration of corticosteroids may confound final clinical outcomes. This issue is even more important when the case is critical, and all interventions can be used as a last resort. Well-designed clinical trials should take such biases into account.

CONCLUSION

The results of this meta-analysis showed that there is no statistical difference between IVIG therapy and the standard care group. Mortality, ICU admission, mechanical ventilation, length of hospital stay, and length of ICU stay were not significantly improved among IVIG recipients. However, statistical indifference is not precisely meaning to clinical indifference, and there is a need to conduct more RCTs.

Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

M. Peikanpour and F. Dastan contributed to the conceptualization and design of the study; S. Rezaei and B. Fatemi contributed to systematic searching, screening, article selection, data extraction, data analysis, coordination, and manuscript drafting; A. Saffaei contributed to the data analysis and drafting of the manuscript; F. Dastan and M. Peikanpour contributed to the interpretation of results and supervision of execution. All authors critically revised the manuscript and have contributed to the final approval of the version to be submitted.

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