Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Immunopharmacology 96 (2021) 107732

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Efficacy of IVIG (intravenous immunoglobulin) for corona virus disease 2019 (COVID-19): A meta-analysis

Huai-rong Xiang [a], Xuan Cheng [a], Yun Li [a], Wen-wen Luo [a], Qi-zhi Zhang [a], Wen-xing Peng [a,b,*]

[a] Department of Pharmacy, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[b] Institute of Clinical Pharmacy, Central South University, Changsha, Hunan 410011, China

ARTICLE INFO

Keywords:
COVID-19
IVIG
Efficacy
Meta-analysis

ABSTRACT

Background: The benefit of IVIG (Intravenous Immunoglobulin) therapy for COVID-19 remains controversial. We performed a meta-analysis to investigate the efficacy of IVIG treatment in patients with COVID-19.
Methods: We searched articles from Web of Science, PubMed, Embase, the Cochrane Library, MedRxiv between 1 January 2020 and February 17, 2021. We selected randomized clinical trials and observational studies with a control group to assess the efficiency of IVIG in treating patients with COVID-19. Subjects were divided into 'non-severe', 'severe' and 'critical' three subgroups based on the information of the study and the World Health Organization (WHO) definition of severity. We pooled the data of mortality and other outcomes using either a fixed-effect model or a random-effects model.
Results: Our meta-analysis retrieved 4 clinical trials and 3 cohort studies including 825 hospitalized patients. The severity of COVID-19 is associated with the efficiency of IVIG. In critical subgroup, IVIG could reduce the mortality compared with the control group [RR = 0.57 (0.42–0.79, I^2 = 025%). But there was no significant difference in the severe or non-severe subgroups.
Conclusion: IVIG has demonstrated clinical efficacy on critical ill patients with COVID-19. There may be a relationship between the efficacy of IVIG and the COVID-19 disease severity. Well-designed clinical trials to identify the clinical and biochemical characteristics in COVID-19 patients' population that could benefit from IVIG are warranted in the future.

1. Introduction

In 2019, a novel coronavirus disease (COVID-19) which caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has aroused an outbreak worldwide. COVID-19 has been diagnosed in 110.7 million cases and over 2.4 million deaths since the start of the pandemic [1]. The high infection rate and mortality pose an unprecedented challenge to clinicians. Numerous clinical trials, retrospective studies and observational studies about SARS-Cov-2 disease are underway, and we found some effective antiviral agents against the infection but the lack of standardized therapy makes the condition worse. In parallel with the development of new antiviral agents and vaccines in this disease, it is necessary to research the efficacy of existing therapeutic such as Intravenous immunoglobulin (IVIG).

IVIG is a kind of blood product from healthy donors containing a polyclonal IgG antibody. Known for its anti-inflammatory reactions, it has been used to treat patients with inflammatory diseases including Kawasaki diseases, multiple sclerosis and so on [2]. The SARS-Cov-2 virus is a member of coronavirus family. Based on the experience of treating previous coronavirus diseases such as severe acute respiratory syndrome (SARS) [3], Middle East respiratory syndrome (MERS) [4] and swine-origin influenza virus (SOIV) H1N1 [5], though no sufficient clinical data, it might be believed that IVIG could be used in COVID-19 patients and be one of worthwhile therapeutic options. The controversy over the efficacy of IVIG for improving in clinical symptoms and mortality, nevertheless, has been occurring with the increasing number of COVID-19 patients [6–8]. There still exist types of studies which have evaluated the efficiency of IVIG in patients with COVID-19 so far [9,10]. A meta-analysis to review these evidences is greatly essential for the use of IVIG for COVID-19. We performed a meta-analysis by selecting literature from five databases to synthesize the results of well-done randomized clinical trial (RCTs) and observational studies to tested

* Corresponding author at: Department of Pharmacy, The Second Xiangya Hospital, Central South University, 139, Middle Renmin Road, Changsha, Hunan 410011, China.
E-mail address: pwx.csu@csu.edu.cn (W.-x. Peng).

https://doi.org/10.1016/j.intimp.2021.107732
Received 16 March 2021; Received in revised form 12 April 2021; Accepted 26 April 2021
Available online 30 April 2021

the significance of IVIG therapy and give some advice for clinical treatment.

2. Methods

This meta-analysis was described by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA-P) statement [11]. The protocol for this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021238498).

2.1. Search strategy

Two reviewers (Yun Li and Xuan Cheng) searched Web of Science, PubMed, Embase, the Cochrane Library, MedRxiv for clinical trials and observational studies. A combination of search terminologies ("Coronavirus Disease 2019" OR "COVID-19" OR "SARS-Cov-2" OR "2019-nCoV Diseases" OR "COVID 19 Virus Infection") AND ("IVIG" OR "immunoglobulin" OR "IVIG"). Search were down on February 17, 2021. The search was imposed restriction on the date between 1.1 2020 to 2.17 2021. No restriction on the geographical location or language of the studies.

2.2. Selection criteria

Inclusion criteria included:

(1) Study types: Clinical trials and observational studies which patients were divided into treatment group using IVIG and the control group not using IVIG.

(2) Patients: Patients with lab-confirmed COVID-19, aged 18 years and above.

(3) Outcome: The primary outcome measure was defined as mortality. The secondary outcome measures were mechanical ventilation need, length of hospital stay (day) and length of Intensive Care Unit (ICU) stay (day).

Exclusion criteria included:

(1) Studies with insufficient data;

(2) Studies with no control group;

(3) Review articles, viewpoints, editorials, and expert opinion.

2.3. Study selection and data extraction

Two reviewers (Huai-rong Xiang, Wen-wen Luo) independently screened the titles and abstracts of the studies to retrieve articles and extracted data based on the inclusion and exclusion criteria. Any discrepancies would be resolved through discussion (with a third author, if necessary).

Each included article was thoroughly reviewed, the following data and information were extracted:

(1) First author, publication date, region and study type.

(2) Treatment plan (including IVIG dosage, frequency and duration).

(3) Outcome indicators (including 28-mortality, the length of hospital or ICU stays).

Data was extracted and entered to a pre-defined and piloted Microsoft excel database.

2.4. Risk of bias assessment

Two reviewers (Qi-zhi Zhang and Xuan Cheng) independently evaluated the quality of this literature. In case of any disagreement, the third reviewer (Yun Li) consulted for reconciling any difference of opinion. The new Cochrane risk of bias tool [12] was used to evaluate the methodological quality of the RCTs, which includes five domains: 'random sequence generation', 'concealment of allocation schemes', 'blinding', 'completeness of outcome data', and 'selective reporting'. For each domain, risk of bias judgements is 'high', 'unclear' or 'low'. The Newcastle-Ottawa Scale (NOS) [13] was to evaluate the quality of the non-RCTs which comprises patient selection, comparability between two groups, and research results three components. The total score is 9 which was divided into three categories: (a) high risk (1–3); (b) some concerns (4–6); (c) low risk (7–9).

2.5. Statistical analysis

We conducted a subgroup to test the impact of COVID-19 disease severity using the World Health Organization definition of severity [14].

Critical ill group: defined by the criteria for: (1) Acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy. Severe group: defined by any of: (1) Oxygen saturation $< 93\%$ on room air. (2) Respiratory rate > 30 breaths/min in adults (3) PaO2/FiO2 ≤ 300 mmHg. Non-severe group: defined as absence of any criteria for severe or critical COVID-19.

All statistical analysis was conducted by RevMan 5.4 software. Statistical heterogeneity was evaluated by the I-squared (I^2) test. According to the Cochran's Handbook for the systematical reviews of intervention, I^2 value: 0% to 40% may represent not important heterogeneity, 40% to 75% represent moderate heterogeneity, 75% to 100% represent considerable level of heterogeneity. A fixed-effect model was used if $I^2 <$ 50%. When I^2 value $> 60\%$, heterogeneity was considered significant, and the random-effect model was applied. The select indicators were included dichotomous data and continuous data. We used relative risk (RR) for dichotomous data and mean difference (MD) or standard mean difference (SMD) for continuous data with 95% confidence interval (95%CI).

We computed missing means and standard deviations (SDs) from medians, ranges (minimum to maximum), and interquartile ranges (IQRs) using the methods proposed by Hozo et al. [15] and Wan et al. [16].

3. Results

3.1. Description of the results

As shown in Fig. 1, the total search process yielded 5287 records. Following removing duplicates publications 4342 studies were remained. After screening of titles and abstracts we excluded 4213 studies as these include reviews, commentaries, mechanism researches, and irrelevant to COVID-19. After comprehensively screening 129 full text, only 7 eligible studies were included. (RCTs: $n = 4$, Retrospective cohort studies (RCSs): $n = 3$) including 825 patients [17–23]. See Table 1

According to the inclusion criteria of the article and the characteristic of patients at baseline, we divided subjects into 'non-severe' (two studies), 'severe' (four studies) and 'critical' (two studies) three subgroups to address heterogeneity. Due to the Shao et al. study provided both severe and critical patients' outcomes, we defined the data of critical type patients as Shao et al. 2020 (a), and of the severe type patients as Shao et al. 2020(b).

3.2. Quality assessment

The quality of the included RCTs is shown in the Fig. 2. Two RCTs [18,20] provided the methods for the random sequence generation. Only one RCT [19] provided the blinding of participants and personnel and blinding of outcome assessment. All three retrospective cohort studies have adjusted the confounders in the analysis and the range of score is 5–6. See Table 2. Overall, the quality of the seven included studies was low.

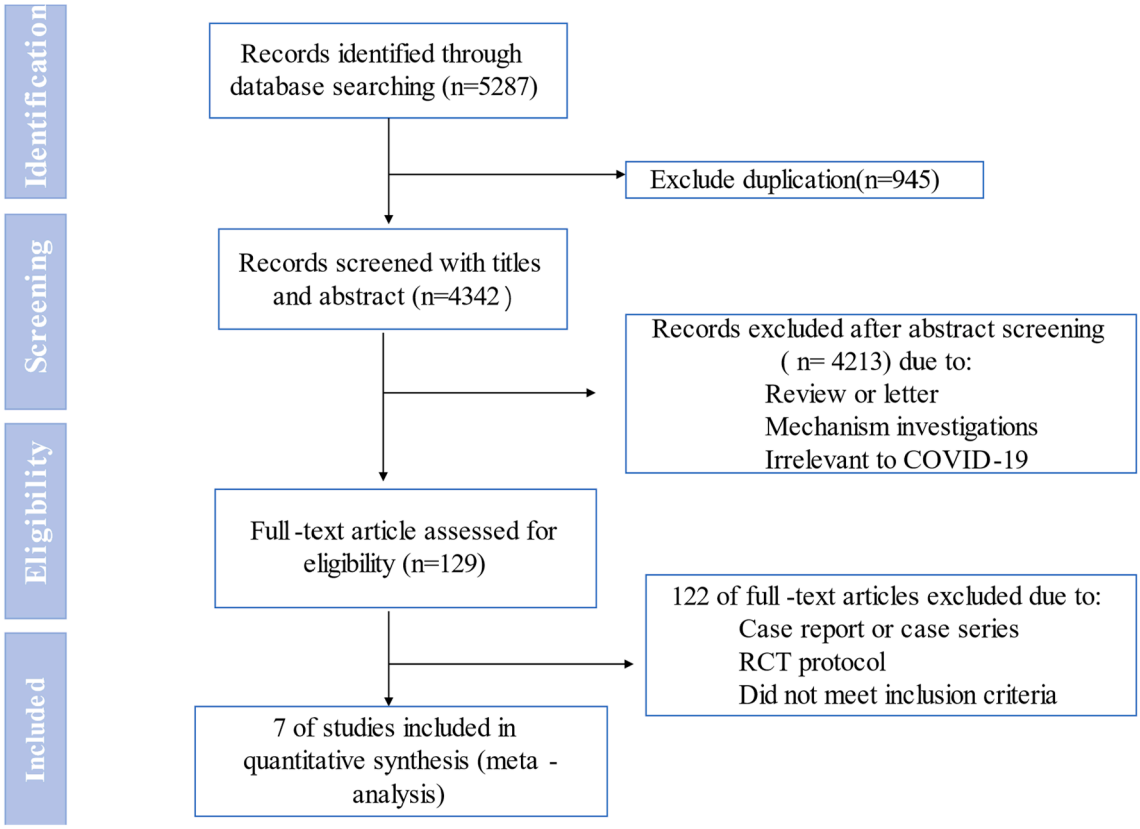

Fig. 1. Flowchart of literature search study selection.

3.3. Mortality

For critical subgroup, the pooled RR was 0.57 (95% CI: 0.42–0.79, I^2 = 0%) which showed the mortality of critical ill patients treated with IVIG was lower compared with the control group. The RR for severe subgroup was 0.76 (95% CI: 0.51–1.14, I^2 = 35%) and for non-severe subgroup was 1.39 (95%CI: 0.23–8.23., I^2 = 20%) which both showed no significant difference. Fig. 3

3.4. Duration of hospitalization

There were six articles reported on the length of hospitalization. For critical subgroup, MD = 10.00 (95%CI: 5.50 – 14.50) which indicated IVIG therapy could prolong the length of hospital stay but only one study available. For severe subgroup the result [MD = 1.75 (−1.94 – 5.45)] demonstrated that IVIG could increase the length of duration in hospitalization but no statistical significance difference. In non-severe subgroup, the pooled MD = −4.40 (−14.98 – 6.19, I^2 = 99%). See Fig. 4.

3.5. Duration of ICU

We only tested the impact of IVIG use on duration of ICU in severe patients because of the limited number of articles. The use of IVIG compared to the control group did not impact the length of hospitalizations. MD = −0.68 (−3.49 – 2.13, I^2 = 84%). See Fig. 5.

4. Discussion

This is the first meta-analysis included 4 RCTs and 3 RCSs investigating the effect of IVIG on clinical outcomes of different severity types patients diagnosed with COVID-19. We analyzed effectiveness of IVIG from these three aspects: mortality, length of duration in hospital or ICU. And our analysis suggested that IVIG may have an impact, with a low level of certainty, in reducing the rate of mortality and prolong the hospital stay in critical patients. We believed that there may be a strong relationship between the efficacy of IVIG and the COVID-19 disease severity.

There was a discrepancy between the random-effect results and fixed-effect results of IVIG versus control group when assessing the length of hospital day. Though the fixed-effect results provided good results that IVIG could increasing the hospital stay in critical and severe subgroup and reducing the days in non-severe subgroup, we still chosen the random-effect meta-analysis results due to the high heterogeneity. In random-effect meta-analysis, the critical subgroup analysis conducted that IVIG could prolong the time of hospitalization while the severe subgroup also showed a slightly trend on prolonging the days in hospital but no statistical significance. Theoretically, if IVIG pose an effective impact, the length of the hospital or ICU stay would be shorter than control group. One possible explanation is that the longer duration of hospitalization in IVIG group may be due to the higher survival rate in IVIG group than control group. So another term, there are more patients survived in IVIG group while similar condition patients in control group had been died earlier. In spite of it all, there are numerous influencing factors to affect the results such as time of the IVIG administration, the function of standard of care and so on. Hence the results should be interpreted with great caution.

The insufficient effects of IVIG therapy in the study may potentially be results of dosage, time of IVIG administration, treatment details (including IVIG use, types and doses of IVIG, and other treatments). In another study, Cao et al. [24] suggests that high-dose of IVIG (0.3–0.5 g per kg weight for five doses) combined corticosteroids could perform a fine outcome and be a valid and safe immunotherapy in COVID-19 patients. All the RCTs we included provided a high dosage which are consistent with Cao et al study's dosage. In Xie et al study [25], the mortality rate of patients with COVID-19 is associated with received IVIG time which suggested that administered early on IVIG treatment.

Table 1
Characteristics of the studies included in the meta-analysis.

Frist author, year	Type of study	country	Type of disease	Sample (male)		Treatment		Summary
				intervention	control	intervention	control	
Gharebaghi 2020	RCT	Iran	Severe; A PCR-confirmed COVID-19 diagnosis, involvement of > than 30% of both lungs (ground-glass opacity) in high-resolution computed tomography (HRCT) (confirmed by two radiologists), O_2saturation($satO_2$) of < 90%, and a lack of adequate response to initial treatment including at least both one antiviral and one chloroquine-class drug.	30 (21)	29 (20)	IVIG (human) flebo gamma 5% DIF GRIFOLS, four vials of 5 gm5 IVIG daily for three consecutive days; receive the same treatments as were introduced initially	Placebo; receive the same treatments as were introduced initially	1. Improve their clinical outcome including serum creatinine, white blood cell which were higher in the control group 2. Reduce mortality rate. 3. Longer duration of hospitalization in the treatment group.
Sakoulas 2020	RCT	USA	Severe: SpO_2 < 96% on > 4 L O_2 by nasal cannula APACHE II: (7, 7.5)	16(10)	17(10)	IVIG 0.5 g/Kg for 3 days and SOC; All received methylprednisolone	Receive any treatment not part of a RCT at the time of enrollment	1. Lower rate of mechanical ventilation; 2.Shorter median hospital length of stay; 3. Shorter median ICU stay; 4. Greater improvement in PaO2/FiO2 at 7 days.
Tabarsi 2021	RCT	Iran	Severe Breaths/min ≥ 30, $SpO_2 \leq 93\%$ PaO_2/ $FiO_2 \leq 300$ mmHg.	52(40)	32(25)	400 mg/kg daily for three doses IVIG, premedicated with 500 mg Acetaminophen, 100 mg Hydrocortisone, and 25 mg Diphenhydramine 30 min before the injection. SOC: oxygen and fluid support, lopinavir/ ritonavir (200/50 mg, Hetero labs), two tablets twice a day, and hydroxychloroquine (Tehran-Daru) 200 mg two times daily.	SOC	1. No significant difference between the two groups in terms of mortality rate and the need for mechanical ventilation; 2. The length of hospital stay was lower for the control group than that of the intervention group; 3. Positive relationship between the time from hospital admission to IVIG initiation and the length of stay in the hospital and ICU among the survivors.
Raman 2021	RCT	India	Non-severe: Pneumonia were defined as: body temperature ≥ 38.0℃ or PaO_2/ FiO2 100–300 mmHg or respiratory rate > 24/ min and oxygen saturation 90–93% on room air or lung involvement confirmed with chest X-ray.	50 (14)	50 (19)	daily received immunoglobulin 0.4 g/kg body weight for 5 days SOC: Azithromycin; Lopinavir/ritonavir; Piperacillin + Tazobactam; Acetaminophen and Pantocid.	SOC	1. Reduce the number of days to clinical improvement, 2. Reduce the duration of use of mechanical ventilation; duration of hospitalization and length of stay in intensive coronary care unit from day 0 to 28. 3. Increased the proportion of patients with negative RT-PCR on day 14.
Shao 2020	RCS	China	Severe , andcritical ill	174 (112)	151 (77)	NM	NM	1. The total duration of disease was longer in the IVIG group 2. Only in patients with critical type, IVIG could significantly reduce the 28-day mortality, decrease the inflammatory response and improve some organ functions; 3.The application of IVIG in the early stage (admission ≤ 7 days) with a high dose (>15 g per day) exhibited significant reduction in 60-day mortality in the critical-type patients.
Esen 2021	RCS	Turkey		51 (37)			SOC	

(*continued on next page*)

Table 1 (*continued*)

Frist author, year	Type of study	country	Type of disease	Sample (male)		Treatment		Summary
				intervention	control	intervention	control	
			Critical (a) respiratory rate > 30/min, (b) signs of dyspnea and respiratory distress. (c)SpO_2 < 90% and PaO_2 < 70 mmHg, despite nasal oxygen support of > 5 L/min. (d) PaO_2/FiO_2 < 300 (mild acute respiratory distress syndrome (ARDS).	42 (31)	a dose 30 g/day IVIG for five consecutive days SOC: hydroxychloroquine (800 mg loading dose, LD; 400 mg/day maintenance dose, MD for 5 days); favipiravir (3200 mg LD; 1200 mg/day MD for 5 days), azithromycin (500 mg LD; 250 mg/day MD for 5 days), oseltamivir (150 mg/day for 5 days), tocilizumab or anakinra depending on inflammatory markers, methylprednisolone (200 mg/day), high dose vasopressors in case of septic shock and vitamin C (6 g/day i.v. for 7 days).		IVIG group significantly prolonged median survival time and reduced plasma levels of C-reactive protein.
Huang 2021	RCS	China	Non-severe; (1) Respiratory distress, respiratory rates ≥ 30/min; (2) Pulse oxygen saturation ≤ 93% in the resting state; (3) Oxygenation index ≤ 300 mmHg; (4) Require mechanical ventilation; (5) Shock; (6) Combined with other organ failures and needed treatment in ICU.	45(23)	90(50)	IVIG SOC: Corticosteroids, Chinese Medicine, Hydroxychloroquine, Thymosin α, Arbidol, Lopinavir/Ritonavir	SOC	In non-severe patients with COVID-19, no benefit was observed with IVIG therapy beyond standard therapy.

Note: IVIG: intravenous immunoglobulin; SOC: standard of care; NM: not mention.

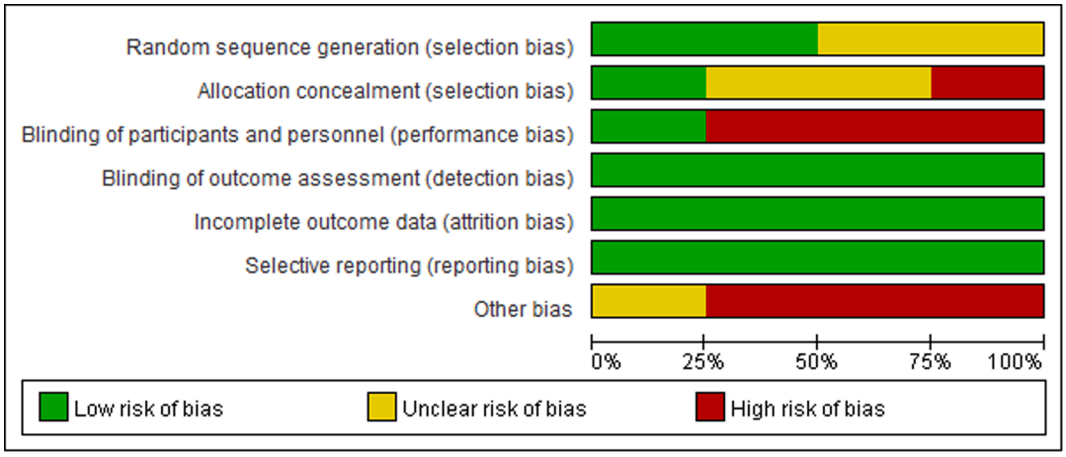

Fig. 2. Risk of bias assessment of the included studies in the systematic review using the new Cochrane risk of bias tool for randomized controlled trials.

Application of IVIG within 48 h of ICU could significantly decrease mortality, the use of mechanical ventilation, shortened duration of ICU and length of hospital stay. Herth et al. [26] also confirmed this viewpoint which early administration of IVIG was correlated with shorter length of hospital duration, while late administration of IVIG was related to longer hospital duration.

Early research demonstrated that after contracting the virus, in the first week, the viral RNA of SARS-Cov2 will reached its highest point, and in the second week, most patients produced anti-viral antibodies against COVID-19, which indicates IVIG should be adopted as early as possible when the patients were diagnosed and hospitalized [27]. It shows that IVIG may be an effective therapeutic intervention when administered early. However, considering the high price and side effect, IVIG was used usually to severe or critical ill patients.

In previous studies, it has suggested that severe cytokine storm has been found to be related to increased death rates in critical COVID-19 patients [28]. IVIG showed multiple effects in enhancing the pro-inflammatory cells activation, and indirectly suppressing T-cell and B-

Table 2
The quality of included Cohort Studies.

Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	Total
Shao 2020			★	★	★★	★	★	★	6
Esen 2021			★	★	★★	★	★	★	6
Huang 2021			★	★	★★	★	★		5

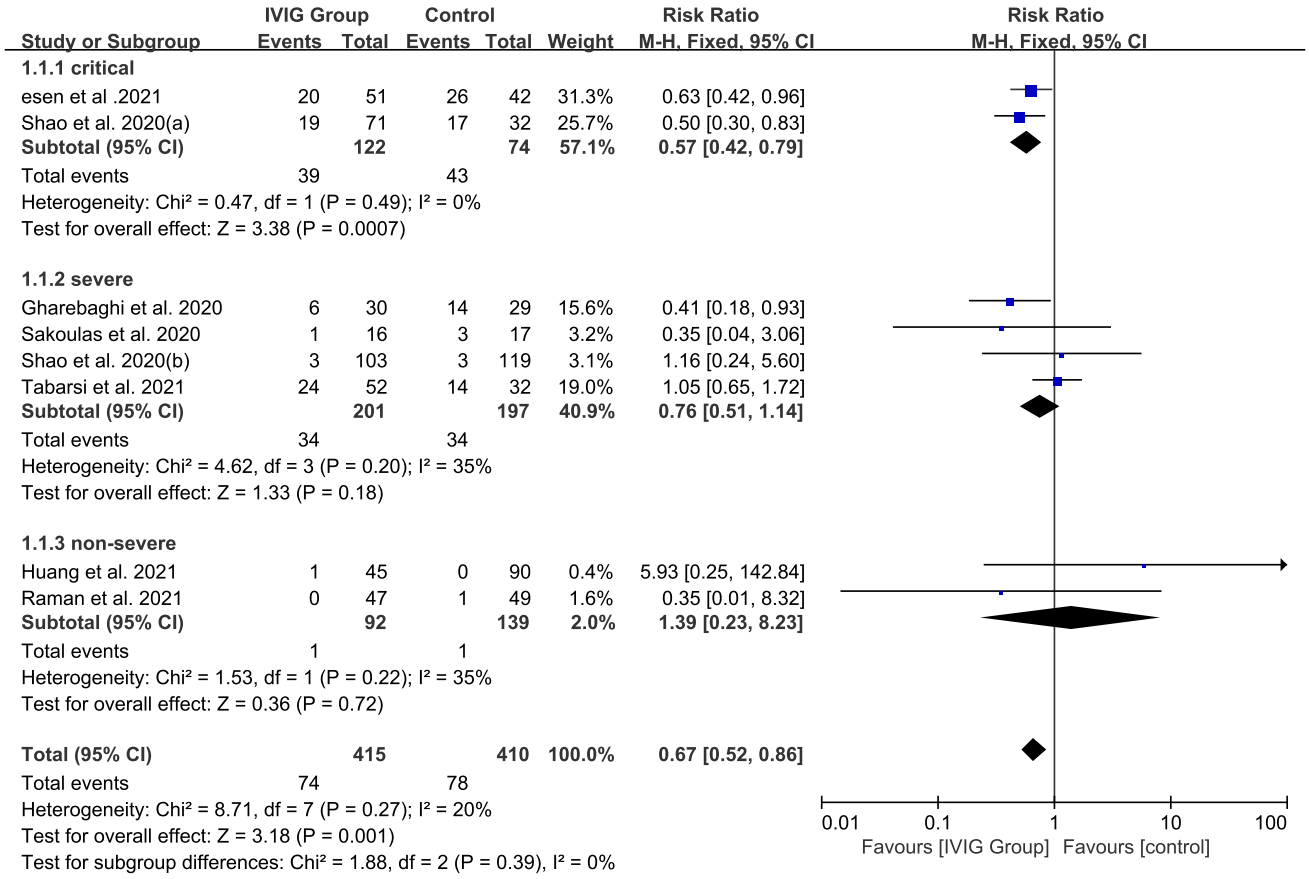

Fig. 3. Efficacy of IVIG on mortality in COVID-19 patients. Weights are from fixed-effects analysis. Note: CI = confidence interval, IVIG = intravenous immunoglobulin.

cell proliferation by cytokines [29–32]. Based on other case series [33,34] that patients treated with IVIG, the results appear to be favorable and consistent which supported IVIG might be beneficial for covid-19 patients especially for severe or critical ill patients. Pei et al. [7] reported an opposite meta- analysis result that IVIG were not associated with reducing mortality in this population. The potential reason may be that neither the retrospective studies nor the available RCTs was included in their pooled results that lead to the quality of the analysis was low. Not only did they not adjust the confounders according the patients' baseline characteristics, but the heterogeneity also was very high.

There are some limitations on our meta-analysis. First, the clinical outcomes of the IVIG therapy couldn't quite represented the abilities to treat COVID-19 patients. Cellular and molecular assessment including the rate of cleaning virus and serum cytokines concentration could evaluate the effect of immunoglobulin more accurately and visually. Second, the analysis was included only four RCTs with small sample sizes. Only one trial was blinded which may subject to bias. Third, the benefits of IVIG are difficult to evaluate when it is coupled with corticosteroids or the recombinant modified IL-1 receptor antagonist, Tocilizumab. Lastly, the dose and timing of IVIG treatment in different center in cohort studies may not be consistent. We still need more RCTs or at least observational studies with a control group to confirm the results of the study.

5. Conclusion

In conclusion, based on low quality evidences, IVIG has demonstrated clinical efficacy on critical ill patients with COVID-19 on reducing the rate of mortality and increasing the length of hospitalization. There may be a strong relationship between the efficacy of IVIG and the COVID-19 disease severity. Well-designed clinical trials to identify the clinical and biochemical characteristics in COVID-19 patients' population that could benefit from IVIG are warranted in the

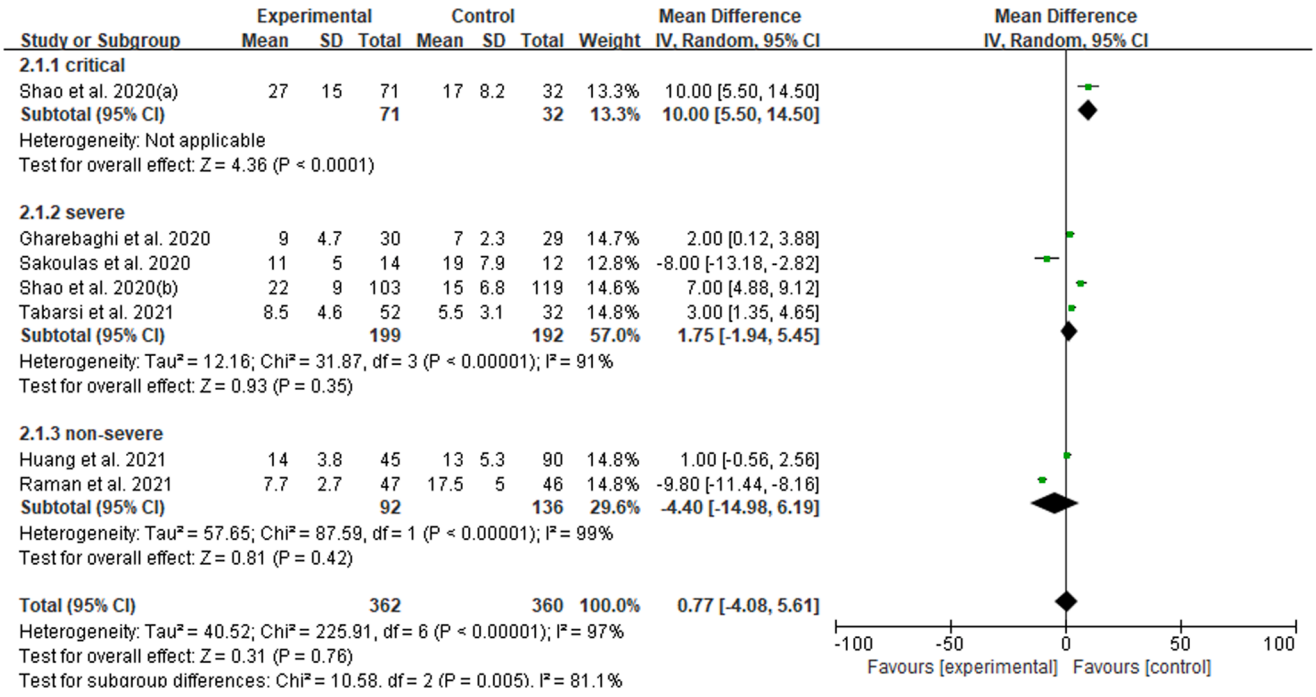

Fig. 4. Efficacy of IVIG on duration of hospitalization in COVID-19 patients. Weights are from fixed-effects analysis. Note: CI = confidence interval, IVIG = intravenous immunoglobulin.

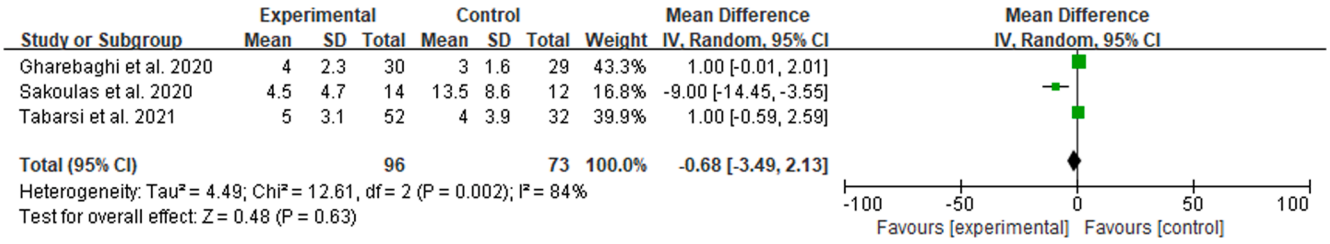

Fig. 5. Efficacy of IVIG on duration of ICU in severe COVID-19 patients. Weights are from fixed-effects analysis. Note: CI = confidence interval, IVIG = intravenous immunoglobulin.

future.

6. Authors' contributions**a

Wenxin Peng, and Huairong Xiang designed this study; Xuan Cheng and Yun Li ran the searched strategy; Huairong Xiang and Wenwen Luo selected articles and extracted data; Qizhi Zhang and Xuan Cheng evaluate the quality of the literature. Huairong Xiang wrote the manuscript, Xuan Cheng, Yun Li, Wenwen Luo and Qizhi Zhang edited. All listed authors reviewed and approved the final manuscript.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.107732.

References

[1] Coronavirus disease (COVID-2019) situation reports. Geneva: World Health Organization; 2020. Available: https://www.who.int/publications/m/item/weekly-epidemiological-update—23-february-2021. [accessed 1 March 2021].
[2] E.E. Perez, J.S. Orange, F. Bonilla, et al., Update on the use of immunoglobulin in human disease: A review of evidence, J. Allergy Clin. Immunol. 139 (3s) (2017) S1–s46.
[3] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (9) (2006) e343.
[4] S. Mustafa, H. Balkhy, M.N. Gabere, Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review, J. Infect. Public Health. 11 (1) (2018) 9–17.
[5] T.C. Luke, A. Casadevall, S.J. Watowich, et al., Hark back: passive immunotherapy for influenza and other serious infections, Crit. Care Med. 38 (4 Suppl) (2010) e66–e73.
[6] V. Tzilas, E. Manali, S. Papiris, et al., Intravenous Immunoglobulin for the Treatment of COVID-19: A Promising Tool, Respiration 99 (12) (2021) 1087–1089.
[7] L. Pei, S. Zhang, L. Huang, et al., Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin in 1142 patients with coronavirus disease 2019: a systematic review and meta-analysis, Pol. Arch. Intern. Med. 130 (9) (2020) 726–733.
[8] J. Zhang, Y. Yang, N. Yang, et al., Effectiveness of intravenous immunoglobulin for children with severe COVID-19: a rapid review, Ann. Transl. Med. 8 (10) (2020) 625.
[9] M. Daneshpazhooh, T. Soori, A. Isazade, et al., Mucous membrane pemphigoid and COVID-19 treated with high-dose intravenous immunoglobulins: a case report, #N/A. 31 (5) (2020) 446–447.
[10] M.V. Sheianov, Y.D. Udalov, S.S. Ochkin, et al., Pulse Therapy With Corticosteroids and Intravenous Immunoglobulin in the Management of Severe Tocilizumab-Resistant COVID-19: A Report of Three Clinical Cases, Cureus. 12 (7) (2020) e9038.
[11] D. Moher, A. Liberati, J. Tetzlaff, et al., Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, PLoS Med. 6 (1000097) (2009).
[12] J.P. Higgins, D.G. Altman, P.C. Gotzsche, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ. 343 (2011) d5928.

[13] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (9) (2010) 603–605.
[14] COVID-19 Clinical management: living guidance. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.
[15] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Med. Res. Methodol. 5 (2005) 13.
[16] X. Wan, W. Wang, J. Liu, et al., Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135.
[17] R.S. R, V.B. Barge, A.K. Darivenula, et al., A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy, J. Infect. Dis. (2021).
[18] G. Sakoulas, M. Geriak, R. Kullar, et al. Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial. medRxiv. 2020:2020.2007.2020.20157891.
[19] N. Gharebaghi, R. Nejadrahim, S.J. Mousavi, et al., The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial, BMC Infect. Dis. 20 (1) (2020) 786.
[20] P. Tabarsi, S. Barati, H. Jamaati, et al., Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial, Int. Immunopharmacol. 90 (107205) (2021).
[21] C. Huang, L. Fei, W. Li, et al., Efficacy Evaluation of Intravenous Immunoglobulin in Non-severe Patients with COVID-19: A Retrospective Cohort Study Based on Propensity Score Matching, Int. J. Infect. Dis.: IJID: off. Publ. Int. Soc. Infect. Dis. (2021).
[22] F. Esen, P.E. Ozcan, G. Orhun, et al., Effects of adjunct treatment with intravenous immunoglobulins on the course of severe COVID-19: results from a retrospective cohort study, Curr. Med. Res. Opin. (2021) 1–14.
[23] Z. Shao, Y. Feng, L. Zhong, et al., Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study, Clin. Transl. Immunol. 9 (10) (2020).
[24] W. Cao, X. Liu, T. Bai, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019, Open Forum. Infect. Dis., 7 (3) (2020) ofaa102.
[25] Y. Xie, S. Cao, H. Dong, et al., Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19, J. Infect. 81 (2) (2020) 318–356.
[26] F.J.F. Herth, G. Sakoulas, F. Haddad, Use of Intravenous Immunoglobulin (Prevagen or Octagam) for the Treatment of COVID-19: Retrospective Case Series, Respiration. 99 (12) (2020) 1145–1153.
[27] A. Saghazadeh, N. Rezaei, Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids, Int. Immunopharmacol., 84 (2020) 106560.
[28] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395 (10223) (2020) 497–506.
[29] J. Hagiwara, M. Yamada, N. Motoda, et al., Intravenous Immunoglobulin Attenuates Cecum Ligation and Puncture-Induced Acute Lung Injury by Inhibiting Apoptosis of Alveolar Epithelial Cells, J. Nippon Med. Sch. 87 (3) (2020) 129–137.
[30] X. Sun, T. Wang, D. Cai, et al., Cytokine storm intervention in the early stages of COVID-19 pneumonia, Cytokine Growth Factor Rev. 53 (2020) 38–42.
[31] M.S. Maddur, J. Vani, P. Hegde, et al. Inhibition of differentiation, amplification, and function of human TH17 cells by intravenous immunoglobulin, J. Allergy Clin. Immunol., 127 (3) (2011) 823–830.e821-827.
[32] M.S. Maddur, S.V. Kaveri, J. Bayry, Circulating Normal IgG as Stimulator of Regulatory T Cells: Lessons from Intravenous Immunoglobulin, Trends Immunol. 38 (11) (2017) 789–792.
[33] Y. Suzuki, Y. Tanino, T. Nikaido, et al., Severe Coronavirus Disease 2019 That Recovered from Respiratory Failure by Treatment That Included High-dose Intravenous Immunoglobulin, Int. Med. (Tokyo Japan) 60 (3) (2021) 457–461.
[34] N. Carannante, G. Fiorentino, A. Corcione, et al., Administration of Immunoglobulins in SARS-CoV-2-Positive Patient Is Associated With Fast Clinical and Radiological Healing: Case Report, Front. Med. (Lausanne) (7) (2020) 388.