

SYSTEMATIC REVIEW



Effect of intravenous immunoglobulin and steroids in acute myocarditis in children: a systematic review and network meta-analysis

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BACKGROUND: Therapeutic benefits of intravenous immunoglobulin (IVIG) and steroids remain inconclusive in optimizing treatment strategies for acute myocarditis.

METHODS: PubMed, EMBASE, Cochrane databases, and Web of Science were searched for studies evaluating the effectiveness of adjunctive IVIG, steroids, or both with standard heart failure treatment in pediatric acute myocarditis. A random-effects network meta-analysis was conducted using frequentist and Bayesian approaches. Effect sizes were calculated as risk ratio (RR) and mean difference (MD). P-scores provided a ranking of treatments.

RESULTS: Thirteen studies comprising 2850 participants were involved. Compared with standard treatment, IVIG reduced in-hospital mortality (RR, 0.52; 95% CI, 0.35–0.76), long-term mortality (RR, 0.5; 95% CI, 0.27–0.98), overall mortality (RR, 0.52; 95% CI, 0.34–0.76), and better composite outcome (RR, 0.61; 95% CI, 0.43–0.88). IVIG was optimal for reducing in-hospital and overall mortality and improving the composite outcome (P-scores = 0.993, 0.999, 0.986). Steroids or their combination with IVIG showed no significant benefit. IVIG improved cardiac function by increasing left ventricular ejection fraction (MD, 6.00%; 95% CI, 0.94–11.06) and reducing left ventricular end-diastolic diameter (MD, –3.77; 95% CI, –7.02 to –0.52).

CONCLUSIONS: Integrating IVIG into standard treatment may significantly enhance outcomes in children with complicated acute myocarditis.

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IMPACT:

- This systematic review and network meta-analysis addresses the gap between clinical trial efficacy and real-world effectiveness in pediatric clinical practice.
- This study suggests that adding IVIG to standard heart failure therapy may improve survival and cardiac function in children with acute complicated myocarditis. The routine use of steroids requires the cautious clinical application.
- High-quality randomized controlled trials are needed to inform guidelines and optimize therapy.

INTRODUCTION

The management of myocarditis in children is a considerable clinical challenge, from the appropriate diagnosis to the intervention and follow-up.^{1,2} The clinical spectrum of acute myocarditis ranges from an asymptomatic illness to life-threatening

conditions.³ Moreover, acute myocarditis is the leading identifiable cause of dilated cardiomyopathy in children.⁴

Supportive therapy remains the cornerstone of myocarditis treatment, and children with myocarditis also receive heart failure treatment in accordance with established guidelines.^{1,5,6} Although

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a significant proportion of children recover spontaneously, in a nonnegligible proportion, acute myocarditis may evolve into chronic cardiomyopathy, require heart transplant, or lead to death.⁴ The pathophysiology of myocardial injury encompasses the following three stages: initial viral infection, subsequent innate immune responses, and, in certain cases, progression to chronic cardiomyopathy.⁷ Targeted therapies are implemented to halt and reverse the autoimmune response in myocarditis. The anti-inflammatory, antiviral, and immunomodulatory effects of intravenous immunoglobulin (IVIG) have been demonstrated, and IVIG is regarded as a treatment option for myocarditis.^{1,8} Steroids have both immunosuppressive and potent anti-inflammatory effects and are recommended for certain types of myocarditis. However, their use for acute myocarditis treatment remains debatable.^{1,5} Researchers have reported conflicting opinions on steroid use because of concerns that steroids may exacerbate the condition; conversely, steroids can be beneficial if their use is tailored to patients with specific histological findings or when they are used in combination with IVIG for patients with fulminant myocarditis.^{9,10} Numerous small-sample retrospective studies and a few randomized controlled trials (RCTs) have examined the efficacy of IVIG for the treatment of myocarditis, with inconsistent results being obtained.¹¹ Pairwise meta-analyses assessing the efficacy of IVIG and steroids have yielded conflicting findings.^{12–15} However, IVIG, steroids, and their combination are widely used in clinical settings.^{1,16–22} Thus, whether sufficient current evidence supports the use of these treatments for acute myocarditis should be determined. We conducted a systematic review and network meta-analysis to assess the effectiveness of adding IVIG, a steroid, or their combination to standard treatment for children with acute myocarditis.

METHODS

Inclusion and exclusion criteria

Articles were selected using the following inclusion criteria: (1) the study design was an RCT, a nonrandomized study (NRS); (2) the studies included children with acute myocarditis; and (3) the studies involved at least two interventions, namely standard heart failure therapy for the control group and adjunctive IVIG, steroids, or their combination in addition to standard heart failure therapy. The exclusion criteria were as follows: (1) studies involving patients with chronic dilated cardiomyopathy (2) studies including children with secondary myocarditis; and (3) studies that did not segregate interventions or assess the relevant outcomes.

Search strategy and study selection

We performed a literature search in the PubMed, EMBASE, Cochrane Library, and Web of Science databases before July 2024. For the literature search, the following medical subject heading terms and keywords were used: children, myocarditis, IVIG, and steroids (Supplemental Method S1). To reduce the risks of reporting and publication bias, no restriction was applied on the publication language or year. Our study was registered with PROSPERO (CRD42024505467).

Data extraction

The two independent reviewers extracted the following data from each study: study design, patient characteristics, interventions, and outcomes. The extracted data were compared, and any disagreement was resolved by a third reviewer.

Methodological quality appraisal

The risk of bias within individual studies was evaluated independently by 2 reviewers utilizing the Cochrane risk-of-bias 2 tool for RCTs and the Risk of Bias in Nonrandomized Studies of Interventions tool for NRSs.²³ A third reviewer was consulted in any case of disagreement.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidence for the outcomes.²⁴ The findings of the network meta-analysis were incorporated into the Confidence in Network Meta-Analysis app.²⁵ Confidence was rated as high, moderate, low, or very low.

Outcomes

The primary outcomes assessed were in-hospital mortality, long-term mortality, overall mortality, cardiac transplant, and composite outcome. In-hospital mortality referred to patient death occurring during hospitalization. Long-term mortality was defined as death occurring in the period from admission through to after discharge, and it was recorded at a specified follow-up endpoint in each study. Overall mortality denoted death reported at the follow-up endpoint in the study. Cardiac transplant was defined as undergoing heart transplant during the study period. The composite outcome combined overall mortality and cardiac transplant.

The secondary outcomes evaluated were changes in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDD). The changes were determined as the differences in these parameters from baseline to the follow-up endpoint in each included study.

Statistical analysis

We performed a random-effects network meta-analysis within the frequentist framework by using the package “netmeta” in RStudio, version 2.9.0. The effect sizes of the binary and continuous outcomes are presented as a risk ratio (RR) and mean difference (MD). The precision of effect sizes is reported as the 95% confidence interval (CI). Because of limited data from the RCTs, we conducted a standard network meta-analysis by naïvely pooling all evidence from the RCTs and NRSs.²⁶ P-scores ranked the interventions, while bead plot-based P-scores summarized rankings across outcomes created using the R package “rankinma” version 0.1.9.²⁷

Before conducting the network meta-analysis, the transitivity assumption was assessed. The statistical heterogeneity of the direct evidence was assessed using the I^2 statistic.²⁸ The incoherence of the network model was examined using the Separate Indirect from Direct Evidence method for exploring local incoherence and the design-by-treatment interaction model for detecting global incoherence.²⁹ To identify the potential sources of heterogeneity, subgroup analyses based on the duration of illness and disease severity, and sensitivity analyses by excluding studies with a high or serious risk of bias were performed. We assessed small-trial effects through a comparison-adjusted funnel plot; subsequently, the asymmetry of the RR was tested using Egger's test.^{30,31}

To verify the robustness of our estimates, we reanalyzed the outcomes in the RCTs and NRSs by using a Bayesian framework. Specifically, observational data were analyzed separately and were then used to inform prior distributions for the RCT model.^{26,32} To down-weight the evidence from the NRSs, we inflated the variance parameter, and to correct for potential overestimation or underestimation, we shifted the mean of the prior information. All models were run using the R package “crossnma”.³³ Further details are presented in Supplemental Method. S2.

The systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.³⁴

RESULTS

Study characteristics

The initial search strategy yielded 3329 articles, from which 45 full-text articles were reviewed; 32 studies were excluded based on the exclusion criteria (Supplemental Table S1). Finally, 2 RCTs and

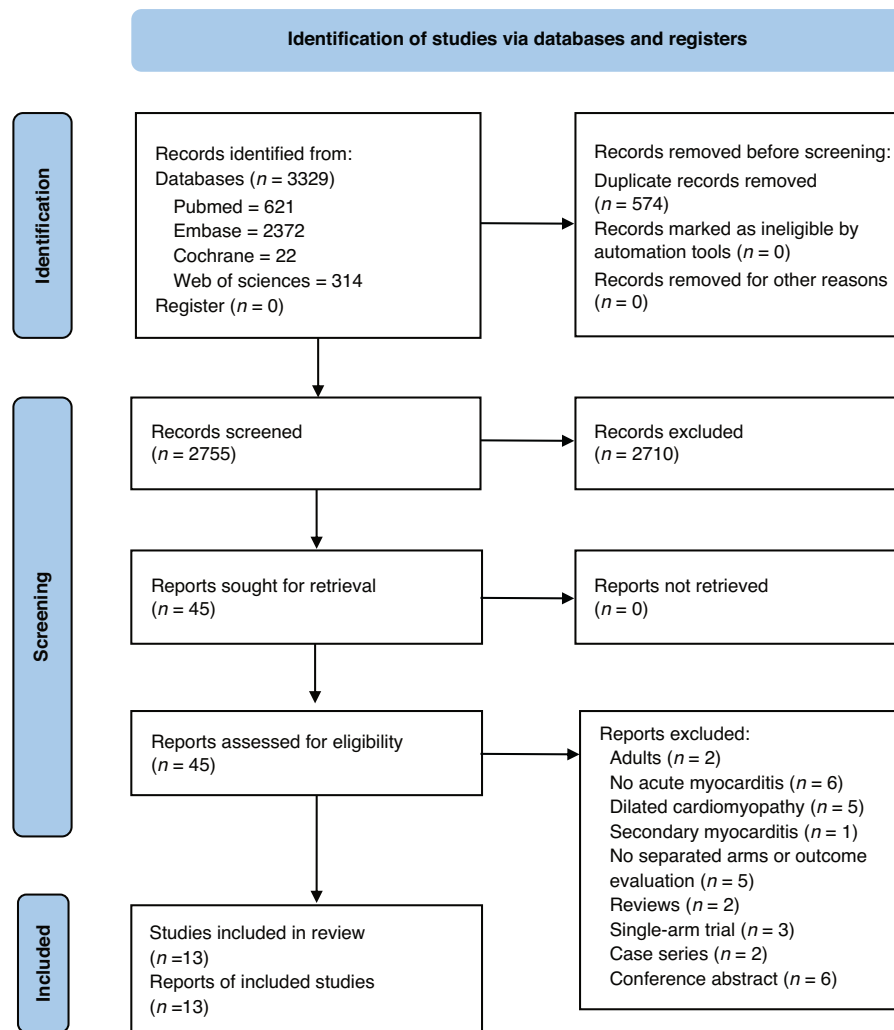


Fig. 1 PRISMA flow diagram of the study selection process

11 retrospective cohort studies were included, totaling 2850 children with acute myocarditis (Fig. 1).^{16,20,22,35–44}

Study characteristics are summarized in Supplemental Table S2. Nine cohort studies compared two intervention arms, one compared three arms, and three compared four arms. Diagnosis of acute myocarditis based on clinical criteria, *International Classification of Diseases* codes, cardiac magnetic resonance, or endomyocardial biopsy, with a mean age at diagnosis ranging from 5.75 months to 12.5 years. The disease duration upon admission was reported as 1 month in seven studies and 3 months in three studies. All studies included patients with complicated acute myocarditis with one or more of the following risks: left ventricular dysfunction, sustained ventricular arrhythmia, heart failure, low cardiac output syndrome, or cardiogenic shock.^{2,45} Three studies specifically included children with acute fulminant myocarditis.^{16,42,43} IVIG was typically administered at a dose of 2 g/kg, whereas the types and doses of steroids varied.

The transitivity was ensured by restricting the analysis to children with acute myocarditis and reviewing their clinical and methodological characteristics to confirm similarity. Three studies examining all four interventions enabled direct comparisons, further strengthening the robustness of the network.

Assessment of risk of bias

Risk-of-bias assessments revealed that one RCT and four cohort studies had a low overall risk of bias,^{20,38,41,42} and five cohort

studies had a moderate risk.^{35,37,39,40,44} Additionally, one RCT and three cohort studies had a high risk of bias (Supplemental Table S3).^{16,22,36,43} The major sources of bias in cohort studies were confounders and intervention classification. The high risk of bias in one RCT was due to bias in the randomization process.³⁶

Primary outcomes

Mortality outcomes. Seven studies ($n = 2177$) contributed to the four-node network model for in-hospital mortality,^{16,20,22,35,40,42} while four studies ($n = 188$) reported long-term mortality with a minimum follow-up period of 6 months.^{38,39,41,44} Eleven studies ($n = 2365$) provided evidence for overall mortality (Fig. 2).^{16,20,22,35,38–42,44} Pooled analyses consistently demonstrated that IVIG significantly reduced mortality compared with standard heart failure therapy, including in-hospital mortality (RR, 0.52; 95% CI, 0.30–0.90), long-term mortality (RR, 0.51; 95% CI, 0.27–0.98), and overall mortality (RR, 0.52; 95% CI, 0.35–0.76). In contrast, steroids or the combination of IVIG and steroids were associated with higher in-hospital and overall mortality compared with standard therapy, though these differences were not statistically significant. No significant differences were observed in other pairwise comparisons (Table 1). For both in-hospital and overall mortality, IVIG ranked highest, followed by standard heart failure therapy, steroids, and the combination of IVIG and steroids (Fig. 3).

Sensitivity analyses corroborated the robustness of these findings. Excluding high-risk-of-bias studies in the in-hospital

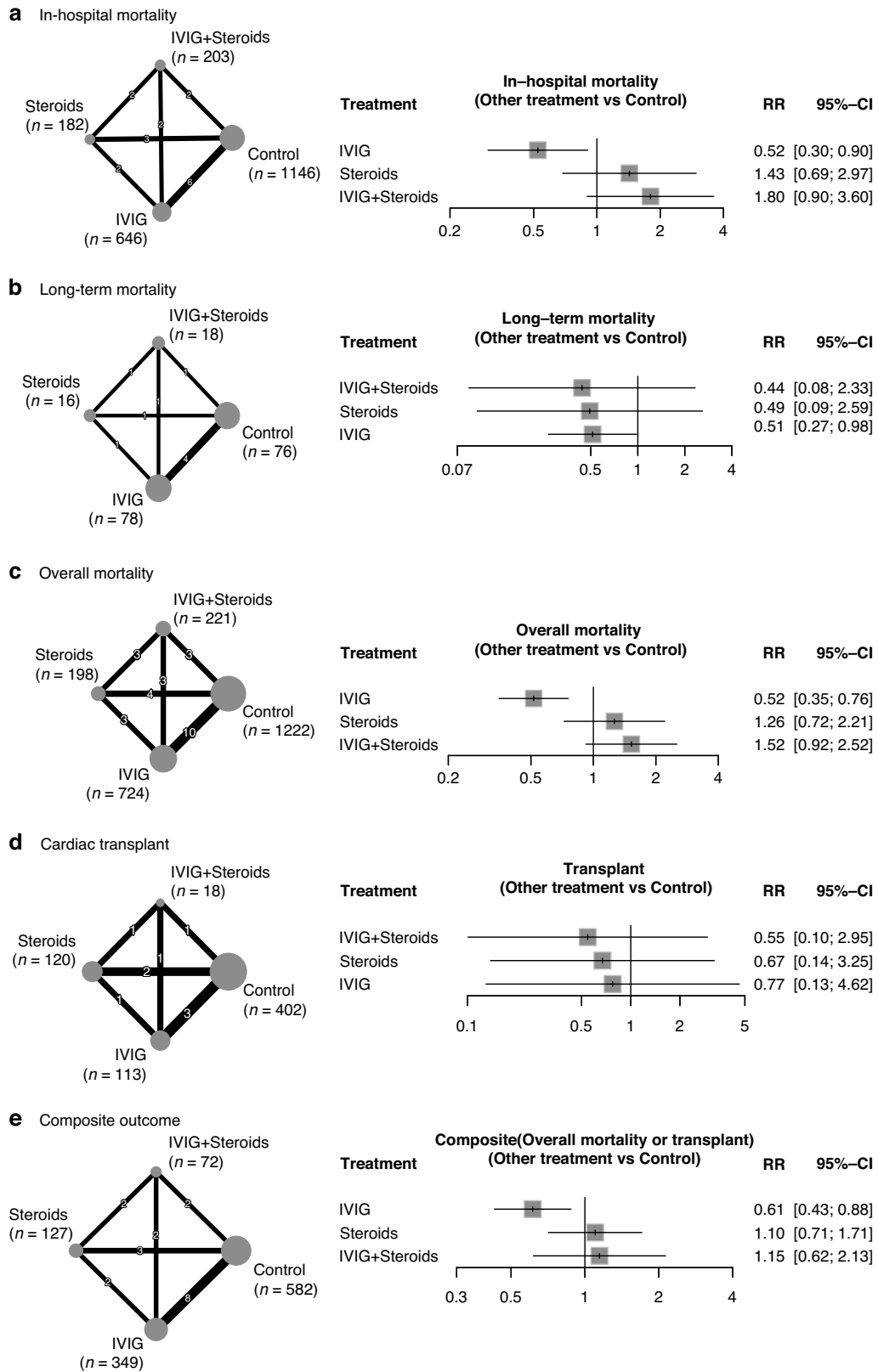


Fig. 2 Network structures across interventions and forest plots comparing interventions with the control approach for the primary outcomes. **a** In-hospital mortality; **b** Long-term mortality; **c** Overall mortality; **d** Cardiac transplant; **e** Composite outcome

Table 1. League tables for primary outcomes

In-hospital mortality (RR, 95% CI)			
IVIG + Steroids	1.18 [0.39–3.59]	3.55 [1.53–8.24]	1.95 [0.92–4.15]
1.26 [0.51–3.08]	Steroids	3.45 [1.01–11.78]	1.46 [0.69–3.11]
3.43 [1.63–7.25]	2.73 [1.17–6.36]	IVIG	0.54 [0.31–0.94]
1.80 [0.90–3.60]	1.43 [0.69–2.97]	0.52 [0.30–0.90]	Control
Long-term mortality (RR, 95% CI)			
IVIG + Steroids	0.89 [0.18–4.52]	0.41 [0.03–5.14]	0.59 [0.10–3.60]
0.89 [0.18–4.52]	Steroids	0.45 [0.04–5.73]	0.66 [0.11–4.01]
0.86 [0.15–4.80]	0.96 [0.17–5.34]	IVIG	0.51 [0.27–0.98]
0.44 [0.08–2.33]	0.49 [0.09–2.59]	0.51 [0.27–0.98]	Control
Overall mortality (RR, 95% CI)			
IVIG + Steroids	1.07 [0.46–2.51]	2.97 [1.54–5.74]	1.63 [0.94–2.83]
1.21 [0.62–2.35]	Steroids	2.58 [0.92–7.23]	1.31 [0.73–2.34]
2.96 [1.70–5.14]	2.45 [1.29–4.65]	IVIG	0.53 [0.36–0.78]
1.52 [0.92–2.52]	1.26 [0.72–2.21]	0.52 [0.35–0.76]	Control
Cardiac transplant (RR, 95% CI)			
IVIG + Steroids	0.89 [0.18–4.52]	0.41 [0.03–5.14]	0.59 [0.10–3.60]
0.81 [0.17–4.00]	Steroids	0.45 [0.04–5.73]	0.80 [0.15–4.13]
0.70 [0.09–5.74]	0.87 [0.11–6.69]	IVIG	0.73 [0.12–4.39]
0.55 [0.10–2.95]	0.67 [0.14–3.25]	0.77 [0.13–4.62]	Control
Composite outcome (RR, 95% CI)			
IVIG + Steroids	0.99 [0.36–2.69]	2.23 [0.97–5.10]	0.98 [0.49–1.96]
1.04 [0.52–2.07]	Steroids	1.43 [0.78–2.60]	1.22 [0.77–1.94]
1.87 [0.98–3.58]	1.80 [1.10–2.93]	IVIG	0.62 [0.43–0.89]
1.15 [0.62–2.13]	1.10 [0.71–1.71]	0.61 [0.43–0.88]	Control

The lower triangle shows the results of network meta-analyses (including direct and indirect evidence) in terms of RRs for treatment in the column vs treatment in the row. The upper triangle shows the results of pairwise meta-analyses for the treatment in the row vs the treatment in the column (direct evidence only).

and overall mortality outcomes confirmed the association of IVIG with reduced mortality (Supplemental Fig. S1). A sensitivity analysis using a Bayesian model for long-term and overall mortality further demonstrated the superiority of IVIG compared to standard therapy (Table 2).

Subgroup analyses also supported the mortality-reducing effects of IVIG on overall mortality in the analysis by disease duration (1 and 3 months) and in the subgroup of patients with complicated myocarditis (Supplemental Figs. S2 and S3). In patients with fulminant myocarditis, both IVIG (RR, 0.43; 95% CI, 0.27–0.67) and the combination of IVIG and steroids (RR, 0.57; 95% CI, 0.36–0.90) significantly reduced mortality compared to standard therapy.

The certainty of evidence was rated as very low for in-hospital mortality, very low to low for long-term mortality, and very low to moderate for overall mortality (Supplemental Tables S4–S6).

Cardiac transplant. The network model included four studies ($n = 653$, Fig. 2d).^{20,39,41} Although the RRs indicated a trend toward reducing the risk of cardiac transplant for IVIG (RR, 0.77; 95% CI, 0.13–4.62), steroids (RR, 0.67; 95% CI, 0.14–3.25), and their combination (RR, 0.55; 95% CI, 0.10–2.05) compared with the control, these results were nonsignificant. The certainty of the evidence for all comparisons was ranked as low (Supplemental Table S7).

Composite outcome. The composite outcome was examined for 12 studies involving 1583 children (Fig. 2e).^{16,20,35,37–44} Compared with standard heart failure therapy, IVIG (RR, 0.61; 95% CI,

0.43–0.88) resulted in a lower risk of cardiac transplant or mortality. However, no significant differences were discovered for other pairwise comparisons (Table 1). IVIG was ranked best for minimizing transplant or mortality risk (P-score = 0.986, Fig. 3), followed by standard therapy (P-score = 0.446), steroids (P-score = 0.296), and the combination of IVIG and steroids (P-score = 0.273).

The results of the subgroup analysis (Supplemental Figs. S4 and S5) and sensitivity analysis (Table 2 and Supplemental Fig. S1) were similar to those of the primary analysis, indicating the robustness of our findings. The certainty of evidence for these comparisons was very low (Supplemental Table S8).

The global metrics of treatment ranking by P-score for all primary outcomes are summarized in the bead plot displayed in Fig. 3b. IVIG resulted in the highest reductions of in-hospital mortality, overall mortality, and the best composite outcome.

Heterogeneity, network consistency, and publication-of-bias

The direct evidence revealed heterogeneity for in-hospital and overall mortality, ranging from low to substantial. However, all comparisons revealed effects with the same direction (Supplemental Tables S9 and S10). No heterogeneity was discovered in the estimates for long-term mortality and cardiac transplant (Supplemental Tables S11 and S12). By contrast, the direct evidence had low to moderate heterogeneity for the composite outcome (Supplemental Table S13).

Robust incoherence testing revealed no significant issues in local and global assessments for most of the primary outcomes, with the composite outcome being the exception (Supplemental Tables S14–S17). Global assessments revealed network

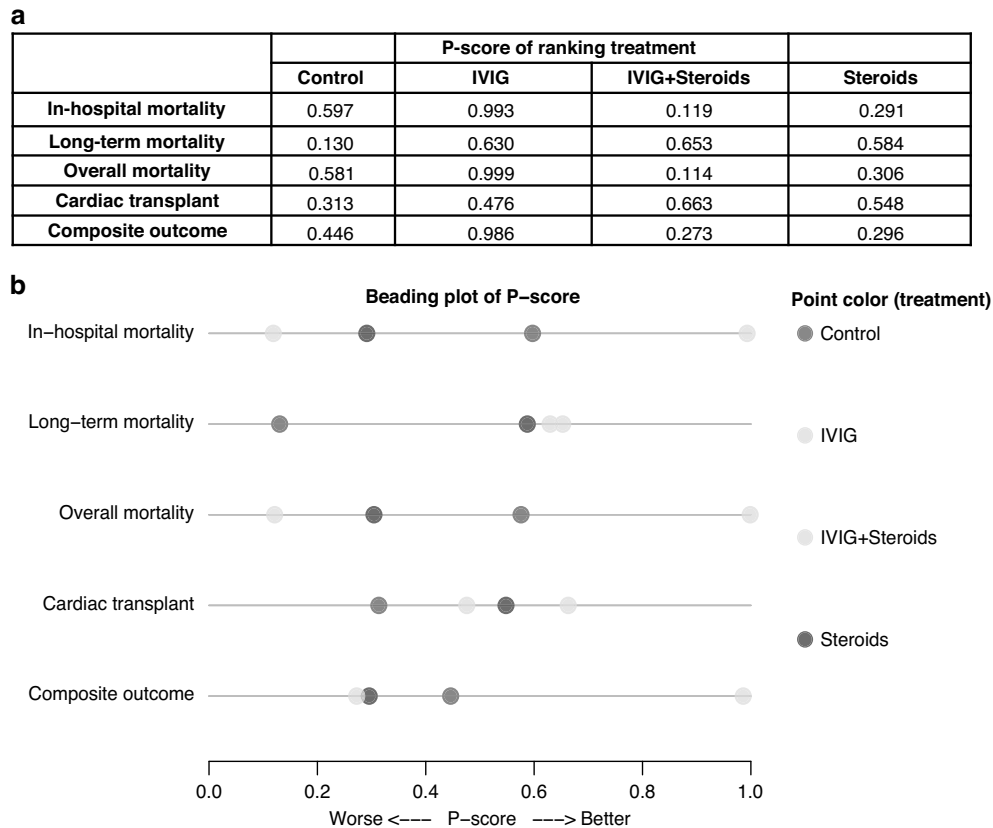


Fig. 3 Treatment rankings based on p-score and beading plot for primary outcome. a P-score table for primary outcomes; **b** P-score-based beading plot for primary outcomes

inconsistency for the composite outcome, although the back-calculation method found no evidence of the local inconsistency (Supplemental Table S18).

No publication bias was detected for all primary outcomes in the comparison-adjusted funnel plot and Egger's test (Supplemental Figs. S6–S9).

Secondary outcomes

For the secondary outcomes, the networks were thin, and power was low. Thus, we only report the results of a meta-analysis comparing IVIG or steroids with standard heart failure therapy. The certainty of the evidence was very low.

Three studies ($n = 182$) reported changes in LVEDD. Compared with standard heart failure therapy, IVIG resulted in a lower LVEDD (MD, -3.77 ; 95% CI, -7.02 to -0.52 , Fig. 4) while the comparison between steroids and standard therapy showed no significant difference. No heterogeneity was found (Supplemental Fig. S10).

Three studies ($n = 121$) reported changes in LVEF. IVIG (MD, 6.00 ; 95% CI, 0.94 – 11.06) or steroids (MD, 12.48 ; 95% CI, 3.57 – 21.40) resulted in a higher LVEF compared with standard heart failure therapy. Substantial heterogeneity was observed but in the same direction (Supplemental Fig. S10).

DISCUSSION

This network meta-analysis comprised 13 studies involving 2850 children with complicated acute myocarditis. The results indicate that adjunctive IVIG is one of the most effective therapies for reducing the risks of mortality and transplant, likely improving cardiac function. No significant differences were discovered between steroids alone or in combination with IVIG compared with standard therapy. However, in the subgroup of acute fulminant myocarditis, overall mortality was lower after treatment

with IVIG and the combination of IVIG and steroids than after standard treatment alone.

IVIG as a treatment strategy for acute myocarditis in children remains contentious. In a Cochrane review in adults and children, Robinson found no difference in effectiveness between IVIG and standard therapy.¹³ The immune response and viral etiology may play more prominent roles in acute myocarditis in children than in adults, potentially explaining the different result.⁴⁶ Similarly, Yen et al. did not demonstrate a clear benefit of IVIG for acute myocarditis in the pediatric population, but this review included studies with mixed cases of unclear acute or secondary myocarditis.^{12,18,47–49} Conversely, previous meta-analyses have revealed the superior performance of IVIG compared with standard therapy, but these findings were obtained in children with general myocarditis.^{15,50,51} In our study, IVIG had the most favorable response profile for pediatric complicated acute myocarditis. Current guidelines recommend IVIG only for severe cases, particularly when viral or autoimmune components are suspected.^{1,2,5,6} With this robustness across various analytical approaches, our findings highlighted the potential of IVIG as a critical component of treatment for acute myocarditis in children.

The therapeutic efficacy of immunosuppression with steroids alone and in combination with IVIG is not supported by clear evidence. Although several RCTs have assessed the effects of immunosuppressive treatments, most have focused on virus-negative chronic myocarditis or dilated cardiomyopathy.^{52–54} Previous reviews have yielded consistent results.^{51,55,56} Our study demonstrated that steroids alone or in combination with IVIG were not beneficial compared with standard treatment. This lack of benefit for steroids might be due to the complex effects on the immune system, potentially exacerbating the condition in some cases. These results align with the current recommendation.^{1,5} Despite the small sample size, in our subgroup of fulminant

Table 2. Nonrandomized study data as prior results with the Bayesian approach

Comparison	No adjust Mean RR (SD)	W = 0.7 Mean RR (SD)	W = 0.5 Mean RR (SD)	W = 0.3 Mean RR (SD)	W = 0.1 Mean RR (SD)	+30% Mean RR (SD)	−30% Mean RR (SD)
Long-term mortality							
IVIG vs Control	0.40 (0.41)	0.41 (0.46)	0.41 (0.45)	0.43 (0.52)	0.42 (0.56)	0.47 (0.40)	0.34 (0.40)
Overall mortality							
IVIG vs Control	0.44 (0.22)	0.44 (0.25)	0.44 (0.28)	0.44 (0.33)	0.45 (0.47)	0.57 (0.21)	0.34 (0.22)
Composite outcome							
IVIG vs Control	0.52 (0.20)	0.51 (0.40)	0.51 (0.27)	0.49 (0.33)	0.47 (0.45)	0.67 (0.21)	0.40(0.21)

Risk ratios (RRs) of primary outcomes in IVIG group versus control group (standard deviation). The results are shown for bias adjustment with weight (W) for different values of W to account for overprecision with no adjustment (W = 1) for gradually down-weighting the data from nonrandomized studies (decrease w) and adjusting for 30% overestimation and underestimation.

myocarditis, the combination of IVIG with steroids showed a trend toward reduced mortality. Recently, Schauer also indicated in pediatric myocarditis, the combination of IVIG and steroids improved ventricular function and survival, but the aforementioned study had only one arm.¹⁷ This suggests a potential benefit of steroids in severe cases; however, further research with larger cohorts is warranted.

No inconsistency was detected for most outcomes in our network meta-analyses, supporting the robustness of the results. Although substantial heterogeneity was present, it was consistent in direction. The considerable heterogeneity may have been due to a range of clinical factors. Initially, not all the participants had confirmed myocarditis. Currently, the use of the gold standard of endomyocardial biopsy has been decreasing due to the risk of invasive procedure.⁵⁷ Cardiac magnetic resonance imaging is gaining popularity as a noninvasive modality, but this technique is not universally performed in children due to its limited availability, the need for sedation, and cost. In clinical settings, most diagnoses of pediatric myocarditis are based on clinical criteria.^{1,18} Additionally, variations in steroid regimen and heart failure therapy across studies likely contributed to the observed heterogeneity.

A major strength of our study is the comprehensive analysis with a large sample size, including both RCTs and comparative observational studies, providing a broad perspective. Notably, we verified the robustness of the results by repeating the analyses using a Bayesian hierarchical model; evidence from NRSs was adjusted to be more statistically precise, reflecting the reality in clinical practice and bridging the efficacy–effectiveness gap. Moreover, although many clinical trials have examined these therapies, previous reviews did not clearly distinguish between patients treated with IVIG, steroids, or their combination.^{15,51}

Our study has several limitations. First, the evidence is of limited quality because of the scarcity of RCTs, leading us to only down-weight results for IVIG. Second, potential confounders in the observational data, along with limited datasets, significantly hindered the analysis of critical factors for therapeutic decision-making, such as severity signs and symptoms or laboratory findings. Third, the lack of data on mechanical support may have confounded the results because these types of support are often required for patients with deteriorating acute myocarditis.^{1,5} Mechanical circulatory support was not utilized in most of the included studies, and some recent studies mentioned its use but provided insufficient details. Therefore, to mitigate its impact, sensitivity analyses were performed by excluding high-risk-of-bias studies. Better-designed studies with higher quality are required to address these gaps.

Conclusion

This systematic review and network meta-analysis revealed that IVIG adjunctive to standard treatment in children with

complicated acute myocarditis is the optimal therapy for minimizing mortality and cardiac transplant risks and improving cardiac function. Neither steroids nor combination therapy had any benefit. Further high-quality RCTs are required to generate additional scientific evidence.

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Ka-Wai Tam and Thi Bao Trang Thai contributed to the conception and design of the study; Thi Bao Trang Thai, Hung Song Nguyen, and Khoi Van Tran searched the literature and extracted the data; Thi Bao Trang Thai, Yi-No Kang, Hoi Huu Vo, Phuc H Phan, Shih-Yen Chen, El-Wui Loh, and Ka-Wai Tam analyzed and interpreted the data; Thi Bao Trang Thai and Yi-No Kang conducted the statistical analysis; and Thi Bao Trang Thai wrote the first draft. All authors contributed to the critical review of the manuscript and approved the final article. Ka-Wai Tam is the guarantor.

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