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Comparison of methylprednisolone alone versus intravenous immunoglobulin plus methylprednisolone for multisystem inflammatory syndrome in children (MIS-C)

Phuc Huu Phan ,[1] Canh Ngoc Hoang,[1] Ha Thu T Nguyen,[2] Tung Viet Cao,[3] Chi Quynh Le,[2] Dien Minh Tran[4,5]

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For numbered affiliations see end of article.

Correspondence to
Dr Phuc Huu Phan; phucph@nch.gov.vn

ABSTRACT

Background As a first-line therapeutic option for multisystem inflammatory syndrome in children (MIS-C) with surging demand, intravenous immunoglobulin (IVIG) is associated with escalating costs and supply shortages, particularly in low-income and middle-income countries. This study compares the effectiveness of methylprednisolone alone versus IVIG combined with methylprednisolone for managing MIS-C.

Methods We conducted a retrospective cohort study from January 2022 to June 2023 at Vietnam National Children's Hospital. We used propensity score matching to compare the short-term outcomes based on immunomodulatory therapy with methylprednisolone alone or IVIG plus methylprednisolone.

Results We included 391 patients, comprising 255 boys and 136 girls, who fulfilled the MIS-C case definition of the US Centers for Disease Control and Prevention. Most patients (80.8%) received intravenous methylprednisolone monotherapy, and 19.2% were administered IVIG in addition to methylprednisolone. In general, the laboratory values indicative of hyperinflammatory and hyperthrombotic states displayed significant early response within 2–3 days after initial treatment, including white cell count (SE=1.77, p<0.001), NEU (SE=0.76, p=0.03), C reactive protein (SE=−46.51, p<0.001), PLT (SE=38.05, p=0.002), fibrinogen (SE=−0.37, p=0.002), d-dimer (SE=−849.8, p=0.02)); while subsequent improvement in cardiac markers was also observed, with pro-B-type natriuretic peptide (SE=−165.2, p<0.001) on day 5 and troponin I (SE=−0.05, p=0.004) on day 7. After propensity score weighting, there were 41 patients in each treatment group. Notably, there were no significant differences in the incidence of cardiac events between treatment groups regarding left ventricular dysfunction and coronary artery dilation or aneurysms (10.3% vs 20.7%, p=0.074 and 63.4% vs 56.1%, p=0.653, respectively). While the median paediatric intensive care unit length of stay (LOS) and hospital LOS were slightly lengthier in the IVIG and methylprednisolone group compared with those of the methylprednisolone group, these differences were not statistically significant ((5 vs 4, p=0.782) and (9 vs 7, p=0.725), respectively).

Conclusions Initial treatment with methylprednisolone monotherapy appears not inferior in effectiveness to adjunctive IVIG plus methylprednisolone in MIS-C. Further investigations in randomised controlled trials deserve to be undergone to clarify if IVIG-sparing glucocorticoids are a viable option for achieving favourable outcomes in MIS-C, particularly in resource-limited settings with barriers approaching IVIG therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current consensus guidelines for treating multisystem inflammatory syndrome in children (MIS-C) recommend a stepwise approach using intravenous immunoglobulin (IVIG) and/or corticosteroids as first-line immunomodulatory therapies.
⇒ High demand for IVIG is associated with escalating costs and supply shortages, particularly in low-income and middle-income countries.
⇒ There are insufficient data to evaluate the efficacy of IVIG-sparing corticosteroid therapy in MIS-C.

WHAT THIS STUDY ADDS

⇒ Initial treatment with methylprednisolone monotherapy appears not inferior in effectiveness to adjunctive IVIG plus methylprednisolone in MIS-C.
⇒ IVIG-sparing glucocorticoids are a viable option for achieving favourable outcomes in MIS-C, particularly in resource-limited settings with barriers approaching IVIG therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Provide valuable evidence on guideline development that puts forward either the best management strategy or leveraging the affordability and availability of corticosteroids as a viable alternative therapy, particularly in resource-limited settings.

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C), also known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), is a novel delayed multisystem hyperinflammatory response that occurs approximately 2–6 weeks after SARS-CoV-2 exposure.[1 2] The clinical manifestations of MIS-C include fever, skin rash, conjunctivitis, oral mucosa changes, hand or foot oedema and gastrointestinal symptoms (abdominal pain, vomiting and diarrhoea).[3 4] Common lab findings indicative of MIS-C were elevated levels of C reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, ferritin, procalcitonin (PCT) and interleukin-6 (IL-6), which expose an overwhelming inflammatory tendency; thus, immunomodulation plays a critical role in disease management.[2 5 6]

The exact mechanisms that trigger MIS-C are still elusive; the early consensus guidelines for the management of this novel entity were initially extrapolated from KD.[2 6 7] Immunoregulatory agents, such as intravenous immunoglobulin (IVIG), corticosteroids and interleukin blockers, are the mainstays in treating MIS-C.[1 2 6] Accordingly, current consensus guidelines for treating MIS-C recommend a stepwise approach using IVIG and/or corticosteroids as first-line immunomodulatory therapies.[6] Low to moderate doses of glucocorticoid (1–2 mg/kg/day) have been reported as sufficient adjunctive therapy in many MIS-C patients, while high doses of intravenous glucocorticoids are recommended in severe patients.[2 5 6] Given MIS-C as an emerging phenotype, affordable treatment options must be accessible for low-resource countries. As a first-line therapeutic option with growing demand, IVIG is associated with rising costs and supply shortages, particularly in Vietnam as well as other low-income and middle-income countries. Moreover, IVIG administration can potentially lead to fluid overload, particularly in patients with heart failure, lung diseases and renal dysfunction.[8] Other concerns recognised as rare complications of high-dose IVIG infusion are haemolysis, thrombotic events, aseptic meningitis, transfusion-related acute lung injury.[8 9] On the other hand, glucocorticoids—a cost-effective therapy—have been used safely and successfully in patients with MIS-C as well as other conditions with hyperinflammatory response, such as KD, macrophage activation syndrome, haemophagocytic lymphohistiocytosis.[2 6 10–12] Corticosteroids are potential immunomodulators with broad-spectrum mechanisms of action in powerful anti-inflammatory effects, including enacting nuclear transrepression of proinflammatory genes and nongenomic activity resulting in reduced immune cell activity and cytokines.[13] However, the immunosuppressive effects of corticosteroids, especially at high doses, may raise significant concerns in cases of incompletely eradicated infection, particularly in contexts with a high burden of infections or tuberculosis (TB) in Vietnam and other low-income and middle-income countries.[14]

There are insufficient data to evaluate the efficacy of IVIG-sparing corticosteroid therapy in MIS-C. Despite features resembling KD, MIS-C is a distinct entity displaying a more intensive degree of hyperinflammation and dysregulated immune responses.[15 16] Furthermore, previous publications reported a high incidence of IVIG resistance in MIS-C,[16] which raised controversies around whether IVIG or corticosteroid monotherapy is sufficient and should be necessary in all MIS-C cases. Therefore, we conducted this study to compare the effectiveness of methylprednisolone alone versus IVIG combined methylprednisolone in short-term outcomes of MIS-C. The results drawn from this paper might provide valuable evidence on guideline development that puts forward either the best management strategy or leveraging the affordability and availability of corticosteroids as a viable alternative therapy, particularly in resource-limited settings.

METHODS

Study setting and participants

We conducted a retrospective cohort study from 1 January 2022 to 30 June 2023 at Vietnam National Children's Hospital (VNCH)—the largest referral tertiary children's hospital in the North of the country, designated with 2300 in-patient beds and 40 paediatric intensive care unit (PICU) beds (see online supplemental 1 for the flow chart of the study).

During the study period, we collected 391 paediatric patients from 1 month to 18 years old who met the MIS-C case definition of the US Centers for Disease Control and Prevention (US CDC).[17] Accordingly, individuals were included if they were aged under 21 years and met the clinical and laboratory criteria: (1) fever >38.0°C for ≥24 hours (subjective or documented fever); (2) elevated laboratory markers of inflammation (CRP, ESR, fibrinogen, PCT, d-dimer, ferritin, lactic acid dehydrogenase (LDH) or interleukin 6 (IL-6); elevated neutrophils, reduced lymphocytes and low albumin); (3) involvement of at least two organs/systems (respiratory, cardiovascular, haematological, renal, gastrointestinal or neurological); (4) current or recent SARS-CoV-2 infection (a positive reverse transcription PCR or positive serological tests (IgM, IgG or IgA) or direct contact with a suspected or confirmed COVID-19 case) and (5) no alternative aetiologies of inflammation (viral/bacterial/fungal/parasite infections, staphylococcal or streptococcal shock syndromes and other inflammatory syndromes). We excluded patients suspected or confirmed with other microbial infections (bacterial, viral, fungal and parasites) or who had received any immunotherapy outside our hospital preadmission or who had insufficient data.

Patient and public involvement

Patients, their families and the public were not involved in the design, conduct, reporting or dissemination of this research.

Data collection

We used standard case report forms to collect data on MIS-C patients, including demographic features such as age, gender, history of SARS-CoV-2 infection, clinical manifestations, laboratory parameters and therapeutic information. In particular, laboratory parameters involved white cell count (WCC) ($\times 10^9$/L), lymphocyte (LYM) count ($\times 10^9$/L), neutrophil (NEU) count ($\times 10^9$/L), haemoglobin (HGB) (g/L), platelet (PLT) count ($\times 10^9$/L), CRP (mg/L), PCT (ng/mL), LDH (u/L), ferritin (ng/mL), albumin (ALB) (g/L), troponin I (ng/mL), pro-B-type natriuretic peptide (proBNP) (pg/mL), fibrinogen (g/L) and d-dimer (ng/mL fibrinogen equivalent unit). These parameters were documented from day 1 to day 7 following the initial therapy administration to assess the time frame for observing a significant laboratory response to these interventions.

Treatment algorithm

Our institutional protocol follows the consensus of reputable international organisations and evidence-based publications based on the illness severity and phenotype classification of MIS-C to initiate immunomodulatory therapy:[2 6 17]

1. KD-like phenotype: complete and incomplete, classified using the American Heart Association criteria.[18] In these cases, typical therapy starts with IVIG (1–2 g/kg) in a single or divided dose combined with methylprednisolone (1–2 mg/kg/day). High-risk children, including those younger than 12 months or with coronary artery changes, were indicated to combine early high doses of intravenous methylprednisolone (10–30 mg/kg/day).
2. Non-specific presentation phenotype: children presenting with shock and/or fever and symptoms involving abdominal pain, gastrointestinal, respiratory or neurological symptoms that do not meet the criteria for KD. Management of children with non-specific presentation phenotype varies according to the severity of the illness. In cases presenting as one of the following: coronary artery abnormality, toxic shock syndrome, progressive disease, extended duration of fever (>5 days), the first-line option is IVIG at the dose of 2 g/kg in a single or divided dose. High-risk children, including those with multiple organ dysfunction and life-threatening complications, such as shock requiring high doses or multiple inotropes, were indicated to early combine high doses of intravenous methylprednisolone (10–30 mg/kg/day). Those with mild disease received a low-moderate dose of methylprednisolone (1–2 mg/kg/day) for 3–5 days, followed by an oral glucocorticoid tapering regimen over 4 weeks.

For all phenotypes, for those who are neither affordable nor eligible for IVIG indication or exhibit instability 24 hours after immunoglobulin infusion, particularly those having ongoing fever, high doses of intravenous methylprednisolone (10–30 mg/kg/day) should be considered as the second-line therapy.

In the cases resistant to IVIG and methylprednisolone, biological therapies (tocilizumab, anakinra and infliximab) were considered a third-line option under thorough consultation by a multidisciplinary team. Low-dose aspirin (3–5 mg/kg/day, maximum 81 mg/day) was prescribed to all MIS-C patients for at least 6 weeks, except for those with a platelet count <80 000/µL, active bleeding, or significant bleeding risk.

In this analysis, we categorised the studied participants into two groups based on the therapy received: methylprednisolone alone group (group A) and IVIG plus methylprednisolone group (group B).

Outcome measurements

We evaluated the following outcomes from the beginning of immunomodulatory administration until hospital discharge:

Primary outcomes:

1. Treatment failure: defined as persistent or recrudescent fever ≥36 hours (%).
2. Duration of fever (days).
3. Duration of inotropic support (days).
4. Requiring respiratory or inotropic support (%) within three initial days.

Secondary outcomes:

1. Hospital length of stay (LOS) (days) and hospital LOS ≥7 days (%).
2. PICU LOS (days) and PICU LOS ≥3 days (%).
3. Reduced left ventricular (LV) ejection fraction (EF) <55% (%).
4. Coronary artery dilation or aneurysm (%).

Statistical analysis

We described categorical variables as frequencies and percentages and continuous variables as the median and IQR. We used the repeated-measures analysis of variance method to assess changes in laboratory values according to the time point from day 1 to day 7 postinitial treatment. This method can highlight significant changes in laboratory values over time following the initial interventions. In addition, propensity score matching (PSM) methods were applied to compare efficacy between two therapies in MIS-C: methylprednisolone alone and IVIG plus methylprednisolone. First, we included multiple covariables in the propensity score model to minimise bias in treatment assignment. The propensity model was generated using logistic regression, incorporating all baseline characteristics and laboratory values. We then calculated a propensity score for each of the studied patients, in which one of the patients on methylprednisolone monotherapy was matched with one of the patients on IVIG plus methylprednisolone therapy using the nearest-neighbour approach with a calliper width of 0.20 SDs. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using STATA software V.17.0 (StataCorp).

RESULTS

Demographic and clinical characteristics of all patients

We included 391 patients (255 boys and 136 girls) who fulfilled the MIS-C case definition of the US CDC in the final analysis. The median age was 85 (range: 2–188) months. All patients presented with persistent fever, with a median fever duration of 6 days prior to hospitalisation. Mucocutaneous symptoms were present in 359 (91.8%) patients, followed by gastrointestinal and respiratory presentations in 246 (62.9%) and 169 (43.2%) patients, respectively. The median PICU LOS and hospital LOS were 4 and 7 days, respectively. 17.4% of patients had coronary abnormalities, whereas shock developed in 140 (35.8%) patients. Overall, two deaths (0.5%) were in our study population (see online supplemental 2).

The majority (80.8%) received intravenous methylprednisolone monotherapy, and 19.2% received IVIG plus methylprednisolone. Among those receiving conjunctive therapy, IVIG combined with low-moderate dose methylprednisolone (1–2 mg/kg/day) accounts for 40 cases (10.2%) and high-dose methylprednisolone (10 mg/kg/day) accounts for 35 cases (8.9%). For the monotherapy group, 61.6% received 1–2 mg/kg/day, 16.4% received 10 mg/kg/day and 2.8% received 30 mg/kg/day (see online supplemental 2).

Assessing treatment response through the analysis of laboratory values over time

On commencing treatment, there were significant variations in PLT (SE=38.05, p=0.002), HGB (SE=−7.3, p=0.001) and fibrinogen (SE=−0.37, p=0.002) values on day 2. Subsequently, remarkable improvements were observed in nearly all laboratory parameters from day 3 postinterventions, including WCC (SE=1.77, p<0.001), NEU (SE=0.76, p=0.03), CRP (SE=−46.51, p<0.001), d-dimer (SE=−849.8, p=0.02) and ALB (SE=−1.62, p<0.001). Subsequent changes were observed in markers related to some extent of cardiac injury, specifically proBNP (SE=−165.2, p<0.001) at day 5 and troponin I (SE=−0.05, p=0.004) at day 7. However, there were no significant changes in LDH and LYM values post 7 days (see table 1 and figure 1).

Outcomes between matched groups in the propensity score model

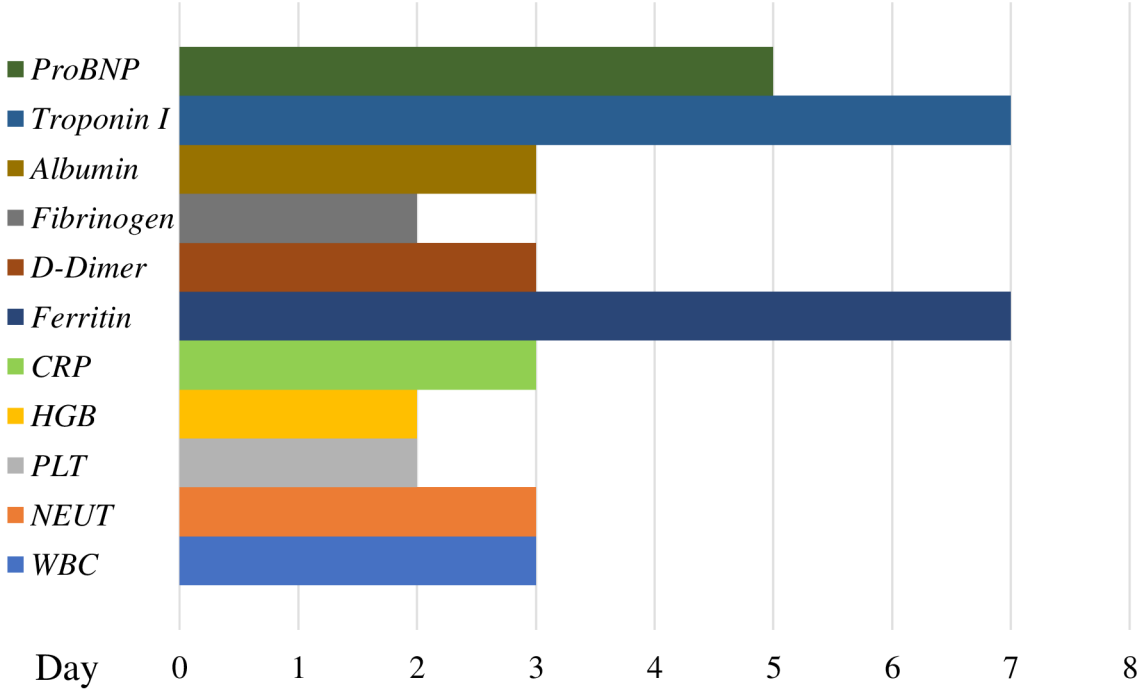
Table 2 provides an overview of the demographic, clinical characteristics, laboratory values and outcomes of patients in the methylprednisolone group (group A) compared with those in the IVIG plus methylprednisolone group (group B) before and after PSM.

Before propensity score weighting, the occurrence of fever, mucocutaneous changes, gastrointestinal symptoms, cardiovascular and respiratory involvement, neurological signs, myalgia and arthralgia did not differ between these two groups. However, analysing laboratory results found that patients on monotherapy are likely to present higher values on the following parameters compared with their counterparts: CRP (117.4 (87.6–185) vs 99 (52–138.9), p<0.001), ferritin (860.5 (283.9–1364) vs 378 (203 – 799), p=0.02) and proBNP (445.5 (119–1103) vs 118.5 (35–369), p<0.001) (table 2). Our results also showed that group A had a significantly higher shock rate than their counterparts (p=0.001). Group A exhibited a significantly lower risk of developing reduced LV EF

Table 1 The changes in laboratory parameters following initial treatments

	Day 2		Day 3		Day 5		Day 7	
Parameters	**SE**	**P value**	**SE**	**P value**	**SE**	**P value**	**SE**	**P value**
Absolute WCC count (×10^9/L) (G/L)	0.17	0.77	**1.77**	**<0.001**	**3.77**	**<0.001**	**5.96**	**<0.001**
Absolute NEU count (×10^9/L) (G/L)	1.48	0.09	**0.76**	**0.03**	0.43	0.26	**1.30**	**0.01**
Absolute LYM count (×10^9/L) (G/L)	−2.46	0.34	−1.84	0.48	−0.96	0.71	0.85	0.74
Absolute PLT count (×10^9/L) (G/L)	**38.05**	**0.002**	**74.60**	**<0.001**	**158.64**	**<0.001**	**310.9**	**<0.001**
HGB (g/L)	**−7.30**	**0.001**	**−6.18**	**<0.001**	**−4.28**	**<0.001**	−2.47	0.13
CRP (mg/L)	−11.03	0.22	**−46.51**	**<0.001**	**−79.34**	**<0.001**	**−97.52**	**<0.001**
Ferritin (ng/mL)	833.36	0.10	482.98	0.15	324.54	0.53	**−281.0**	**0.03**
LDH (U/L)	12.89	0.67	45.59	0.24	−15.73	0.58	−12.46	0.28
D-Dimer (ng/L)	−392.8	0.37	**−849.8**	**0.02**	**−1464.3**	**<0.001**	**−2550.6**	**<0.001**
Fibrinogen (g/L)	**−0.37**	**0.002**	**−0.92**	**<0.001**	**−1.49**	**<0.001**	**−2.06**	**<0.001**
Albumin (g/L)	−1.73	0.09	**−1.62**	**<0.001**	−0.06	0.89	1.27	0.08
Troponin I (ng/mL)	0.05	0.29	66.34	0.32	−0.01	0.77	**−0.05**	**0.004**
ProBNP (pmol/mL)	22.45	0.69	57.81	0.21	**−165.2**	**<0.001**	**−307.1**	**<0.001**

One-way repeated measures ANOVA analyses differences across multiple time points with the same participants. A p<0.05 is statistically significant. Bold font indicates statistical significance.
ANOVA, analysis of variance; CRP, C reactive protein; HGB, haemoglobin; INR, international normalised ratio ; LDH, lactic acid dehydrogenase ; LYM, lymphocyte; NEU, neutrophil; PLT, platelet; proBNP, pro B-type natriuretic peptide; SE, Standard Error; WCC, white cell count.



proBNP, pro B-type natriuretic peptide; CRP, C-reactive protein; HGB, Hemoglobin; PLT, platelet; NEUT, neutrophil; WBC, white blood cell

Figure 1 Estimate timeline for normalising trends in laboratory values after treatment.

(15.4% vs 18.8%, p=0.038) and coronary artery dilation or aneurysm (14.9% vs 28%, p=0.004). However, the two groups did not differ in the occurrence of the remaining outcomes.

The final analysis included 41 patients in each group following the matching process. No differences were observed in the demographic and clinical features and initial laboratory tests between the two matched groups. Both primary and secondary outcomes did not significantly differ between the corticosteroid monotherapy and IVIG plus corticosteroid groups. The proportion of treatment failure (persistent or recrudescent fever ≥36 hours) for those receiving combination therapy differed insignificantly from monotherapy (12.2% vs 7.3%, p=0.712). Notably, there were no significant differences in the incidence of cardiac events between treatment groups regarding reduced LV EF and coronary artery dilation or aneurysms (group (A) and (B): 10.3% vs 20.7%, p=0.074 and 19.5% vs 14.61%, p=0.557, respectively). While the median PICU LOS and hospital LOS were slightly lengthier in the IVIG and methylprednisolone group compared with those of the methylprednisolone group, these differences were not statistically significant ((5 vs 4, p=0.782) and (9 vs 7, p=0.725), respectively) (table 2).

DISCUSSION

Given the disadvantages of IVIG administration, such as high cost, potential shortages and the hazard of adverse effects, which probably strain the approach to this therapy, the findings of our study suggest that corticosteroid monotherapy is not inferior in efficacy to adjunctive treatment (IVIG plus corticosteroids) in MIS-C management. The results drawn from this paper might provide valuable evidence on guideline development that puts forward either the best management strategy or leveraging the affordability and availability of corticosteroids as a viable alternative therapy, particularly in resource-limited settings.

Based on our findings, the laboratory values indicative of hyperinflammatory and hyper-thrombotic states displayed significant early response within 2–3 days after initial treatment, including WCC (SE=1.77, p<0.001), NEU (SE=0.76, p=0.03), CRP (SE=−46.51, p<0.001), PLT (SE=38.05, p=0.002), fibrinogen (SE=−0.37, p=0.002), d-dimer (SE=−849.8, p=0.02)) (table 1 and figure 1). This result aligns with the point that 92.8% of patients responded clinically regarding the signs of fever discontinuation approximately 36 hours after treatment (data not shown). Both fever presence and changes in inflammatory markers are mechanistic descriptions for overwhelming inflammatory responses as the critical role of pathogenesis in MIS-C. Interestingly, subsequent improvement in cardiac markers was also observed, with proBNP (SE=−165.2, p<0.001) on day 5 and troponin I (SE=−0.05, p=0.004) on day 7 (table 1 and figure 1). Similarly, previous data also reported delayed improvement in NT-proBNP levels in MIS-C cases.[19–21] We recommend that the timeline identifying the dynamic of clinical and laboratory factors may assist clinicians in evaluating

Table 2 Demographic, clinical, laboratory characteristics and outcomes of the methylprednisolone (group A) versus IVIG plus methylprednisolone (group B) pre and post propensity score matching

Characteristics	Pre propensity score matching			Post propensity score matching*		
	Group A (N=316)	Group B (N=75)	P value	Group A (N=41)	Group B (N=41)	P value
Demographics						
Age (months), median (IQR)	85.5 (48–114)	72 (28–114)	0.087	77 (49–108)	74 (28–117)	0.857
Male, n (%)	210 (66.5%)	45 (60.0%)	0.292	27 (65.9%)	26 (63.4%)	0.817
Clinical presentations						
Fever, n (%)	316 (100.0%)	75 (100.0%)	_	41 (100.0%)	41 (100.0%)	_
Duration of fever (days), median (IQR)	6 (4–7)	6 (5–6)	0.912	6 (4–8)	6 (4.5–6.5)	0.550
Muco-cutaneous involvement, n (%)	290 (91.8%)	69 (92.0%)	0.948	39 (95.1%)	36 (87.8%)	0.432
Cardiovascular involvement, n (%)	72 (22.8%)	21 (28.0%)	0.366	15 (36.6%)	14 (34.2%)	0.500
Respiratory involvement, n (%)	128 (40.5%)	41 (54.7%)	**0.028**	17 (41.5%)	21 (51.2%)	0.507
Gastrointestinal involvement, n (%)	194 (61.4%)	52 (69.3%)	0.232	23 (56.1%)	27 (65.9%)	0.497
Neurologic involvement, n (%)	58 (18.4%)	21 (28.0%)	0.078	9 (22.0%)	9 (22.0%)	_
Lymphadenopathy, n (%)	127 (40.2%)	35 (46.7%)	0.362	15 (36.6%)	18 (43.9%)	0.653
Arthralgia, n (%)	7 (2.2%)	5 (6.7%)	0.059	1 (2.4%)	1 (2.4%)	_
Myalgia, n (%)	11 (3.5%)	4 (5.3%)	0.753	3 (7.3%)	4 (9.8%)	0.693
Shock, n (%)	97 (30.7%)	43 (57.3%)	**0.001**	16 (39.2%)	23 (56.1%)	0.122
Laboratory parameters, median (IQR)						
Absolute WCC count ($\times 10^9$/L) (G/L)	9.9 (7.3–12.7)	9.6 (6.9–13.4)	0.842	10.5 (7.6–12.9)	9.7 (7.3–12.4)	0.419
Absolute NEU count ($\times 10^9$/L) (G/L)	7.9 (5.4–10.3)	7.1 (5. 0–10.4)	0.454	7.5 (5.4–9.9)	7.7 (4.9–10.1)	0.584
Absolute LYM count ($\times 10^9$/L) (G/L)	1.5 (0.9–2.4)	1.2 (0.8–2.0)	0.071	1.3 (0.9–2.1)	1.2 (0.8–2.1)	0.520
Absolute PLT count ($\times 10^9$/L) (G/L)	153 (112–210)	177 (120–251)	0.273	166 (99–256.6)	148.5 (112–219)	0.619
HGB (g/L)	109.5 (104–117.5)	116 (106–123)	**0.008**	116 (104–122)	112 (106–119)	0.656
CRP (mg/L)	117.4 (87.6–185)	99 (52–138.9)	**<0.001**	116.5 (39.1–143.7)	108.8 (69.8–169)	0.398
Ferritin (ng/mL)	860.5 (283.9–1364)	378 (203–799)	**0.02**	339 (203–864)	343 (220–679)	0.111
LDH (U/L)	303.7 (270–414.8)	305.7 (259.8–363.7)	0.374	309 (266–379.5)	300 (272.2–439)	0.621
D-Dimer (ng/L)	3174 (1880–5465)	2000 (1270–3882)	0.052	3374 (1661–7700)	2590 (1515.5–3773.5)	0.097
Fibrinogen (g/L)	4.7 (3.9–5.4)	4.5 (3.8–5.1)	0.239	4.7 (3.9–5.2)	4.6 (3. 9–5.5)	0.920
Albumin (g/L)	31.1 (28.1–36.9)	33 (30.2–36.6)	**0.044**	31.5 (28.9–36.3)	31 (27.6–36.9)	0.880
Troponin I (ng/mL)	0.08 (0.01–0.19)	0.02 (0.01–0.08)	0.074	0.035 (0.01–0.18)	0.06 (0.01–0.2)	0.915
ProBNP (pmol/mL)	445.5 (119–1103)	118.5 (35–369)	**<0.001**	269.5 (98.9–713)	319.5 (102.6–855.5)	0.212

Continued

Table 2 Continued

Characteristics	Pre propensity score matching			Post propensity score matching*		
	Group A (N=316)	Group B (N=75)	P value	Group A (N=41)	Group B (N=41)	P value
Outcomes						
Treatment failure, n (%)	22 (7%)	6 (5.4%)	0.803	3 (7.3%)	5 (12.2%)	0.712
Duration of inotropic support (days), median (IQR)	2 (1–2)	2 (1–3)	0.632	2 (1–2)	2 (1–3)	0.556
Duration of fever (days), median (IQR)	6 (4–7)	6 (5–7)	0.882	6 (4–8)	6 (4.5–6.5)	0.073
Requiring respiratory support within 3 days after initial therapy, n (%)	11/275 (4.0%)	3/48 (6.3%)	0.480	5 (12.2%)	3 (7.3%)	0.457
Requiring inotropes within 3 days after initial therapy, n (%)	15/305 (4.9%)	6/58 (10.3%)	0.105	4 (9.8%)	6 (14.6%)	0.737
Reduced LV EF<55%, n (%)	26/169 (15.4%)	6/32 (18.8%)	**0.038**	3/29 (10.3%)	6/29 (20.7%)	0.074
Hospital LOS (days), median (IQR)	7 (6–9)	9 (7–10)	0.160	7 (5–)	9 (7–10)	0.725
Hospital LOS≥7 days, n (%)	146 (46.6%)	36 (48%)	0.780	15 (36.6%)	19 (46.3%)	0.892
PICU LOS (days), median (IQR)	4 (2–6)	4 (2–6.5)	0.605	4 (2–7)	5 (2–9)	0.782
PICU LOS≥3 days, n (%)	78/102 (76.6%)	29/59 (49.2%)	0.627	13/23 (56.5%)	15/27 (55.6%)	0.945
Coronary artery dilation or aneurysm after initial therapy, n (%)	40/312 (12.8%)	18/67 (26.9%)	0.004	8 (19.5%)	6 (14.6%)	0.557

Data are presented as median (IQR: Q1–Q3) or number (%).
*Each patient in the IVIG and methylprednisolone group was matched with a comparable patient in the methylprednisolone group after propensity score matching. A p<0.05 is statistically significant. Bold font indicates statistical significance.
CRP, C reactive protein; EF, ejection fraction; HGB, haemoglobin; INR, international normalised ratio; IQR, Interquartile Range; IVIG, intravenous immunoglobuline; LDH, lactic acid dehydrogenase; LOS, length of stay; LV, left ventricular; LYM, lymphocyte; NEU, neutrophil; PICU, paediatric intensive care unit; PLT, platelet; proBNP, pro-B-type natriuretic peptide; WCC, white cell count.

whether MIS-C cases respond sufficiently to present treatment and timely intervention for inadequately resolved cases. However, the available data on this issue are currently limited; further studies are needed.

As mentioned before, the overwhelming inflammatory host response is a milestone mechanism of the pathogenesis of MIS-C, leading to hyperinflammation and cytokine storm.[21–23] This inflammatory response increases the permeability of capillaries and the expression of vascular endothelial growth factor, which in turn reduces the total mass of albumin and can result in shock. Despite being considered the same umbrella of inflammatory disorders, MIS-C presented with more aggressive and long-lasting cytokine responses than KD.[24] This difference could explain why the incidence of shock in MIS-C is higher than coronary abnormalities, which are more characteristic of KD. In line with previous studies, the shock developed in 140 (%), while the coronary dilation or aneurysm was 17.5% of participants in our study.[25] Our analysing laboratory results found that patients on monotherapy showed higher values on the following parameters compared with their counterparts: CRP (117.4 (87.6–185) vs 99 (52–138.9), p<0.001), ferritin (860.5 (283.9–1364) vs 378 (203 – 799), p=0.02), and proBNP (445.5 (119–1103) vs 118.5 (35–369), p<0.001). This aligns with a significantly higher shock rate in group A than in their counterparts respectively (p=0.001) (table 2). Interestingly, after treatment, the need for vasopressor maintenance was not significantly different between the two groups in the propensity-matched model (15/305 (4.9%) vs 6/58 (10.3%), p=0.105). Both glucocorticoids and IVIG have a broad target to immune components, leading to a downgrade of the hyperinflammatory cascade in MIS-C, which may explain their efficacy in MIS-C management. Glucocorticoids inhibit many of the events in an inflammatory response via genomic and non-genomic mechanisms.[13] Notably, glucocorticoids constrain transcription of many genes encoding proinflammatory cytokines and chemokines, particularly NF-κB as a pivotal regulator of immune function.[26] At the same time, non-genomic effects exert rapidly in various immune and transformed cells, including multiple T-cell subsets, neutrophils, macrophages.[27] IVIG inhibits innate and adaptive immunity activation, including macrophages, monocytes, dendritic cells and T and B lymphocytes.[28] In addition, either IVIG or glucocorticosteroids interfere with complement activation and cytokine network, particularly with negative regulation of IL-1, IFN-γ, and IL-2.[27 29] However, MIS-C is a new entity, and the initial treatment guidelines have been developed based on KD treatment. Moreover, MIS-C is characterised by a more intense inflammatory activation, which has given rise to ongoing controversies about the extent of the effectiveness of IVIG or corticosteroid therapies.[24] Consequently, further well-structured research studies are essential to clarify this point. Several studies have compared the outcomes of patients receiving IVIG alone versus IVIG and corticosteroids in MIS-C. The results showed that patients who received adjunctive therapy had a lower risk of treatment failure, haemodynamic support, cardiovascular dysfunction and shorter ICU LOS.[16 30–32] Nevertheless, evidence on the efficacy of corticosteroid monotherapy remains limited. An observational analysis of the BATS cohort in July 2021 concluded no differences in outcomes regarding organ failure, inflammation, coronary-artery aneurysm or hospital discharge between treatment with glucocorticoids or IVIG as single or dual agents.[33] However, the authors noted a lower frequency of immunomodulatory escalation in patients receiving IVIG plus glucocorticoids than in those receiving either IVIG or glucocorticoids alone, which might be due to more severe conditions in the former group compared with the latter, as evidenced by higher levels of troponin and minor modifications of the data collection procedure and analysis.[33] Channon-Wells *et al* then published data from 2,101 MIS-C patients from 39 countries and 121 sites updated to the original BATS, the most extensive study of immunomodulator options in MIS-C to our knowledge.[34] The data uncovered similar adjusted ORs for ventilation, inotropic support or death among different therapies, with 1.09 (95% CI 0.75 to 1.58; p=1.00) for IVIG plus glucocorticoids and 0.93 (95% CI 0.58 to 1.47; p=1.00) for glucocorticoids alone. The occurrence and resolution of the coronary artery aneurysm were comparable between treatment groups.[34] Similarly, our results revealed that using corticosteroids as the initial treatment did not increase the requirement of inotropic or respiratory support in the propensity score model matched (table 2). Via mechanisms of neutralisation of the superantigen and cytokines, efficacy in improving cardiovascular deterioration of IVIG was broadly recognised in hyperinflammatory states, particularly in toxic shock syndrome.[35] In MIS-C, neutrophils exhibit spontaneously increased release of circulating neutrophil extracellular traps driven by vascular inflammation and endothelial damage.[24] The effectiveness of glucocorticoids in the vascular system in MIS-C might be endorsed because the therapy acutely impedes vasodilation and vascular permeability following inflammatory insults, directly influencing inotropic requirement.[26] Similar to the BATS cohort, our results also recognised no disparity in the incidence of coronary artery aneurysms between the two groups (table 2). Previous reports have highlighted the role of glucocorticosteroids as adjunctive therapy to IVIG in reducing the incidence of coronary aneurysms in KD.[10 36] Interestingly, a high IL-6 concentration has been identified as a critical predictor of coronary artery involvement and resistance to IVIG therapy in KD.[37 38] While high-dose IVIG administration did not affect IL-6 induced by IL-1β produced by coronary artery endothelial cell damage in KD, corticosteroids can negatively regulate IL-6 gene expression via downregulating the nuclear factor kappa B (NF-κB) pathway.[39] On the other hand, although both MIS-C and KD seem to have a common inflammatory pattern, the cytokine profile in MIS-C showed a higher concentration of some extent of cytokines, including IL-6.[15 24] Similar to KD, given that

coronary artery lesions are also one of the most severe sequelae and the primary determinant of the long-term quality of life in MIS-C, additional research and analysis should be done to compare the role of corticosteroids and IVIG for coronary outcomes in MIS-C.

According to Villacis-Nunez *et al*, corticosteroid monotherapy shortens the duration of the corticosteroid course and hospital LOS compared with dual therapy.[16] The authors explained this imbalance by the heterogeneity of the severe disease and inflammatory state between groups, which is related to higher levels of D-dimer, ferritin and BNP in the IVIG plus corticosteroids group.[16] Using the post-PSM analysis, we observed the comparable median PICU LOS and hospital LOS in the methylprednisolone alone group and those of the IVIG and methylprednisolone group (4 vs 5 with p=0.782 and 7 vs 9 with p=0.725, respectively). Our results also noted that monotherapy with methylprednisolone had a similar proportion of treatment failure (those with persistent or recrudescent fever ≥36 hours) and fever duration to combination therapy with IVIG plus methylprednisolone (table 2). The BATS study reported that conjunctive therapy contributed to a shorter length of fever than monotherapy with IVIG or glucocorticoids alone.[34] In contrast, the RECOVERY trial found that intravenous methylprednisolone shortened hospital LOS, but no effect was observed in patients treated with IVIG.[25] However, unlike the BATS study, this trial mainly focused on comparing the effectiveness of IVIG, methylprednisolone, tocilizumab and anakinra with usual care, not directly comparing the effectiveness of the IVIG and methylprednisolone; subsequent investigations must thoroughly reevaluate this issue.

Our study had several limitations. First, the significant limitations were the retrospective design, single hospital-based study, and small sample size for comparison (only 41 participants in each group in the propensity score model). Further randomised controlled trials in large sample sizes should be set up to reevaluate our findings. Also, propensity matching cannot eliminate all biases because other unmeasured covariates may exist. Second, we cannot comprehensively evaluate and compare the efficacy of specific types and doses of immunotherapy based on MIS-C phenotype or disease severity; well-designed research is required to address this issue. Third, given that there is no case with IVIG alone and biological therapy in our cohort, we could not assess the effectiveness of these potential therapies in MIS-C management. Fourth, side effect expectations are a critical factor influencing therapy acceptance; not comparing the two groups' side effects is one of the considerable apprehensions in our paper. Notably, the immunosuppressive effect of corticosteroids is a significant concern in the context of the high burden of infectious diseases or TB in Vietnam and other low-income and middle-income countries.[14] Finally, our work is only starting to investigate the differences in the effect of these immunotherapies in the short term; the next steps forward in understanding how these therapeutic options impact the long-term outcomes are needed to identify the optimal strategy in MIS-C.

CONCLUSIONS

Initial treatment with methylprednisolone monotherapy appears not inferior in effectiveness to adjunctive IVIG plus methylprednisolone for MIS-C. Further investigations in randomised controlled trials deserve to be undergone to clarify if IVIG-sparing glucocorticoids are a viable option for achieving favourable outcomes in MIS-C, particularly in resource-limited settings with barriers approaching IVIG therapy.

Author affiliations
[1]Pediatric Intensive Care Unit, Vietnam National Children's Hospital, Ha Noi, Viet Nam
[2]Immunology, Allergy, and Rheumatology, Vietnam National Children's Hospital, Ha Noi, Viet Nam
[3]Heart Center, Vietnam National Children's Hospital, Ha Noi, Viet Nam
[4]Vietnam National Children's Hospital, Ha Noi, Viet Nam
[5]Faculty of Medicine and Pharmacy, Vietnam National University, Hanoi, Viet Nam

X Phuc Huu Phan @phucph

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ORCID iD
Phuc Huu Phan http://orcid.org/0000-0002-0381-446X

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