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ORIGINAL ARTICLE

Stepwise response-guided treatment protocol superior to thrombopoietin receptor agonist-based second-line therapy for severe persistent/chronic immune thrombocytopenia: a multicenter prospective study from China

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Abstract

Background: The first second-line international recommendation for children with severe persistent/chronic immune thrombocytopenia is thrombopoietin receptor agonist (TPO-RA)-based treatment; however, <30% can achieve sustained response off-treatment (SRoT), leading to a heavy medical burden.

Objectives: This study aimed to confirm the efficacy of the stepwise response-guided treatment protocol compared with TPO-RA–based second-line therapy for children with severe P/CITP.

Methods: The stepwise response-guided treatment protocol is an individualized stratified immune thrombocytopenia treatment starting with high-dose dexamethasone, then adding rituximab and TPO-RAs in sequential order according to treatment response. A prospective, multicenter clinical cohort study enrolled severe P/CITP children with a 1-year follow-up. We compared the treatment outcome response of platelet count, bleeding control, and treatment-related side effects and cost outcomes (escalation status, SRoT, and treatment costs) between the stepwise group and the TPO-RA–based second-line treatment group (TPO-RA group).

Results: The study enrolled 143 cases of severe P/CITP children with a 12-month follow-up period. There were no differences in baseline characteristics between the stepwise and TPO-RA groups ($P > .05$). Response/remission rates and bleeding grades showed no differences ($P > .05$), but there were fewer side effects related to treatment in the stepwise group (9.0%; $P < .00$). A total of 74% in the stepwise group achieved SRoT while none in the TPO-RA group did. The cost of treatment was significantly

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lower in the stepwise group compared with the TPO-RA group over the 12-month follow-up period (USD 68.26/kg vs USD 384.76/kg, $P < .00$).

Conclusion: The stepwise response-guided treatment protocol effectively stratifies children with severe P/CITP based on treatment response, enabling individualized treatment strategies. This protocol achieves comparable efficacy and safety while reducing the treatment burden compared with TPO-RA–based second-line therapy, making it a preferable option for children with severe P/CITP.

KEYWORDS
children, persistent/chronic immune thrombocytopenia, thrombopoietin receptor agonists, second-line therapy, stepwise treatment

Essentials

- Treating children with immune thrombocytopenia can be a heavy medical burden.
- We compared traditional treatments with a stepwise response-guided protocol.
- The stepwise protocol helps children achieve longer-lasting responses without ongoing treatment.
- In Chinese children with ITP, the stepwise protocol is effective and affordable.

1 | INTRODUCTION

Primary immune thrombocytopenia (ITP) is the most common acquired immune-mediated bleeding disorder in children. The main clinical symptoms include skin and mucosal bleeding, although some patients may experience potentially life-threatening bleeding events. While 70% of children with ITP may achieve spontaneous remission within 6 months, 30% progress to persistent/chronic ITP [1]. Furthermore, if the platelet count (PLT) falls below 30×10^9/L, children are at significant risk for bleeding; this condition is known as severe persistent/chronic ITP, which requires effective treatment.

Current international guidelines recommend using thrombopoietin receptor agonists (TPO-RAs) as second-line therapy for severe persistent/chronic ITP. This can be done either as monotherapy or in combination with immunosuppressive agents such as high-dose dexamethasone (HD-DXM) or rituximab (RTX) [2]. Despite being proven safe and efficacious, TPO-RAs are challenging to discontinue, with sustained response off-treatment (SRoT) rates reported remaining unclear, from <30% to >50% [3,4]. Consequently, prolonged TPO-RA usage, often spanning several years, imposes a significant medical burden. Also, SRoT in children was reported in several studies, but data from large-scale prospective studies are lacking [5,6].

Previously, we implemented an "escalating strategy" or "stepwise response-guided treatment protocol" (for simplicity, hereafter referred to as the stepwise protocol) based on the clinical treatment response, beginning with HD-DXM, followed by low-dose RTX. Finally, we added TPO-RAs for severe persistent/chronic ITP children in our single center. Retrospective studies indicated that this individualized and stratified approach was cost-effective, particularly in reducing treatment duration and achieving TPO-RA withdrawal [7].

To validate and assess the efficacy and cost-effectiveness of treatment intervention, we conducted a prospective, multicenter, clinical cohort study involving severe persistent/chronic ITP children from April 2020 to June 2024.

2 | METHODS

2.1 | Study design

A prospective, multicenter, clinical cohort study of children with severe persistent/chronic ITP was initiated in April 2020. Enrollment was terminated in June 2023, and data analysis was completed in June 2024. All enrolled cases underwent follow-up, and data were collected from 3 pediatric platelet clinics (ChiCTR2100048162). This study was conducted in accordance with the Helsinki Declaration.

2.2 | Inclusion and exclusion criteria

We enrolled 143 analyzable patients according to the following inclusion criteria: 1) diagnosis with severe persistent/chronic ITP [8]; 2) aged 1 to 14 years; 3) consent obtained from the child and/or parents/caregivers, with informed consent signed; and 4) compliance with follow-up in the clinics.

Exclusion criteria were as follows: 1) secondary ITP, such as systemic lupus erythematosus; 2) life-threatening bleeding at the time of enrollment (2021 Chinese Guideline) [8]; 3) noncompliance with treatment, neither the stepwise protocol nor TPO-RA–based second-line treatment; and 4) inability to follow-up for 12 months.

2.3 | Definitions

Severe persistent/chronic ITP: PLT is less than 30×10^9/L with clinical bleeding and requires treatment. ITP lasts 3 to 12 months (persistent ITP) or more than 12 months (chronic ITP).

Response [9]: PLT at 6 months. Classified into (1) complete response: PLT $\geq 100 \times 10^9$/L without bleeding; (2) partial response: PLT (30-100) $\times 10^9$/L and a greater than 2-fold increase in PLT from baseline without bleeding; and (3) no response: could not meet partial response criteria.

Remission: PLT at 12 months. Classified into: (1) complete remission: PLT $\geq 100 \times 10^9$/L without bleeding; (2) partial remission: PLT (30-100) $\times 10^9$/L and a greater than 2-fold increase in PLT from baseline without bleeding; and (3) no remission: could not meet partial remission criteria.

SRoT: PLT $\geq 30 \times 10^9$/L without bleeding and requires treatment at least 6 months off-treatment.

Bleeding score: according to the 2021 Chinese Guideline [8].

Rescue therapy: during the study, immunoglobulin, corticosteroid pulse therapy (<1 week), or platelet transfusion were used to rapidly increase platelets due to deficient levels or severe bleeding risk.

Main treatment-related side effects included (1) hepatic impairment: bilirubin or transaminase levels were 2 times higher than the upper limit; (2) high intraocular pressure (IOP): IOP > 21 mm Hg; (3) hypertension: systolic and/or diastolic blood pressure exceeding 2 SDs from the mean for each age; and (4) thrombocytosis: 2 consecutive PLT $> 400 \times 10^9$/L at 3-day intervals [10].

2.4 | Procedures

Treatment decisions were based on collaborative discussions between the clinics' parents or caregivers and the pediatricians. Patients were categorized into 2 groups: the stepwise group and the TPO-RA group. The stepwise group received treatment according to the stepwise protocol, progressing through step I (HD-DXM), step II (low-dose RTX), and step III (TPO-RAs) based on the clinical bleeding phenotype and platelet response. In contrast, the TPO-RA group received either TPO-RA monotherapy or TPO-RA–based combination therapies from the outset. Clinical data were collected at baseline and during follow-up, which occurred at least 12 months later.

The stepwise protocol in the stepwise group, as well as the criteria for determining whether to escalate treatment, were as follows (Figure 1): 1) step I: HD-DXM (dexamethasone at a dosage of 0.6 mg/kg/d, with a maximum of 40 mg/d) either intravenously or orally for 4 consecutive days per course. Each course lasted for 28 days, and a total of 6 courses were to be administered. If the complete response was achieved after 1 to 2 courses, then the drug was withdrawn after 4 courses. If the patient attained a partial response after 3 courses, then the 6 courses were fulfilled. If no response was observed after 3 courses, step II was escalated. 2) Step II: a low dose of RTX (375 mg/m^2, maximum dose 600 mg, given once) was administered. Step III began if no response was observed between weeks 6 and 12. If a partial response was achieved, then 6 HD-DXM courses were completed. 3) Step III: oral TPO-RA (eltrombopag, hytrombopag, or avatrombopag) was administered with dosage adjustments based on the drug's instructions, previous studies, and the patient's condition.

TPO-RA strategy in the TPO-RA group included 1) a monotherapy group: patients using TPO-RAs alone without following the stepwise protocol and 2) a combination therapy group: patients using TPO-RAs in combination with either HD-DXM or RTX directly.

2.5 | Outcomes

A comparison of the stepwise group and the TPO-RA group at 6 and 12 months was performed for (1) treatment efficacy to assess response and remission rates, bleeding scores at 6 and 12 months, and any treatment-related side effects noted at 12 months and (2) treatment cost to examine the escalation status of the stepwise group, SRoT rate, and overall treatment costs, including medication and rescue therapies, within 12 months for both groups. The medications evaluated for the treatment of ITP included high-dose HD-DXM, RTX, and TPO-RAs.

2.6 | Statistics analysis

Statistical analyses were conducted using SPSS version 19 software (IBM, SPSS Inc), focusing on differences in response and remission rates between groups, complete with CIs and odds ratios (ORs). Quantitative data with a normal distribution were reported as means ± SD and analyzed using *t*-tests. Data with a skewed distribution were presented as medians, including IQR or ranges, and examined with the Wilcoxon–Mann–Whitney U-test for group differences. A 2-tailed $P < .05$ was considered statistically significant.

3 | RESULT

3.1 | Baseline

There were 143 analyzable cases (Figure 2); 110 were in the stepwise group, and 33 in the TPO-RA group. Baseline characteristics were comparable between the 2 groups ($P > .05$; Table 1).

3.2 | Treatment efficacy

At 6 months, the response rates for the stepwise group were 91 out of 110 cases (82.8%) compared with 24 out of 30 cases (80.0%) for the TPO-RA group, yielding an OR of 0.73 (95% CI, 0.30-2.32; $P = .73$). Complete response rates were 29 out of 110 cases (26.4%) in the stepwise group and 10 out of 30 cases (33.3%) in the TPO-RA group,

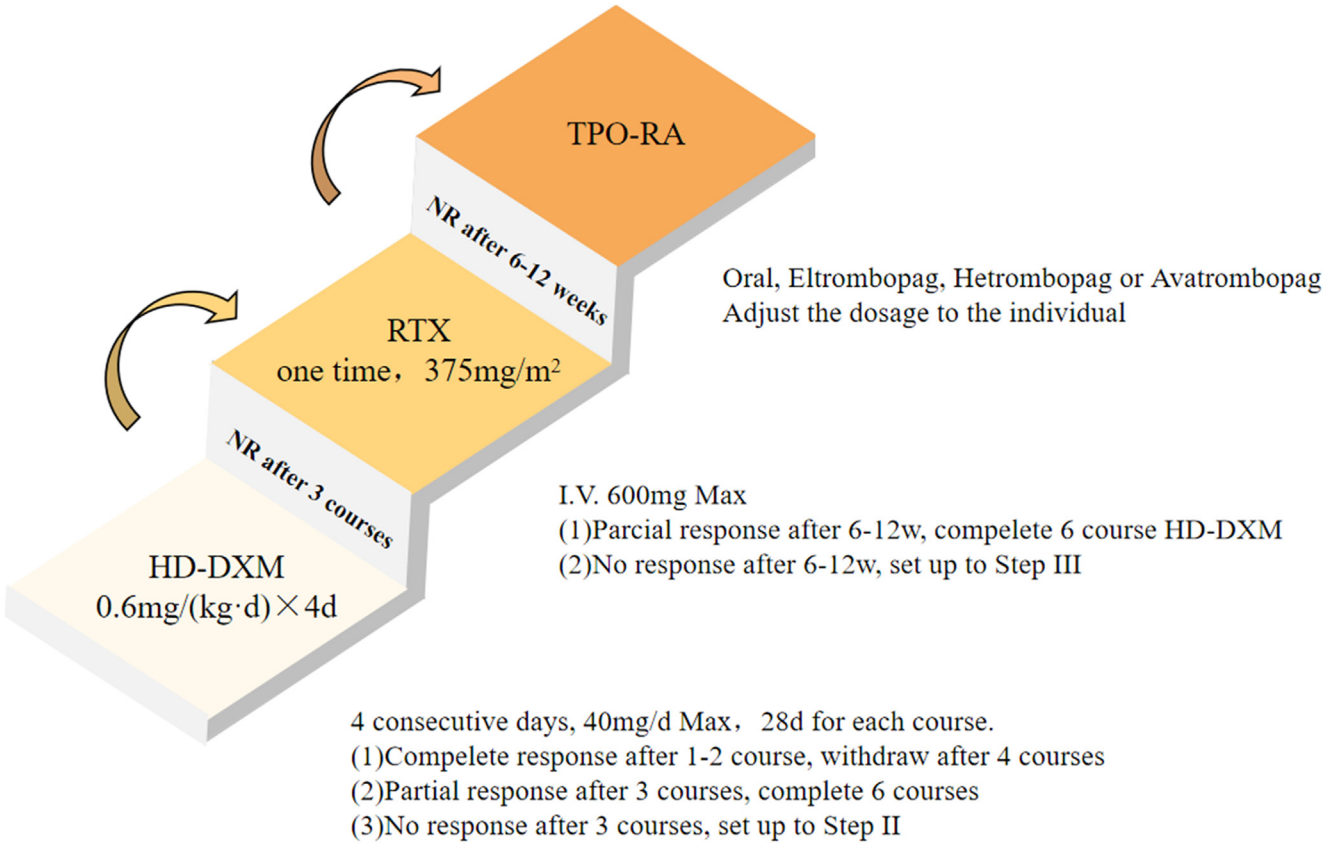

FIGURE 1 The stepwise protocol design. HD-DXM, high-dose dexamethasone; i.v., intravenously; NR, no response; RTX, rituximab; TPO-RA, thrombopoietin receptor agonist.

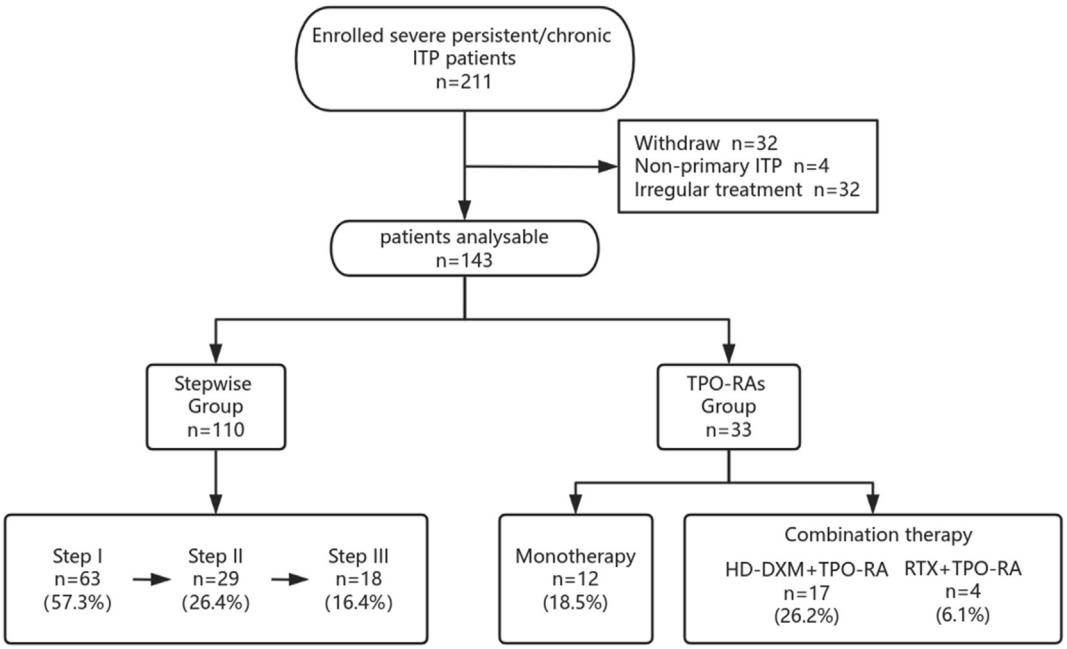

FIGURE 2 Flowchart of study enrollment, grouping, and therapeutic management. HD-DXM, high-dose dexamethasone; ITP, immune thrombocytopenia; RTX, rituximab; P/CITP, persistent/chronic immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

TABLE 1 Baseline characteristics of the different groups.

Characteristic	Stepwise group *n* = 110	TPO-RA group (*n* = 33)	
		Monotherapy group *n* = 12	Combination therapy group *n* = 21
Gender (male:female)	53:57	8:4	11:10
Race (*n*)			
Asian	110	12	21
Baseline age (y), median (IQR)	6.65 (4.71-10.24)	6.89 (4.22-9.49)	8.44 (6.48-10.75)
Baseline PLT, (10^9/L), median (IQR)	24.00 (12.75-40.25)	19.00 (12.25-65.00)	17.00 (6.50-44.00)
Baseline bleeding score, grade (*n*)			
Grade 0	28	3	3
Grade 1	47	4	6
Grade 2	24	4	5
Grade > 2	11	1	7
Time since ITP diagnosis (mo), median (IQR)	14.00 (8.75-24.00)	14.00 (6.50-33.75)	24.00 (8.50-69.00)
Phases of the disease (PITP:CITP)	43:67	5:7	10:11

CIPT, chronic immune thrombocytopenia; ITP, immune thrombocytopenia; PITP, persistent immune thrombocytopenia; PLT, platelet count; TPO-RA, thrombopoietin receptor agonist.

with an OR of 1.40 (95% CI, 0.59-3.32; *P* = .45). No statistically significant differences were noted in responses (*P* = .63).

Compared with the stepwise group, the response rates for the monotherapy group at 6 months were 9 out of 12 cases (75.0%), with an OR of 0.63 (95% CI, 0.15-2.53; *P* = .45). The complete response rate for this group was 41.7%, with an OR of 1.99 (95% CI, 0.59-6.78; *P* = .31).

For the combination therapy group, the response rates at 6 months were 15 out of 18 cases (83.3%), resulting in an OR of 1.04 (95% CI, 0.27-3.96; *P* = 1.00). The complete response rates for this group were 27.8%, with an OR of 1.04 (95% CI, 0.35-3.28; *P* = 1.00).

Moreover, no significant differences were found when comparing complete, partial, and no responses between the stepwise group and the monotherapy group (*P* = .31) or the combination therapies group (*P* = .92; Figure 3).

At 12 months, the remission rates for the stepwise group vs the TPO-RA group were 99 out of 109 cases (90.9%) compared with 18 out of 21 cases (85.7%), with an OR of 0.61 (95% CI, 0.15-2.42; *P* = .44). The complete remission rates were 49 out of 109 cases (44.9%) vs 10 out of 21 cases (47.6%), yielding an OR of 1.13 (95% CI, 0.44-2.84; *P* = .82). No statistically significant differences in complete, partial, or no remission were observed (*P* = .70).

In comparison with the stepwise group, the remission rates for the monotherapy group at 12 months were 4 out of 5 cases (80.0%), with an OR of 0.40 (95% CI, 0.41-3.97; *P* = .40). The complete remission rate was 40.0%, with an OR of 0.82 (95% CI, 0.13-5.08; *P* = .71).

In comparison with the stepwise group, the remission rates for the combination therapies group at 12 months were 14 out of 16 cases (87.5%), with an OR of 0.71 (95% CI, 0.14-3.57; *P* = .65). The complete remission rate was 50.0%, with an OR of 1.22 (95% CI, 0.43-3.50; *P* = 1.00).

Furthermore, there were also no significant differences when comparing complete, partial, and no remission between the stepwise group and monotherapy group (*P* = .62) or the combination therapies group (*P* = .80).

The treatment effect of the stepwise group on platelet number recovery was comparable to that of the TPO-RA group.

In terms of bleeding control, at 6 months, the proportions of grades 0, 1 to 2, and > 2 for the stepwise group vs the TPO-RA group were 83.6% vs 83.3%, 14.5% vs 16.7%, and 1.8% vs 0% (*P* = 1.00), respectively. At 12 months, the respective percentages were 92.7% vs 95.2%, 6.4% vs 0%, and 0.9% vs 4.8% (*P* = .32). In Figure 3, when comparing the stepwise group with the monotherapy group, the bleeding scores at 6 months were 75.0%, 25.0%, and 0% (*P* = .51), respectively, and at 12 months, they were 80.0%, 20.0%, and 0% (*P* = .34), respectively. For the combination therapy group, the scores at 6 months were 88.9%, 11.1%, and 0% (*P* = 1.00), respectively, and 100%, 0%, and 0% at 12 months (*P* = .65), respectively.

Overall, the stepwise group demonstrated the same treatment effect as the TPO-RA group in terms of bleeding control.

A total of 10 side effects (9.0%) were reported in 110 patients from the stepwise group, including 8 increased IOP and 2 other side effects (1 rash and 1 fatigue). In the TPO-RA group, 13 side effects occurred among 33 patients, comprising 4 cases of thrombocytosis, 2 cases of increased IOP, 3 cases of hepatic impairment, and 4 other events (1 cushingoid facies, 1 allergy, and 2 cases of hypertension). The incidence rate of side effects was significantly lower in the stepwise group than in the TPO-RA group (*P* < .00).

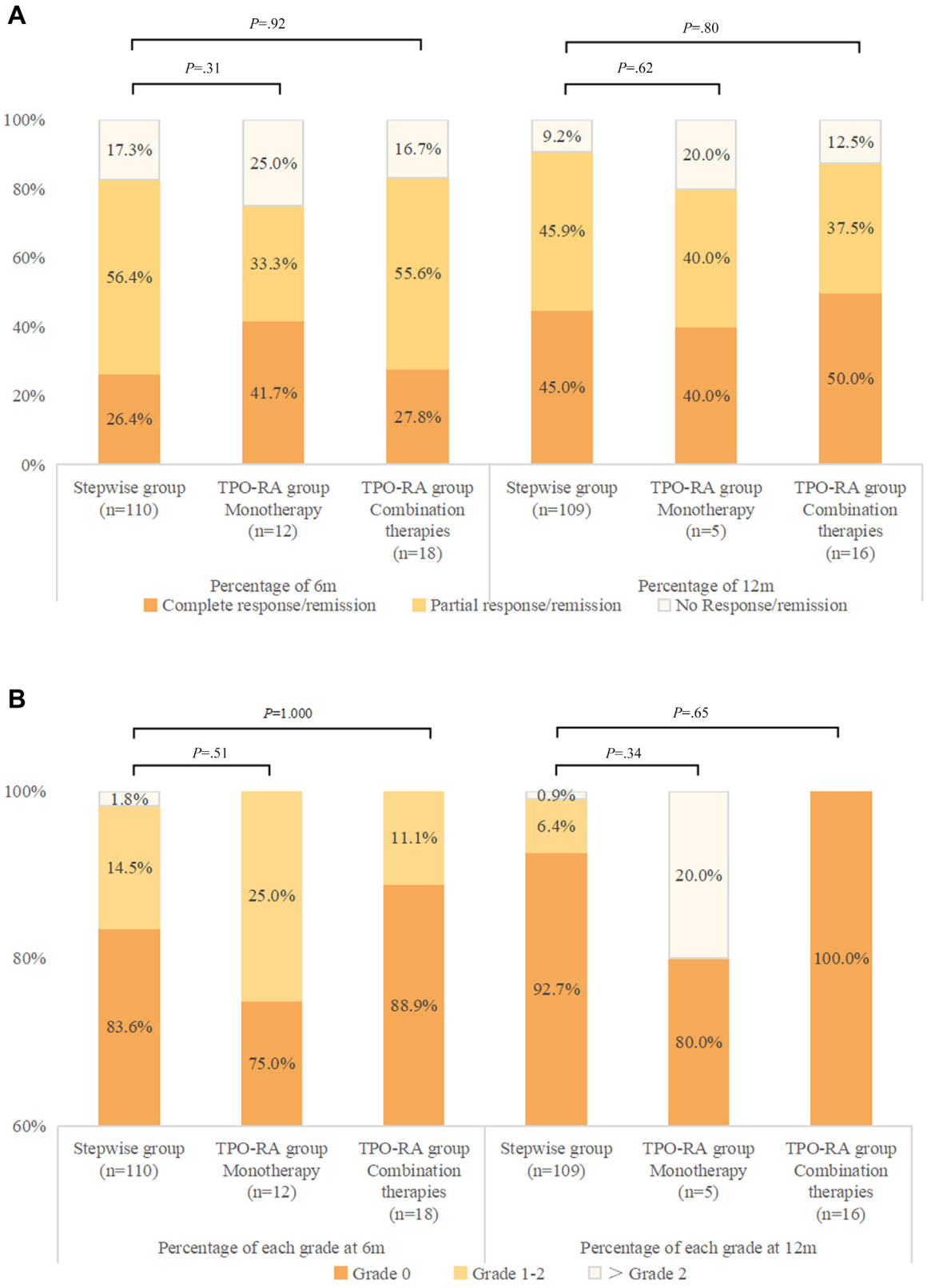

FIGURE 3 Comparison of (A) response/remission of platelet count and (B) bleeding control between the stepwise group and the thrombopoietin receptor agonist (TPO-RA) group at 6 and 12 months. Due to the loss of follow-up, only 109 participants in the stepwise group were available for analysis after 12 months. While in the TPO-RA group, 30 participants remained available after 6 months and 21 after 12 months.

3.3 | Treatment cost

In the stepwise group (Figure 2), the escalation status was as follows: only 16.4% (18 out of 110 patients) were upgraded to step III, 57.3% (63 out of 110 patients) remained at step I, and 26.4% (29 out of 110 patients) stayed at step II.

SRoT was achieved in 74.5% (82 cases) of the stepwise group, with a median treatment duration of 150 days (IQR, 75-180) compared with 0% in the TPO-RA group.

The median treatment costs were USD 68.26 per kg for the stepwise group, USD 395.11 per kg for monotherapy, and USD 373.85 per kg for combination therapies ($P < .00$). The cost for the stepwise group was significantly lower than that of the TPO-RA group (Table 2).

4 | DISCUSSION

The treatment strategy for severe persistent/chronic ITP, especially in children, should balance practicality (maintaining PLT to prevent bleeding), safety (avoiding adverse effects), and affordability (minimizing medical costs). However, achieving these goals remains challenging [11].

The international and domestic guidelines recommend TPO-RAs (or TPO-RAs combined with an immunosuppressant such as RTX or dexamethasone) as the first consideration among second-line treatments [2,12]. However, RTX was reported in several studies with poor long-term efficacy and higher rates of rescue therapy [13]. While the efficacy and safety of TPO-RAs are well established, the challenges associated with its prolonged use and the difficulty of discontinuation remain significant limitations, potentially increasing the medical burden on children with ITP.

A prospective, single-arm trial was designed to investigate the SRoT of eltrombopag among 105 adult patients after corticosteroid treatment failure; only 30.5% of patients achieved SRoT and maintained PLT $\geq 30 \times 10^9$/L after discontinuation without bleeding or rescue therapy by 12 months. Only 19% of them achieved SRoT until 24 months [14]. In a retrospective study of severe persistent/chronic ITP children, 143 were treated with eltrombopag monotherapy; although 69.2% responded over a 2.8-year follow-up time, 35.4% withdrew eltrombopag, and 25.3% achieved SRoT [15]. In our study, despite a slower tapering speed of TPO-RAs, none of the children in the TPO-RA group achieved SRoT within a year, underscoring the challenges of SRoT and prolonged TPO-RA use, which may lead to increased medical burdens.

Although TPO-RA–based combination therapies may enhance effectiveness, they carry a significant risk of overtreatment and side effects. In a multicenter retrospective study of 39 adults using TPO-RAs and immunosuppressants, 48.7% achieved a durable response, but 31% experienced severe side effects [16]. Another retrospective study involving 18 patients (12 adults and 6 children) reported a 72% response rate but a 61.1% side effect incidence over a median 5-month treatment period [17]. Similarly, 39.4% of our combination therapy patients experienced at least 1 event of side effects for 1 year.

In our study, the median duration before enrollment was 14 (IQR, 9-25) months. It suggested that most persistent/chronic ITP children fail previous treatment, and second-line monotherapy may not be sufficient. Combination therapies pose higher risks of side effects. However, pediatric ITP has high spontaneous remission rates; some children may face overtreatment. Only 16% of children in our study required TPO-RAs, further supporting the potential for overtreatment in some cases.

The previous retrospective single-center studies showed that among 30 chronic ITP cases, the response rate of the stepwise protocol was higher at 68.2% and 80.0% at 12 months [7]. The other prospective study enrolled 63 cases and showed that the stepwise protocol had a better overall response rate (94% vs 33%, $P < .00$) [18]. In this study, 82.8% of the stepwise group and 80.0% of the TPO-RA group achieved response at 6 months, and 90.9% of the stepwise group and 85.7% of the TPO-RA group achieved remission at 12 months. Bleeding events decreased significantly in both groups, with similar percentages of grade 0 bleeding between the stepwise group and the TPO-RA group at 6 and 12 months.

The stepwise protocol demonstrated comparable short-term efficacy with TPO-RA monotherapy or combination therapies in response, remission, and bleeding control. Notably, 83.6% of the stepwise group patients discontinued treatment successfully compared with none in the TPO-RA group. While the current international tendency is to bring forward TPO-RA treatment, there is an accompanying cost increase [19]. The shorter disease course offers several benefits; by stratifying, our protocol significantly reduces treatment costs.

TABLE 2 The treatment costs for 12 months in the different groups (USD/kg/y).

Item	Stepwise group $n = 86$	TPO-RA group (monotherapy) $n = 12$	TPO-RA group (combination therapies) $n = 18$
Cost of medicines, median (range)	0.05 (0.01-1399.25)	395.11 (88.81-1233.44)	357.04 (90.40-1090.65)
Cost of rescue therapies, median (range)	17.07 (0-136.45)	0 (0-34.11)	17.05 (0-68.27)
Total cost, median (range)	68.26 (0.01-1415.30)	395.11 (100.88-1267.57)	373.85 (107.39-1106.94)

Due to the loss of follow-up, the treatment cost data at 12 months included 86 cases in the stepwise group and 18 cases in the TPO-RA group (combination therapy).

TPO-RA, thrombopoietin receptor agonist.

This study demonstrated that the stepwise protocol reduces overtreatment risks and provides a systematic, individualized approach that maximizes the benefits of first- and second-line therapies. There are several limitations to this study. (1) This study is not a randomized clinical trial, so potential biases may exist. Therefore, we controlled for nonrandomization bias as much as possible and found the baseline levels between groups to be comparable. (2) The upper limit of follow-up in this study was 12 months, which is a limitation in the evaluation of efficacy. Follow-up of these patients continues, and we hope that additional time points will inform longer-term efficacy and dose tapering and discontinuation. (3) Based on the patient-doctor shared decision-making, the study could not consider only 1 TPO-RA, which could increase heterogeneity. We hope to conduct further studies in the future to compare the differences between TPO-RAs in the stepwise protocol. (4) The lower tapering speed of TPO-RAs in this study resulted in fewer SRoT cases within a year, suggesting a need for further research on optimizing TPO-RA withdrawal strategies [20,21].

Our prospective multicenter study highlights the stepwise protocol as a more economical, effective, and safer approach than TPO-RA–based therapies. Future research will explore new agents, such as fostamatinib and daratumumab, to refine this protocol further [22,23].

5 | CONCLUSIONS

The stepwise protocol for severe pediatric ITP achieved high response rates, fewer side effects, and reduced treatment burdens. It also enabled more patients to successfully discontinue treatment, which may be a promising option and superior to TPO-RAs alone or in combination.

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AUTHOR CONTRIBUTIONS

R.W., Jie Ma., and L.F. conceived the protocol for this analysis. X.L. and L.F. performed the statistical analyses. Jingyao Ma., Z.W., Y.L., Y.H., N.W., and L.W. provided analyzable medical records and verified the data. L.F. and X.L. wrote the paper in collaboration with R.W., Z.C., and X.C. with input from all coauthors. All coauthors read the report, made suggestions about its content, and agreed with the submission of the manuscript.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

DATA AVAILABILITY

The present study used original data, which have been obtained with permission from the Institutional Review Board. The data are not publicly available due to privacy or ethical restrictions.

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