Original Article

Real-world experience of thrombopoietin receptor agonists in pediatric immune thrombocytopenia: a report from a Chinese tertiary children's hospital

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Background: Primary immune thrombocytopenia (ITP) is the most common bleeding disorder in children. There are approximately 20% pediatric ITP patients respond poor to corticosteroids as first-line treatment. Recently thrombopoietin receptor agonists (TPO-RAs) have been used to treat refractory ITP and have achieved certain therapeutic effects. To investigate the efficacy and safety of TPO-RAs in the treatment of pediatric ITP, we conducted this real-world study.

Methods: Fifty-three pediatric patients with ITP who did not respond well to corticosteroids were treated with TPO-RAs. Clinical data, including therapeutic response rate, changes in platelet (PLT) count, and adverse events (AEs) were collected.

Results: Of the 51 evaluable patients, 37 (72.5%) responded to TPO-RAs. Patients aged >4 years had a higher response rate than those aged ≤4 years (81.1% *vs.* 50.0%, P=0.04). There was no effect of sex, duration of disease, prior therapy, *Mycoplasma pneumoniae* (MP) immunoglobulin M (IgM) positivity, antinuclear antibody (ANA) positivity, CD4/CD8 ratio or baseline PLT count on the response rate (P>0.05). Other than 10 patients with PLT counts that exceeded the upper limit of normal, AEs were sporadic, including increased aminotransferase levels, cough, headache, and vomiting.

Conclusions: TPO-RAs exhibited good clinical efficacy in pediatric ITP patients who failed to respond to first-line treatment, especially patients aged >4 years, and the side effects were minor.

Keywords: Thrombopoietin receptor agonists (TPO-RAs); immune thrombocytopenia (ITP); pediatric; efficacy; real-world

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Introduction

Primary immune thrombocytopenia (ITP) is an immune-mediated disease characterized by a lower-than-normal PLT count and increased bleeding risk. The decreased PLT count is due to the accelerated destruction of PLT and/or suppressed PLT production. Diagnosis is based on a PLT count of $<100\times10^9$/L and the exclusion of other potential underlying causes of thrombocytopenia. It is the

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most common bleeding disorder in children. First-line treatment options include corticosteroids and intravenous immunoglobulin (IVIG), which aim to reduce autoantibody-mediated PLT destruction, and the overall efficiency is approximately 80% in pediatric patients (1,2). However, there is a subset of pediatric patients who do not respond well to first-line treatments. These patients face the threat of bleeding, and their quality of life is significantly affected.

Thrombopoietin receptor agonists (TPO-RAs) include eltrombopag, herombopag, avatrombopag and romiplostim. TPO-RAs increase PLT count by activating the C-MPL receptor, subsequently enhancing megakaryopoiesis in the bone marrow (3). Practice guidelines from the American Society of Hematology (ASH) recommend the use of TPO-RAs in children with ITP who do not respond to first-line treatment (4). In recent years, an increasing number of pediatric ITP patients who do not respond well to corticosteroids have been treated with TPO-RAs worldwide. A few randomized controlled trials (RCTs) have focused on the effects and side effects of TPO-RAs in adults, but for pediatric patients, such studies are fewer. At the same time, RCTs have exposed some deficiencies, prompting researchers to look at real-world evidence. Here, we present the results of a real-world study from a Chinese tertiary children's hospital, with the aim of recording and analyzing the efficacy and safety profile of TPO-RA therapy in pediatric patients with ITP. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-48/rc).

Highlight box

Key findings

- Thrombopoietin receptor agonists (TPO-RAs) exhibited good clinical efficacy in pediatric immune thrombocytopenia (ITP) patients who failed to respond to first-line treatment, especially in patients older than 4 years.

What is known and what is new?

- TPO-RAs have been used in refractory ITP patients, and their effects have attracted widespread attention, but the real-world report of TPO-RAs in pediatric ITP is rare.
- Here we present our real-world experience about the response rate and the safety of TPO-RAs in pediatric ITP.

What is the implication, and what should change now?

- In subsequent studies, the study population size should be expanded, and the factors influencing the efficacy of TPO-RAs and their safety need to be further studied.

Methods

This was a retrospective, single-center study conducted at a tertiary children's hospital in the eastern China. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical approval and informed consent were waived by the Ethics Committee of Human Experimentation of the Children's Hospital of Soochow University because data were collected anonymously and retrospectively from the hospital's data. The patients' medical treatment details were obtained from outpatient clinics and inpatient hospital admission/discharge notes. Missing data were minimized by making phone calls to the patients' families. Romiplostim is still not available in China, but eltrombopag, herombopag and avatrombopag were used to treat ITP patients who did not respond well to corticosteroids.

Patients

Fifty-three patients diagnosed with ITP and treated with TPO-RAs were recruited for this study. All of them were primary ITP, and there were no cases of secondary ITP. None of the patients responded well to corticosteroids as first-line therapy, and some patients also failed to respond to other therapies, such as cyclosporin, rituximab and rapamycin. The patients' demographics and baseline characteristics at the initiation of TPO-RA treatment are detailed in *Table 1*. The age distribution is shown in *Figure 1*.

Therapeutic effect evaluation

Patients with a baseline PLT count $<50\times10^9$/L were evaluated for the effect of TPO-RAs. Response was defined as PLT counts $\geq50\times10^9$/L and doubled from the baseline count. Complete response was defined as a PLT count $\geq100\times10^9$/L, and partial response was defined as a PLT count of 50×10^9/L–100×10^9/L. All children were treated with TPO-RA for at least 2 weeks, and then the decision to continue or discontinue the treatment was made based on the PLT level. To eliminate the effect of concomitant therapy with IVIG at the initiation of TPO-RA treatment in patients with an observable response within 1 month of therapy, we re-evaluated the PLT count again at 1 month after TPO-RA initiation. Patients with a subsequent decrease in PLT count of less 50×10^9/L were excluded.

Relapse was defined as a PLT count $<50\times10^9$/L after achieving a response during the TPO-RA treatment or after discontinuation.

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Table 1 Patient demographics and baseline characteristics at the initiation of TPO-RA treatment

Characteristics	Values
Patients	53
Age (months)	90 [3.5–192]
Male	26 (49.1)
Platelet count (×10^9/L)	15 [2–55]
Bleeding symptoms	
Cutaneous	32 (60.4)
Cutaneous & mucosal	7 (13.2)
Internal organs	0 (0.0)
ANA positive	19 (44.2)
MP IgM positive	16 (40.0)
Inverted CD4/CD8 ratio	15 (46.9)
Duration of ITP (months)	5 [0.33–84]
Number of previous ITP therapies	
1	42 (79.2)
2	8 (15.1)
3	3 (5.7)
Times treated with TPO-RA†	61
TPO-RA	
Eltrombopag	37 (60.7)
Herombopag	9 (14.8)
Avatrombopag	15 (24.6)

Data are presented as n, median [range] or n (%). †, some cases received more than one type of TPO-RA treatment, so the number of treatment times is greater than the total number of cases. TPO-RA, thrombopoietin receptor agonist; ANA, antinuclear antibody; MP, *Mycoplasma pneumoniae*; IgM, immunoglobulin M; ITP, immune thrombocytopenia.

Follow-up

The follow-up time was defined as the time from the initiation of TPO-RAs to the last follow-up evaluation. The median follow-up duration was 12 months (range, 0.6–45 months).

Statistical analysis

Quantitative values were reported as medians, and qualitative data were reported as percentages. Patient response rates were compared between groups using the Chi-squared test or Fisher's exact probability method. All tests were two-sided, and P<0.05 was considered significant. Statistical analyses were performed using SPSS software (version 19.0).

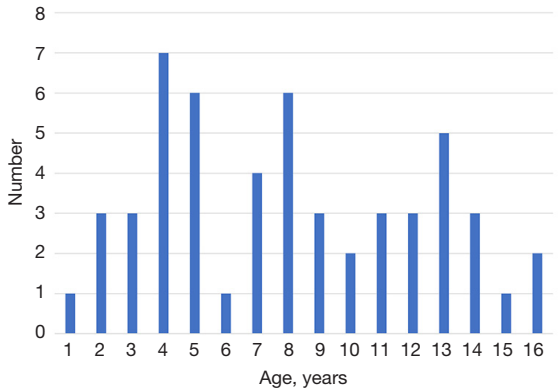

Figure 1 Age distribution of patients receiving TPO-RAs. TPO-RAs, thrombopoietin receptor agonists.

Results

A total of 53 patients were analyzed in this study. Adverse events (AEs) recorded included headache, vomiting, loss of appetite, increased aminotransferase level and cough. The incidences of AEs were low and are shown in *Table 2*. In addition, 10 patients had elevated PLT counts >300×10^9/L, and no thrombosis occurred.

In our study cohort, one started TPO-RAs with a PLT count >50×10^9/L, and one was followed for less than 1 month, so there were 51 patients available for the response rate analysis. As shown in *Table 2*, a total of 37 (72.5%) patients responded. The median time to response was 6 days, and the peak PLT count was 166×10^9/L. Out of 11 patients with concomitant therapy at TPO-RA initiation, 7 (63.6%) had the concomitant therapy withdrawn successfully during TPO-RA exposure. Until the last follow-up, 5 patients relapsed, 4 of whom relapsed during treatment and 1 relapsed after drug withdrawal. Excluding these 5 patients who relapsed, there were 32 patients who still achieved a response with a PLT count >50×10^9/L. Of those, 14 (37.8%) patients were undergoing TPO-RA tapering, 14 (37.8%) patients were treated with no dose reduction, and 4 patients stopped TPO-RA treatment, including 1 patient with a PLT count >100×10^9/L and 3 patients with a PLT count of 50×10^9/L–100×10^9/L.

Eight patients switched between TPO-RAs for different reasons: 3 switched due to no treatment response, 2 due to

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Table 2 Safety and efficacy of TPO-RAs in the treatment of pediatric ITP

Characteristics	Values
Patients	53
Adverse events	18 (34.0)
Headache	1 (1.9)
Loss of appetite	1 (1.9)
Vomiting	1 (1.9)
Increased aminotransferase level	2 (3.8)
Cough	3 (5.7)
PLT count >300×10^9/L	10 (18.9)
Response	37 (72.5)
Time to response (days)	6 [2–60]
Time to PLT count doubled (days)	5 [1–60]
Time to PLT count ≥50×10^9/L (days)	5 [2–27]
Peak PLT count (×10^9/L)	166 [64–861]
Maintained response after withdrawal	4 (10.8)
PLTs 50×10^9/L–100×10^9/L	3 (8.1)
PLTs >100×10^9/L	1 (2.7)
Dose reduction	14 (37.8)
Relapse	5 (13.5)
After withdrawal	1 (2.7)
During treatment	4 (10.8)
Concomitant therapy withdrawal	7 (63.6)
Patients on TPO-RA at last follow-up	28 (52.8)

Data are presented as n, median [range] or n (%). TPO-RA, thrombopoietin receptor agonist; ITP, immune thrombocytopenia; PLT, platelet.

loss of response, 2 due to increased aminotransferase levels, and 1 due to high price. Among the 3 patients who switched due to no treatment response, 1 patient achieved a response, and for the 2 patients with lost responses, both achieved a response again after switching.

We performed subgroup analysis and found that patients aged >4 years had a higher response rate than those aged ≤4 years (81.1% *vs.* 50.0%, P=0.04). However, there was no effect of sex, duration of disease, number of previous ITP therapies, *Mycoplasma pneumoniae* (MP) immunoglobulin M (IgM) positivity, antinuclear antibody (ANA) positivity, CD4/CD8 ratio or baseline PLT count on the response rate (all P>0.05) (*Figure 2*).

Discussion

ITP is the most common hemorrhagic disease in childhood. Although children respond better to first-line corticosteroid treatment than adults, approximately 20% of childhood patients do not respond well (1,2). Rituximab is an alternative approach to treat refractory ITP in children and adults. A meta-analysis of pediatric studies showed a 39% complete response rate with a median response duration of only 12.8 months (5), and in an RCT study, no benefit of rituximab was observed (6). For immunosuppressive drugs such as cyclosporin, AEs must be considered, and the effects are not satisfactory (4). Splenectomy is only suitable for older children with ITP, and carries risks such as infection. The advent of TPO-RAs heralded a paradigm shift in the treatment of ITP. TPO-RAs have a unique mechanism of increasing PLT count by promoting megakaryocyte proliferation/differentiation. International consensuses, such as International Consensus Report (ICR) 2019 (7) and American Society of Hematology (ASH) 2019 (4), recommended against long-term corticosteroid therapy to avoid side effects and suggested TPO-RAs as second-line therapy. In recent years, an increasing number of children with ITP have received TPO-RA therapy in China, but there are few reports in the literature on this topic. We performed this real-world study with the objective of analyzing the efficacy and safety of the three TPO-RAs available in China.

Usually, patients have a very low PLT count when TPO-RAs are initiated. To avoid severe hemorrhagic events, IVIG is often administered concurrently due to its ability to increase the PLT count in ITP patients. However, this increase in PLT count is generally not sustained beyond a month. To eliminate the effect of IVIG, we re-evaluated the PLT count at 1 month after the initiation of TPO-RAs and excluded patients with PLT counts below 50×10^9/L to make our conclusion more reliable. In our study, a 72.5% overall response rate was recorded, which is similar to those reported in other studies. In the PETIT study (8), 62% of patients who received eltrombopag achieved the primary endpoint of a PLT count of 50×10^9/L or more at least once without rescue, and in the open-label period of PETIT2 (9), patients taking eltrombopag achieved a response rate of 80%. In the ICON2 study (10), 71% of patients had a consecutive PLT count response during the first 3 months of treatment with TPO-RAs. Response rates in pediatric ITP patients were slightly lower than those in

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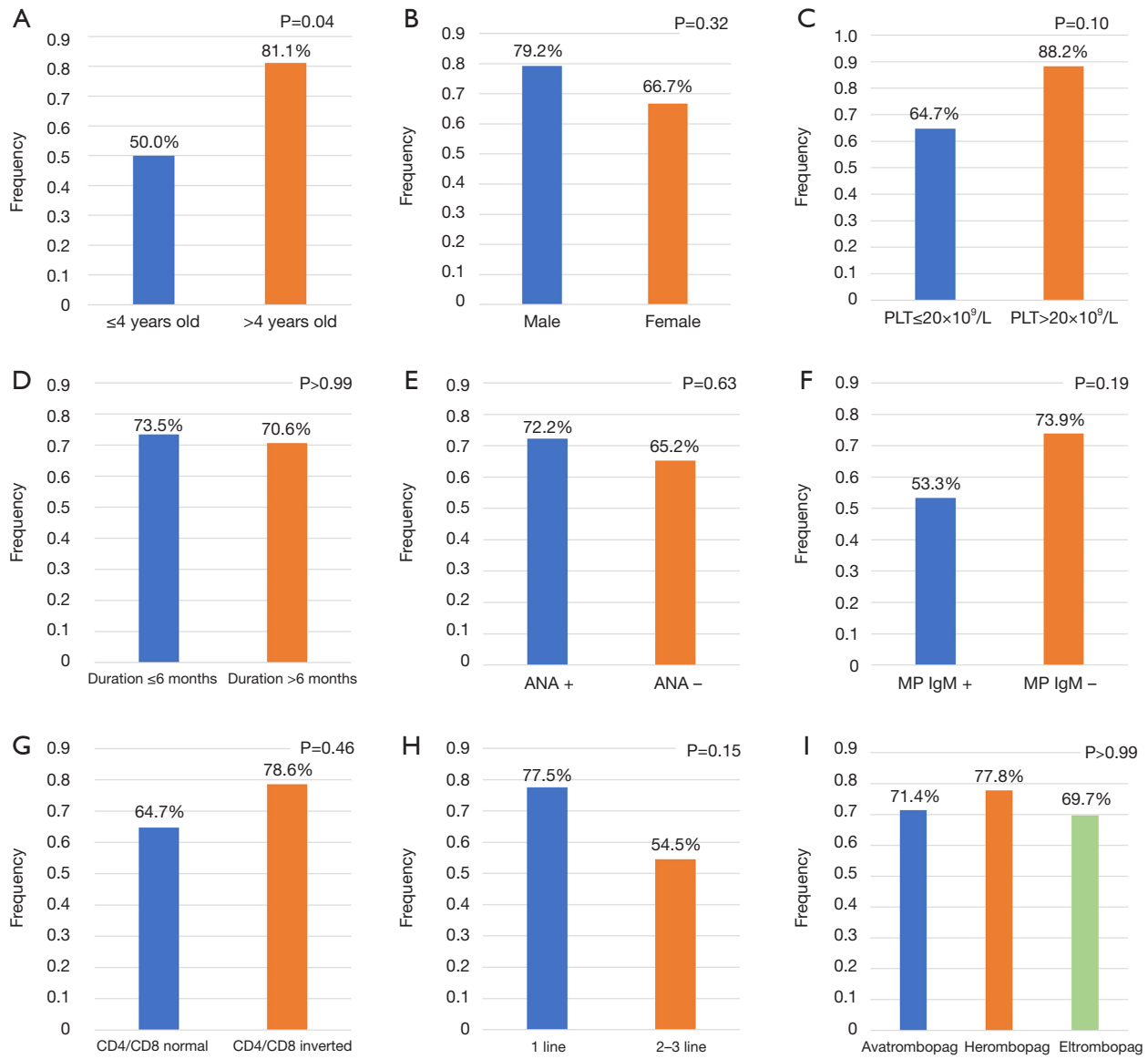

Figure 2 Response rate in different subgroups. Patients aged >4 years achieved a higher response rate than those aged ≤4 years (P=0.04) (A). Factors such as sex (B), baseline PLT count (C), duration of ITP (D), ANA+ or ANA– (E), MP IgM+ or MP IgM– (F), normal or inverted CD4/CD8 ratio (G), and number of previous ITP therapies (H) did not have an effect on the response rate (all P>0.05). There was no significant difference in response rate among the subgroups treated with avatrombopag, herombopag and eltrombopag (P>0.99) (I). PLT, platelet; ANA, antinuclear antibody; MP, *Mycoplasma pneumoniae*; IgM, immunoglobulin M; ITP, immune thrombocytopenia.

adult ITP patients, which ranged from 81.1–90% (11-18). We believe that age may contribute to this difference. In our study cohort, older cases seemed to have better treatment outcomes, so we attempted to divide the cases into two groups based on age for comparison. The results showed the largest statistical difference in response rates when cases were divided into those >4 years and those ≤4 years. We think that this finding will be a useful reference for physicians to make treatment decisions.

We observed that patients with a baseline PLT count ≥20×10^9/L seemingly had a higher response rate than those with a lower PLT count, but the difference was not significant (P=0.10). In the study by Wong *et al.* (15), a baseline PLT count >15×10^9/L indicated a statistically

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higher response rate than a PLT count <15×10^9/L. More studies with larger sample sizes are needed to verify this conclusion. In some reports, MP infection (19), inverted CD4/CD8 ratio (20) and ANA positivity (21) had adverse effects on the results of ITP treatment, but we found that these factors did not influence the response rate (all P>0.05). Sex, duration of ITP, and number of previous therapies also had no statistically significant effect on the response rate (all P>0.05). When comparing the three different TPO-RAs, we found that their response rates were similar (P>0.99).

The median time to response has been reported as 8–35 days (11-14) after initiation of TPO-RAs. In our report, the median time to response was shorter than that in previous reports. The concomitant use of IVIG in some patients may contribute to this difference, which is a limitation of a real-world study. In addition, the potential impact of a higher starting baseline PLT count, the duration of the disease, and the number of prior ITP treatments should be considered and need further research.

Consistent with other reports (8,9,11,14,18), our study indicated that TPO-RAs can reduce the use of concomitant drugs for ITP. We found that 63.6% patients successfully withdrew from concomitant therapy, including cyclosporin and rapamycin; thus, the side effects and costs of these therapies can also be reduced.

Among the 37 patients who achieved a response, 9 patients discontinued TPO-RAs, including 5 who relapsed and 4 who maintained responses after discontinuation. There were 28 (75.7%) patients still in treatment with TPO-RAs at the last contact. González-López *et al.* (18) reported that eltrombopag was discontinued in 29.3% patients who achieved complete response, and 51% of evaluable patients continued to have a sustained response after 6 months of discontinuation. In our real-world analysis, it is difficult to draw a conclusion on the outcome of TPO-RA discontinuation due to the small sample size and relatively short follow-up period.

In clinical practice, doctors may switch to an alternative TPO-RA if the PLT count falls rapidly. The benefits of switching between TPO-RAs have been reported (22-25). In our study cohort, 5 patients switched TPO-RAs due to no treatment response or loss of response; among them, 3 responded after the switch. These limited data preliminarily showed that TPO-RA switching had satisfactory efficacy in pediatric patients.

According to previous reports (15-17), AEs of TPO-RAs usually include headache, pain in the extremities, back pain, pneumonia, fatigue, rash, diarrhea, thrombosis, cataracts, increased alanine aminotransferase levels, and anemia. In general, the reported incidence of these AEs are low, and the safety of TPO-RAs is considered high. In our study, few AEs were documented, and all were mild. Sporadic AEs included headache, vomiting, loss of appetite, and cough. Elevated PLT counts were more common, but no thrombosis occurred. Two patients' aminotransferase levels increased during treatment and resolved after switching to another TPO-RA. These data indicate that the safety of TPO-RAs in children may exceed that in adults, but due to the real-world nature of the study cohort, the AE information was mainly obtained from parent reports and was not as strict as that in an RCT, which may partly contribute to the low incidence of AEs.

TPO-RAs have only been marketed in China in recent years and have not yet entered the medical insurance catalog for many pediatric patients. However, the prices are high. Considering the high price, some patients stopped TPO-RA treatment after 10–15 days if they did not achieve a response. If these patients continued the treatment for a longer time, some of them may have obtained a response. This may partly account for the lower response rate than that of adult patients.

Our study had a small sample, and it also had all the limitations of a retrospective real-world study, including the lack of a strict TPO-RAs dosing regimen, partly because the instruction manuals did not provide an appropriate dosage for children, and some patients had their dosages adjusted due to therapeutic outcomes. The effects after TPO-RA discontinuation could not be analyzed because the follow-up time was short and few patients discontinued before the end of data collection. Thus, further research is warranted in a variety of settings and with more patients with longer follow-up periods.

Conclusions

TPO-RAs have a high response rate in childhood ITP patients, especially those aged ≥4 years old. They are well tolerated with minor side effects. Thus, TPO-RAs are effective in childhood ITP patients who fail to respond to first-line therapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-48/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical approval and informed consent were waived by the Ethics Committee of Human Experimentation of the Children's Hospital of Soochow University because data were collected anonymously and retrospectively from the hospital's data.

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