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ORIGINAL RESEARCH

Can COVID-19 Increase Platelet in Adult Immune Thrombocytopenia During the TPO-RA Administration? A Real-World Observational Study

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Introduction: COVID-19 infection has brought new challenges to the treatment of adult patients with immune thrombocytopenia (ITP). In adult ITP patients, there have been no relevant reports exploring the incidence, clinical characteristics, and risk factors of platelet elevation after COVID-19 infection.

Materials and Methods: A total of 66 patients with previously diagnosed ITP from December 2022 to February 2023 in a single-center were collected and analyzed for this real-world clinical retrospective observational study.

Results: In the platelet count increased group (n = 19), 13 patients (68.4%) were using thrombopoietin receptor agonists (TPO-RA) treatment at the time of COVID-19 infection; the median platelet count was 52 (2–207) $\times 10^9$/L at the last visit before infection and 108 (19–453) $\times 10^9$/L at the first visit after infection. In the platelet count stable group (n = 19) and platelet count decreased group (n = 28), 9 (47.4%) and 8 (28.6%) patients were using TPO-RA at the time of infection, respectively. ITP patients treated with TPO-RA had a significantly higher risk of increased platelet count than those not treated with TPO-RA at the time of infection (platelet count increased group vs platelet count decreased group: OR: 5.745, p = 0.009; platelet count increased group vs the non-increased group: OR: 3.616, p = 0.031). In the platelet count increased group, the median platelet count at 6 months post-infection was 67 (14–235) $\times 10^9$/L, which was significantly higher than the platelet level at the last visit before infection (p = 0.040).

Conclusion: This study showed that some adult ITP patients had an increase in platelet count after COVID-19 infection, and this phenomenon was strongly associated with the use of TPO-RA at the time of infection. Although no thrombotic events were observed in this study, it reminds clinicians that they should be alert to the possibility of thrombotic events in the long-term management of adult ITP patients during the COVID-19 pandemic.

Keywords: immune thrombocytopenia, thrombopoietin receptor agonists, COVID-19, thrombosis

Introduction

Since the novel coronavirus (COVID-19) outbreak in December 2019, the COVID-19 pandemic caused by SARS-CoV-2 virus has brought new challenges to the management of adult patients with immune thrombocytopenia (ITP). The occurrence and recurrence of ITP is closely associated with viral infections such as cytomegalovirus, hepatitis C virus (HCV) and Epstein-Barr virus (EBV).[1] Antibodies induced by viral infections may cross-react with platelets thereby leading to platelet destruction.[2] COVID-19 infection has been identified as a risk factor for the development of ITP,[3] and the occurrence and relapse of ITP induced by COVID-19 infection has been frequently reported.[4–7] This may be related to the direct invasion of hematopoietic stem cells in the bone marrow by COVID-19, autoimmune destruction of platelets

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and increased platelet depletion due to the formation of microthrombi.[8,9] Corticosteroids and high-dose intravenous immunoglobulin (IVIG) are the most commonly used regimens for the treatment of COVID-19 associated thrombocytopenia.

However, two small-sample cases studies found that patients with chronic ITP (cITP) develop early thrombocytosis after COVID-19 infection, which is common in cITP treated with thrombopoietin receptor agonists (TPO-RA).[10,11] A single-center observational cohort study conducted at Beijing Children's Hospital demonstrates a transient rise in platelet counts after COVID-19 infection in cITP children treated with TPO-RA.[12] However, in adult ITP patients, there have been no relevant reports exploring the incidence, clinical characteristics, and risk factors of platelet elevation after COVID-19 infection. To further verify and explore the impact of COVID-19 infection in adult ITP patients, this study retrospectively analyzed the clinical data of adult patients with ITP in our center from December 2022 to February 2023 to provide a reference for the management of adult ITP patients during the COVID-19 pandemic.

Materials and Methods

Data Collection

A total of 66 patients with previously diagnosed ITP in the First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) from December 2022 to February 2023 were collected for this real-world clinical retrospective observational study. Patient's selection criteria: (1) diagnosed as ITP; (2) infected COVID-19 during this period; (3) age above 18 years old.

The diagnosis and follow-up information of ITP patients were obtained from the electronic medical record system or telephone follow-up. The data collected included demographic data, ITP treatment modalities, platelet count at the last visit before COVID-19 infection and platelet count at the first visit after COVID-19 infection. Platelet counts at 3 months and 6 months post-COVID-19 infection were tracked for ITP patients in the platelet count increased group. This study protocol was approved by the medical research ethics committee of the First Affiliated Hospital of University of Science and Technology of China and was conducted in accordance with the Declaration of Helsinki (2023-RE-322). Informed consent was waived by the medical research ethics committee of the First Affiliated Hospital of University of Science and Technology of China because of retrospective nature of the study.

Classifications

According to the platelet counts of the patients at the first visit after COVID-19 infection, the patients were divided into platelet count increased group, platelet count stable group and platelet count decreased group. "Platelet count increased group" was defined as an increase of more than 20% in the platelet count at the first visit after COVID-19 infection compared with the last visit before infection. "Platelet count stable group" was defined as the platelet count fluctuating by less than 20% at the first visit after COVID-19 infection compared to the last visit before infection. "Platelet count decreased group" was defined as a decrease of more than 20% in the platelet count at the first visit after COVID-19 infection compared with the last visit before infection.

Definitions and Statistical Analysis

Newly diagnosed ITP (nITP) is defined for patients with ITP within 3 months of diagnosis; persistent ITP (pITP) is defined for patients with ITP lasting between 3 and 12 months from diagnosis; chronic ITP (cITP) is defined for patients with ITP lasting for more than 12 months.[13] First-line treatment refers to conventional treatment with glucocorticoids and/or intravenous immunoglobulin to improve platelet count; second-line treatment involved the use of one or more of the following three therapies: thrombopoietic agents, rituximab, or splenectomy; third-line treatment refers to the use of therapeutic regimens supported by prospective multicenter clinical trials including decitabine, all-trans retinoic acid (ATRA) in combination with danazol, and other drugs.[14]

Continuous variables were described as means and standard deviations or medians and ranges. Categorical variables were described as frequencies and proportions. Continuous variables were compared between groups by Kruskal–Wallis *H*-test. Test for association between categorical variables used by chi-square test or Fisher's exact test (if applicable). The

potential risk factors associated with fluctuation in platelet counts were further explored using binary logistic regression analysis. Increased, stable, or decreased platelet counts were used as dependent variables, and age, gender, whether corticosteroids were being used at the time of infection, and whether TPO-RA was being used at the time of infection as the independent variables. SPSS26.0 software was used for statistical analysis and differences were considered statistically significant at $p< 0.05$.

Results

Clinical Characteristics

A total of 66 adult ITP patients with COVID-19 infection were enrolled, including 25 (37.9%) males and 41 (62.1%) females, with an average age of 48±16 years. Among them, 10 patients (15.1%) had other autoimmune diseases (6 patients with undifferentiated connective tissue disease, 2 patients with hypothyroidism, 1 patient with Sjogren's syndrome and 1 patient with Evans syndrome), and 3 patients (4.5%) underwent previous splenectomy. There were 11 patients (16.7%) with nITP, 16 patients (24.2%) with pITP, and 39 patients (59.1%) with cITP. Before COVID-19 infection, 18 patients (27.3%) of these patients had received no prior treatment, 10 patients (15.1%) had received first-line treatment, 37 patients (56.1%) had received second-line treatment, and 1 patient (1.5%) had received third-line treatment (Table 1).

Table 1 Clinical Characteristics

Characteristics	All Patients (n=66)
Age [years, Mean±SD]	48±16
Gender [n (%)]	
Male	25 (37.9)
Female	41 (62.1)
ITP status [n (%)]	
Newly diagnosed ITP	11 (16.7)
Persistent ITP	16 (24.2)
Chronic ITP	39 (59.1)
History of autoimmune disease other than ITP [n (%)]	
Undifferentiated connective tissue disease	6 (9.1)
Hypothyroidism	2 (3.0)
Sjogren syndrome	1 (1.5)
Evans syndrome	1 (1.5)
Splenectomy [n (%)]	3 (4.5)
ITP treatment lines before COVID-19 [n (%)]	
Untreated	18 (27.3)
1	10 (15.1)
2	37 (56.1)
3	1 (1.5)
Treatment at the last visit before infection [n (%)]	
No current treatment	23 (34.8)
Corticosteroid only	11 (16.7)
TPO-RA only	22 (33.3)
TPO-RA + corticosteroid	3 (4.5)
Other drug combinations*	7 (10.6)
Platelet count at the last visit before infection [$\times 10^9$/L, Median (range)]	64 (2–246)
Time from last visit before infection to infection [days, Median (range)]	16 (1–110)
Platelet count at the first visit after infection [$\times 10^9$/L, Median (range)]	40 (2–453)
Time from infection to first visit after infection [days, Median (range)]	16 (1–82)

Abbreviations: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists. *Other drug combinations including Eltrombopag plus Cyclosporine (n=1), Eltrombopag plus Danazol (n=1), Hetrombopag plus Cyclosporine (n=1), Hetrombopag plus Corticosteroid plus Cyclosporine (n=1), Hetrombopag plus Corticosteroid plus Rituximab (n=1), Corticosteroid plus Azathioprine plus Danazol (n=1), Decitabine plus Chidamide (n=1).

At the time of COVID-19 infection, 11 patients (16.7%) received corticosteroids monotherapy, 22 patients (33.3%) received TPO-RA regimens monotherapy, 3 patients (4.6%) received corticosteroids and TPO-RA combinations and 7 patients (10.6%) received other combinations treatment. Twenty-three patients (34.8%) did not receive any regimens. TPO-RA using details were shown in Supplementary Table 1.

COVID-19 Infection and Platelet Count Fluctuation

The median platelet count of 66 ITP patients at the last visit before COVID-19 infection was 64 (2–246) $\times 10^9$/L, and the median time from the last visit before infection to COVID-19 infection was 16 (1–110) days. The median platelet count at the first visit after infection was 40 (2–453) $\times 10^9$/L, and the median time from COVID-19 infection to the first visit was 16 (1–82) days (Table 1). After COVID-19 infection, the platelet count of 19 patients (28.8%) increased by more than 20% compared with that before infection (platelet count increased group), of which 14 patients (73.7%) increased by more than 50%. The platelet count of 19 patients (28.8%) was stable which fluctuated within 20% compared with that before infection (platelet count stable group). Twenty-eight patients (42.4%) had a reduction in platelet count of more than 20% (platelet count decreased group), of which 17 (60.7%) patients had a decrease of 50% or more (Figure 1).

There were 19 patients in the platelet count increased group, including 6 (31.6%) males and 13 (68.4%) females, with an average age of 51±14 years. Among these patients, 2 patients (10.5%) were nITP, 4 patients (21.1%) were pITP, and 13 patients (68.4%) were cITP. One patient (5.3%) had received first-line treatment, 13 patients (68.4%) had received second-line treatment, 1 patient (5.3%) had received third-line treatment, and four patients (21.1%) had received no previous treatment. At the time of COVID-19 infection, 4 patients (21.1%) were using corticosteroids and 13 patients (68.4%) were using TPO-RA. The median platelet count at the last visit before infection was 52 (2–207) $\times 10^9$/L, and the median platelet count at the first visit after infection was 108 (19–453)$\times 10^9$/L. The median time from the last visit before infection to COVID-19 infection was 13 (1–67) days, and the median time from infection to the first visit after infection was 20 (2–47) days (Table 2).

A total of 19 patients in the platelet count stable group include 8 (42.1%) males and 11 (57.9%) females, with an average age of 44±16 years. Of these patients, 9 (47.4%) were using TPO-RA at the time of infection. The median platelet count at the last visit before infection was 64 (14–246) $\times$ 10^9/L, and the median platelet count at the first visit after infection was 64 (12–259) $\times 10^9$/L. The median time from the last visit before infection to COVID-19 infection was 20 (4–86) days, and the median time from infection to the first visit after infection was 21 (5–57) days (Table 2). There were 28 patients in the platelet count decreased group, including 11 (39.3%) males and 17 (60.7%) females, with a mean

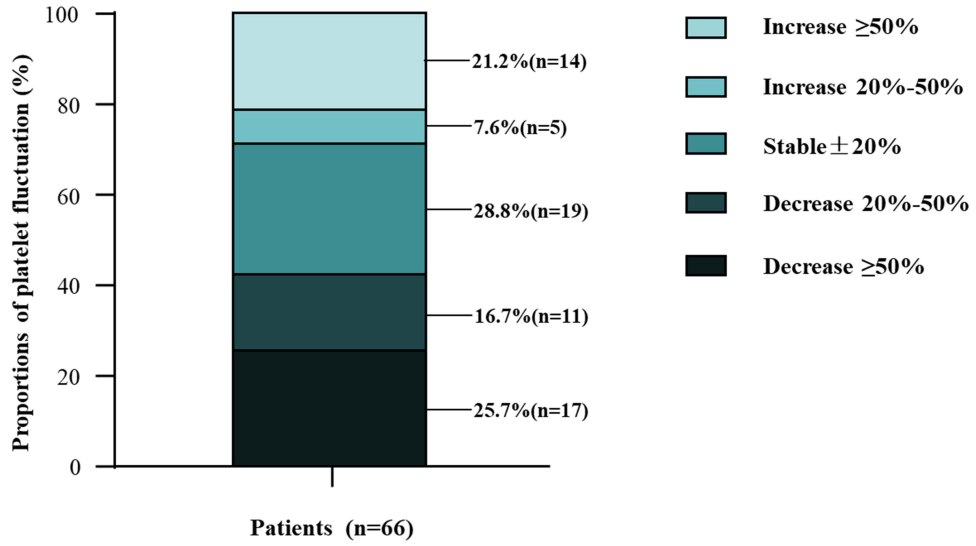

Figure 1 COVID-19 infection and platelet count fluctuation. After COVID-19 infection, the platelet count of 19 patients increased by more than 20% compared with that before infection, of which 14 patients increased by more than 50%. The platelet count of 19 patients was stable which fluctuated within 20% compared with that before infection. Twenty-eight patients had a reduction in platelet count of more than 20%, of which 17 patients had a decrease of 50% or more.

Table 2 Clinical Characteristics of the Increased, Stable and Decreased Platelet Count Groups

Characteristics	Increased Platelet Count (n=19)	Stable Platelet Count (n=19)	Decreased Platelet Count (n=28)	*P*-value
Age [years, Mean±SD]	51±14	44±16	48±18	0.427
Gender [n (%)]				0.783
Male	6 (31.6)	8 (42.1)	11 (39.3)	
Female	13 (68.4)	11 (57.9)	17 (60.7)	
ITP status [n (%)]				0.532
Newly diagnosed ITP	2 (10.5)	3 (15.8)	6 (21.4)	
Persistent ITP	4 (21.1)	3 (15.8)	9 (32.2)	
Chronic ITP	13 (68.4)	13 (68.4)	13 (46.4)	
ITP treatment lines before COVID-19 [n (%)]				0.079
Untreated	4 (21.1)	5 (26.3)	9 (32.1)	
1	1 (5.3)	1 (5.3)	8 (28.6)	
2	13 (68.4)	13 (68.4)	11 (39.3)	
3	1 (5.3)	0	0	
Treated with corticosteroid at the last visit before infection [n (%)]	4 (21.1)	5 (26.3)	8 (28.6)	0.936
Treated with TPO-RA at the last visit before infection [n (%)]	13 (68.4)	9 (47.4)	8 (28.6)	0.020
Platelet count at the last visit before infection [$\times10^9$/L, Median (range)]	52 (2–207)	64 (14–246)	71 (14–227)	0.182
Time from last visit before infection to infection [days, Median (range)]	13 (1–67)	20 (4–86)	14 (2–110)	0.381
Platelet count at the first visit after infection [$\times10^9$/L, Median (range)]	108 (19–453)	64 (12–259)	23 (2–90)	<0.001
Time from infection to first visit after infection [days, Median (range)]	20 (2–47)	21 (5–57)	13 (1–82)	0.104

Abbreviations: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.

age of 48 ± 18 years. Among them, 8 patients (28.6%) were receiving TPO-RA before infection. The median platelet count at the last visit before infection was 71 (14–227) $\times10^9$/L, and the median platelet count at the first visit after infection was 23 (2–90) $\times10^9$/L. The median time from the last visit before infection to COVID-19 infection was 14 (2–110) days, and the median time from infection to the first visit after infection was 13 (1–82) days (Table 2).

Risk Assessment of Platelet Count Elevation After COVID-19 Infection

There were no significant differences in age, gender, ITP stage, previous treatment lines, use of corticosteroids at the time of infection, platelet count at the last visit before infection, the time from the last visit before infection to COVID-19 infection, and the time from COVID-19 infection to the first visit after infection among the ITP patients with above three groups. However, there was a significant difference in whether TPO-RA was being used at the time of infection (p=0.020) (Table 2).

ITP patients treated with TPO-RA had a significantly higher risk of increased platelet count than those not treated with TPO-RA at the time of infection [platelet count increased group vs platelet count decreased group: OR (95% CI): 5.745 (1.556–21.216), p=0.009; platelet count increased group vs the non-increased group (stable and decreased groups): OR (95% CI): 3.616 (1.123–11.648), p=0.031] (Figure 2).

Dynamics of Platelet Levels in Patients in the Platelet Count Increased Group

In the platelet count increased group, the median platelet count at the first visit after COVID-19 infection was 108 (19–453)$\times10^9$/L, which was significantly higher than that at the last visit before infection [52 (2–207)$\times10^9$/L] (p<0.001) (Figure 3A). The median platelet count at 3 months post-infection was 58 (9–240) $\times10^9$/L, which was slightly higher than that at the last visit before infection (p=0.180)(Figure 3B). The median platelet count at 6 months post-infection was 67 (14–235) $\times$ 10^9/L, which was significantly higher than the platelet level at the last visit before infection (p=0.040) (Figure 3C). Although platelet counts at 3 months and 6 months after infection were significantly lower than those at the first visit after infection (p=0.011, 0.038) (Figure 3D); however, there was no difference between platelet counts at 3 months and 6 months (p=0.561) (Figure 3D).

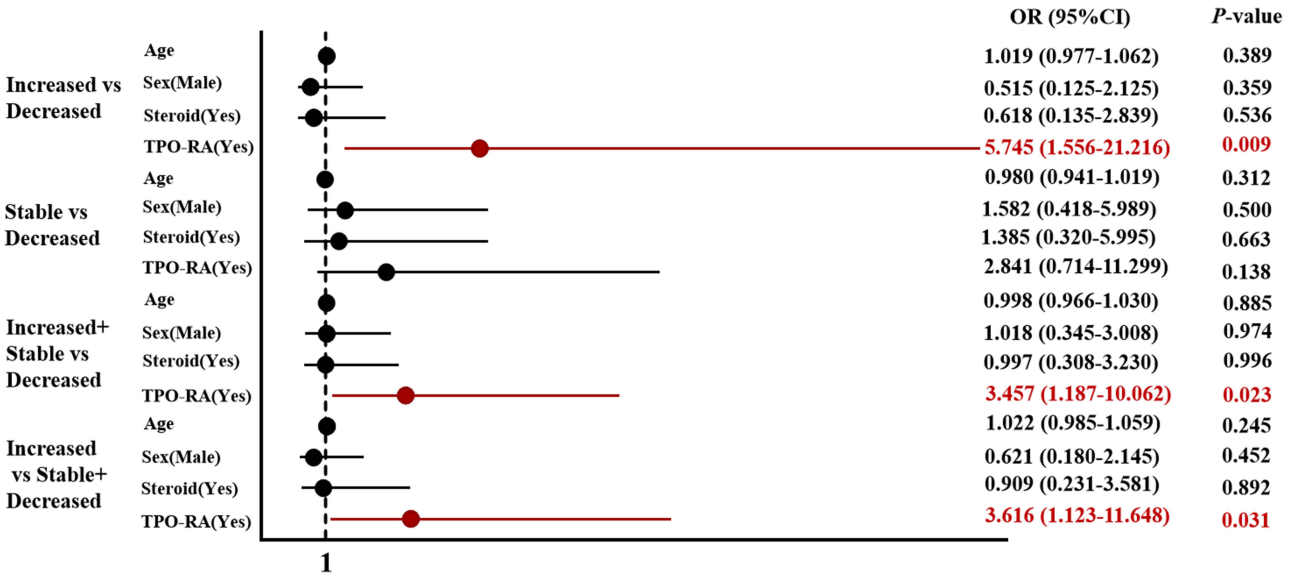

Figure 2 Risk factors of ITP patients with increased platelet count after COVID-19 infection.

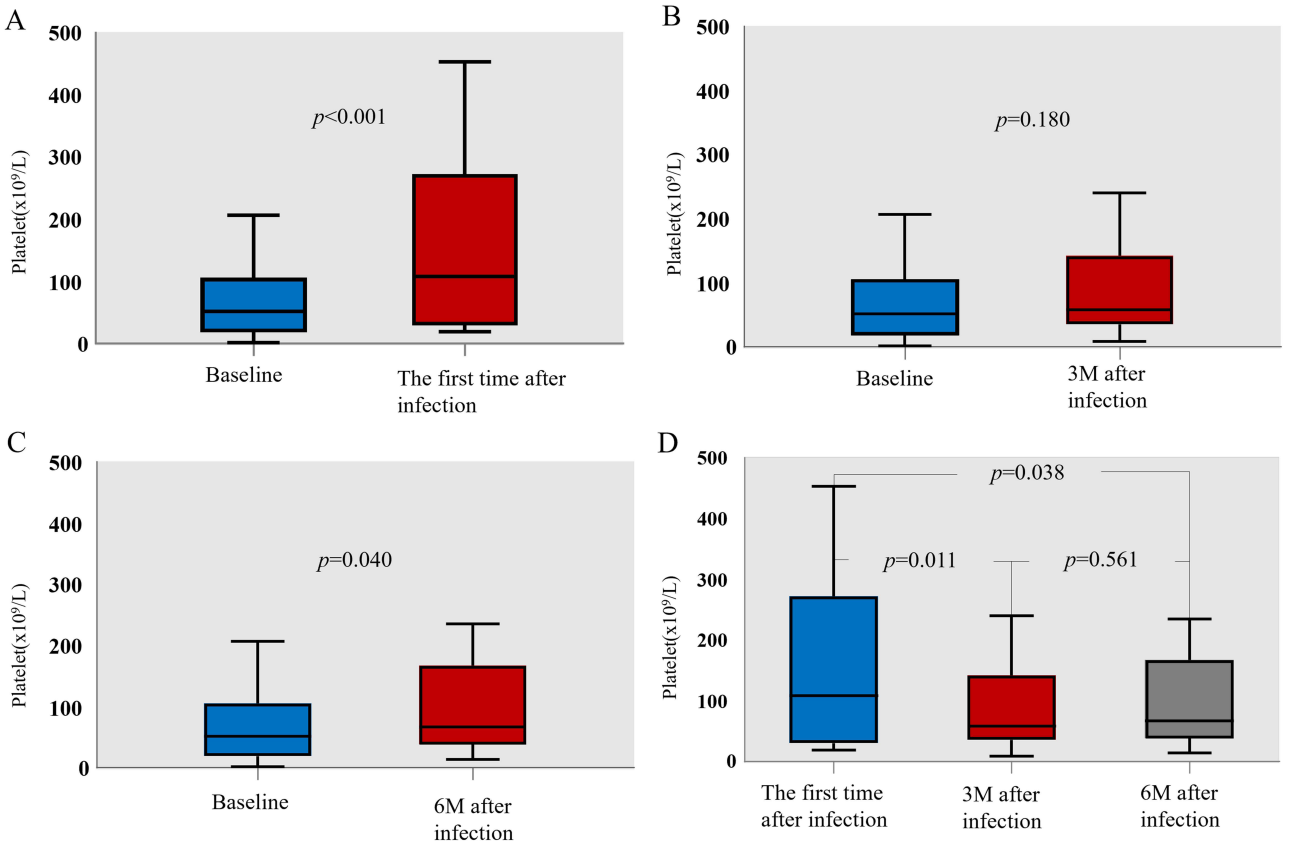

Figure 3 Changes of platelet counts in patients of platelet count increased group. Platelet counts at the first visit after COVID-19 infection compared with the last visit before infection (**A**). Platelet counts at the 3 months after COVID-19 infection compared with the last visit before infection (**B**). Platelet counts at the 6 months after COVID-19 infection compared with the last visit before infection (**C**). Platelet counts at the first visit, at the 3 months and 6 months after COVID-19 infection which compared with each other (**D**).

Discussion

In this study, 28.8% of adult ITP patients had an increase in platelet count after COVID-19 infection (more than 20% above baseline). Logistic regression analysis showed that platelet count elevation was strongly associated with the use of TPO-RA. This is consistent with two previous small-sample cases studies,[10,11] and a study of pediatric ITP patients that reported a transient increase in platelet counts after COVID-19 infection in cITP patients treated with TPO-RA;[12] the peak rise in platelet counts occurred 1–2 weeks after COVID-19 infection, and platelet counts returned to pre-infection levels 3–4 weeks after infection.[10–12] However, this study indicated that, in the platelet count increased group, platelet counts elevation mostly occurred within 1 month after COVID-19 infection; the platelet count was slightly increased at 3 months after infection and the platelet count was still at a higher level at 6 months after infection when compared with that before infection (p=0.180, 0.040).

TPO-RA use synergized with cytokines and lymphopenia caused by COVID-19 infection might contribute to the elevation of platelet count in ITP patients. After COVID-19 infection, there was a significant increase in the levels of many inflammatory cytokines, such as IL-6, IL-11 and tumor necrosis factor (TNF-α).[15] Related studies have shown that these cytokines could promote megakaryocyte production,[16] and Stone et al suggested that IL-6 promotes megakaryopoiesis by stimulating hepatic TPO expression.[17] In addition, SARS-CoV-2 virus can directly infect and induce apoptosis of lymphocytes and relevant studies have shown a decrease in peripheral blood lymphocytes in COVID-19-infected patients, especially CD4+ and CD8+ T lymphocytes,[18] which leads to a decrease in platelet antibody production and further reduces platelet destruction. In the future, we will further expand the sample size and further analyse whether the duration, dose and frequency of TPO-RA use affects the extent of platelet increase.

This study suggested that COVID-19 infection in ITP patients treated with TPO-RA may lead to a further increase in platelet counts. Although no thrombotic events were observed in this study, it reminds clinicians that they should be paid close attention to the possibility of thrombotic events in the long-term management of ITP. Firstly, although ITP is an acquired autoimmune hemorrhagic disease, ITP itself is also a high-risk factor for thrombosis;[19] a meta-analysis of three large population-based observational studies which conducted in Denmark, the United Kingdom and the United States indicated that the annual incidence of arterial and venous thrombotic events in patients with ITP ranged from 1.0 to 2.8 per 100 and 0.4 to 0.7 per 100, respectively, which were significantly higher than that in non-ITP patients (0.7 to 1.8 per 100 patients and 0.1 to 0.4 per 100 patients, respectively).[20] Secondly, pro-inflammatory cytokines release, platelet adhesion and aggregation, endothelial inflammation and injury, thrombin generation caused by SARS-CoV-2 virus infection might lead to immunothrombosis.[21,22] Epidemiologic studies indicated a high incidence of venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients with COVID-19;[23–25] COVID-19 might also be associated with an increased incidence of arterial thrombotic events such as ischemic stroke and limb ischemia, especially in patients with severe COVID-19.[26–28] Thirdly, TPO-RA increases platelet production by binding to and activating the thrombopoietin receptor on the membrane of megakaryocytes.[29] Studies have shown that the incidence of arterial and venous thrombotic events in cITP patients treated with TPO-RA is 2 to 3 times higher than that in patients who do not receive TPO-RA,[30,31] which may be related to megakaryocyte activation and platelet production rapid elevation.

Conclusion

In conclusion, this study showed that some adult ITP patients had an increase in platelet count after COVID-19 infection, and this phenomenon was strongly associated with the use of TPO-RA at the time of infection. However, there are some limitations in this study. First, this was a retrospective study with a small sample size and the follow-up time was relatively short. In addition, there is no clear and uniform time point which designed for observing the platelet levels fluctuation after COVID-19 infection due to the essence of retrospective research, resulting in the possibility that the recording of platelet counts after infection may be somewhat biased from the actual situation. Finally, this study did not focus on the changes of coagulation function, including D-dimer levels, in patients with elevated platelet counts during the follow-up period; therefore, there is insufficient data to prove the possibility of thrombotic events in this group patients.

Abbreviations

ITP, Thrombocytopenia; TPO-RA, Thrombopoietin receptor agonists; COVID-19, Novel coronavirus; cITP, Chronic ITP; nITP, Newly diagnosed ITP; pITP, Persistent ITP; ATRA, All-trans retinoic acid; TNF-α, Tumor necrosis factor; VTEs, Venous thromboembolic events; DVT, Deep vein thrombosis; PE, Pulmonary embolism.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics and Consent to Participate

This study was approved by the ethics committees of the First Affiliated Hospital of University of Science and Technology of China and was conducted in accordance with the Declaration of Helsinki (2023-RE-322). Informed consent was waived by the medical research ethics committee of the First Affiliated Hospital of University of Science and Technology of China because of retrospective nature of the study. All data were secured, protected, and accessed only for the authors. Personal information relating to the data that identifies the research subject is replaced with a numerical number. The descriptive data were summarized by tables and figures.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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