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REVIEW

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Immune thrombocytopenic purpura secondary to COVID-19 vaccination: A systematic review

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Abstract

Introduction: This systematic review aimed to retrieve patients diagnosed with de novo immune thrombocytopenic purpura (ITP) after COVID-19 immunization to determine their epidemiological characteristics, clinical course, therapeutic strategies, and outcome.

Materials and Methods: We conducted the review using four major databases, comprising PubMed, Scopus, Web of Science, and the Cochrane library, until April 2022. A systematic search was performed in duplicate to access eligible articles in English. Furthermore, a manual search was applied to the chosen papers' references to enhance the search sensitivity. Data were extracted and analyzed with the SPSS 20.1 software.

Results: A total of 77 patients with de novo COVID-19 vaccine-associated ITP were identified from 41 studies, including 31 case reports and 10 case series. The median age of patients who developed COVID-19 vaccine-associated ITP was 54 years (IQR 36–72 years). The mRNA-based COVID-19 vaccines, including BNT16B2b2 and mRNA-1273, were most implicated (75.4%). Those were followed by the adenovirus vector-based vaccines, inclusive of ChAdOx1 nCoV-19 and vAd26.COV2.S. No report was found relating ITP to other COVID-19 vaccines. Most cases (79.2%) developed ITP after the first dose of COVID-19 vaccination. 75% of the patients developed ITP within 12 days of vaccination, indicating a shorter lag time compared to ITP after routine childhood vaccinations. Sixty-seven patients (87%) patients were hospitalized. The management pattern was similar to primary ITP, and systemic glucocorticoids, IVIg, or both were the basis of the treatment in most patients. Most patients achieved therapeutic goals; only two individuals required a secondary admission, and one patient who presented with intracranial hemorrhage died of the complication.

Conclusions: De novo ITP is a rare complication of COVID-19 vaccination, and corresponding reports belong to mRNA-based and adenovirus vector-based vaccines, in order of frequency. This frequency pattern may be related to the scale of administration of individual vaccines and their potency in inducing autoimmunity. The more the COVID-19 vaccine is potent to induce antigenic challenge, the shorter the lag time

Ali Bidari and Sara Asgarian contributed equally to this study (Co-first authors).

would be. Most patients had a benign course and responded to typical treatments of primary ITP.

KEYWORDS
COVID-19, idiopathic thrombocytopenic purpura, immune thrombocytopenia, platelet, SARS-CoV-2, vaccine

NOVELTY STATEMENT

What is the new aspect of your work?

This study is the first systematic review on one of the rare but potentially life-threatening adverse effects of SARS-CoV-2 vaccination.

What is the central finding of your work?

Clinical presentations of COVID-19 vaccine-associated ITP (COVID-19 VITP) are very similar to idiopathic ITP and the mRNA-based and adenovirus vector-based vaccines are the most common culprits of COVID-19 VITP, respectively.

What is (or could be) the specific clinical relevance of your work?

Most COVID-19 VITP cases have a benign disease course and respond to treatment appropriately.

1 | INTRODUCTION

Since the emergence of SARS-CoV-2 in 2019, COVID-19 is still an ongoing pandemic that has devastated global health. It has resulted in an iconic international cooperative effort to produce and distribute vaccines to limit the outbreak, safeguard human lives, and avert further socio-economic impacts.[1–4] COVID-19 vaccines have shown substantial efficacy in clinical trials and real-world data.[5]

However, the safety and adverse effects of the COVID-19 vaccines have been a major public concern, resulting in vaccine hesitancy that necessitates ongoing and comprehensive observation and research.[6–9] Contrary to mild and moderate local or systemic adverse effects that may occur after vaccination, intense medical consequences are uncommon.[2,10,11] Several case series, nevertheless, revealed hematological problems such as immune thrombocytopenic purpura (ITP) induced by vaccination.[8,12]

ITP is an autoimmune disease of platelet destruction resulting in a platelet count below 100 000 per cubic millimeter and has an incidence of two to five cases per 100 000 person-years.[13,14] Even today, it is quite frustrating that ITP remains a diagnosis of exclusion.[15] The most common type of ITP is the idiopathic primary condition, though it can also be found secondary to other conditions, such as systemic autoimmune disorders, medications, a variety of infections, and vaccinations.[14,16] The latter is termed vaccine-associated ITP and has been reported following different types of vaccines. This phenomenon, still rare, has been diagnosed more frequently since employing programs for massive vaccination against COVID-19.[17] Similar to primary ITP, COVID-19 vaccine-associated ITP can manifest with a broad range of bleeding symptoms, from petechiae to fatal bleeding.[18,19] Nonetheless, it remains unclear whether COVID-19 vaccine-associated ITP is self-limited or persists and progresses to chronic ITP.[17]

The recent literature has witnessed a surge in research on COVID-19 vaccine-associated ITP. Several reports or case series have shown new presentations of ITP following different COVID-19 vaccinations.[7,12,20] However, none of the prior works provide systematic information concerning the subject.

This systematic review aimed to highlight the characteristics of COVID-19 vaccine-associated ITP by analyzing the reaction onset, clinical manifestations, laboratory features, and management strategies based on pooled data extracted from the literature.

2 | MATERIALS AND METHOD

2.1 | Protocol and registration

This systematic review was conducted, and the results were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

2.2 | Search strategy and databases

Two researchers (APM and SA) conducted an independent search on major databases, including PubMed, Scopus, Web of Science, and Cochrane library, and retrieved all eligible articles published until 13 April, 2022. The adopted search keywords were COVID-19,

coronavirus disease 2019, SARS-CoV-2, vaccine, vaccination, specific COVID-19 vaccine names, AND ITP, immune thrombocytopenia, ITP, idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, petechiae, bleeding and their close word variations in addition to the related MESH terms. Table S1 represents the search strategy applied to each database. Furthermore, a manual search was performed through the selected articles' references to avoid missing relevant studies.

2.3 | Eligibility criteria

The eligible articles included case reports, case series, and observational studies that reported at least one case of de novo ITP following COVID-19 vaccination. Our search was limited to the original clinical studies published in English and did not include in vitro or animal studies. To enhance search validity, we sought to exclude reports and studies on vaccine-induced immune thrombotic thrombocytopenia (VITT), cerebral venous sinus thrombosis (CVST), disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP) or inferring evidence of thrombosis, COVID-19 infection-induced ITP, or thrombocytopenia with any justification other than ITP. In addition, any case with evidence of previous episodes of ITP suggesting a relapse or exacerbation (depending on chronological interlude) was set aside from the final analysis.

2.4 | Screening

After removing study duplicates from the initial search results, two reviewers (APM and SA) independently screened the titles and abstracts of the retrieved articles to check gross relevancy. Afterward, MGM, SA, DN, and SRA formed two separate groups and scrutinized initially selected articles' full text to ascertain eligibility. Subsequently, the two groups cross-checked their results as a quality control measure. Disagreements were resolved in online meeting sessions held with the guidance of AB as the senior researcher.

2.5 | Case duplicates removal

We exerted a careful effort across included studies to eliminate case duplicates. For that purpose, a computer-assisted algorithm was generated. Eligible cases were extracted from included studies, and a trio of variables, including age, gender, and vaccine type, was used collectively for screening duplicates according to the algorithm. In this step, potential duplicates were indexed. Subsequently, two independent researchers (AP and MGM) reviewed the index cases for other available details such as demographic data, clinical manifestations, and applied management. Lastly, we removed verified duplicates.

2.6 | Data extraction

Data extraction was initiated by generating a structured database containing articles' titles, authors, and publication dates. Then, the following detailed information was obtained for every patient: the medical and drug history, vaccine brand and dose, time lag to develop ITP, selected clinical findings, and relevant laboratory markers such as platelet count prior to vaccination, platelet count at admission, the nadir platelet count, anti-platelet antibodies (nonspecific anti-platelet IgG antibodies, anti-platelet factor IV, anti GP IIb/IIIa), peripheral blood smear and bone marrow aspiration/biopsy findings, mode and setting of the treatment, length of hospital stay, and convalescent platelet count. Any patients with positive anti-platelet factor IV in laboratory data were excluded.

2.7 | Statistical analysis

Descriptive data were reported using frequency, median, mean, and standard deviation. Comparison across groups was made using Chi-square and Kruskal–Wallis test for qualitative and quantitative data, respectively. p values less than .05 were considered statistically significant. SPSS 20.1 software was used for all analyses.

3 | RESULTS

3.1 | Summary of evidence

A total of 1040 published articles were identified from four different databases: PubMed, Scopus, Web of Science, and Cochrane. Thereof, 320 articles were duplicated and removed. The remaining articles were screened for gross eligibility by evaluating titles and abstracts. As a result, 95 articles were selected. From excluded, most pertained to VITT. In the last screening step, the articles' full texts were scanned and scrutinized to determine whether they fulfilled all eligibility criteria. Accordingly, 54 articles were dismissed from the final analysis for various reasons; the most common were ITP relapse (14 articles) and inadequate data (12 articles). Eventually, we adopted 41 articles for our systematic review. Figure 1 depicts the PRISMA chart.

3.2 | Baseline characteristics

A total of 77 patients with de novo post-COVID-19 vaccination ITP were identified from 41 articles, including 31 case reports and 10 case series. Females were dominant, comprising 46 (59.7%) of the entire selected cases. The median age of the study population was 54 years (IQR 36–72 years). The culprit COVID-19 vaccine types in the study population included BNT16B2b2 mRNA vaccine (Pfizer-BioNTech) in 35 cases (45.5%), mRNA-1273 vaccine (Moderna) in 23 cases (29.9%), ChAdOx1 nCoV-19 vaccine (AstraZeneca) 17 cases (22.1%), and Ad26.COV2.S vaccine (Johnson & Johnson) in two cases (2.6%).

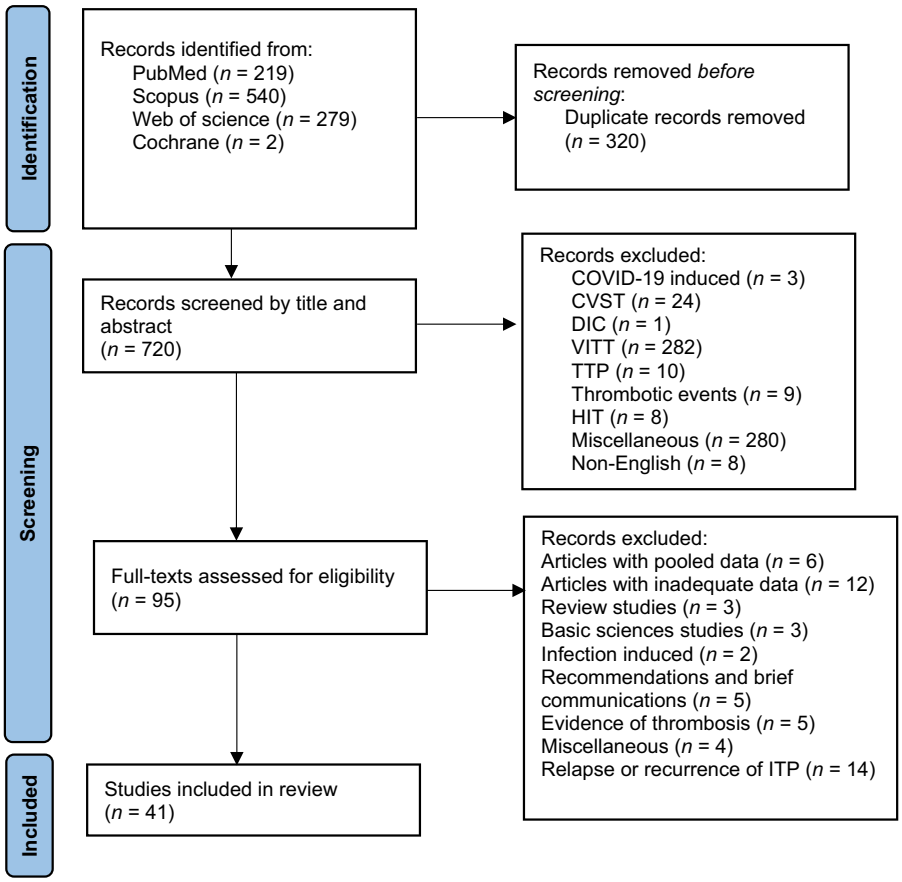

FIGURE 1 PRISMA chart

Sixty-one patients (79.2%) were diagnosed with ITP after receiving the first vaccine dose for COVID-19, 14 patients (18.2%) after the second dose, one patient following the booster dose (1.3%), and the dose number was not specified in another case. The first and second vaccine doses were from the same brand for patients who developed ITP after the second dose. The premorbid autoimmune disease was cited in only eight patients (10.4%). The information for each case in all included studies are represented in Tables 1 and 2 demonstrates the summary of the entire extracted cases.

3.3 | ITP lag time and manifestations

Among 71 patients with available data, the median time between vaccination and the clinical presentation of ITP was 7 days (IQR 3–12). While ITP in 75% of cases had been presented by day 12 of vaccination, a lag time from 1 to 35 days was observed. The median lag times for the four different types of vaccines were calculated separately. The figure for BNT16B2b2 mRNA vaccine was 5 days (IQR 3–7.7), for mRNA-1273 vaccine was 7.5 days (IQR 1.75–13.5), for ChAdOx1 nCoV-19 vaccine was 11.0 days (IQR 5–16), and for Ad26.COV2.S vaccine was 24.5 days. Kruskal–Wallis test was conducted to examine the differences on duration onset of ITP reaction according to the types of vaccines administered. A significant difference (Chi square = 10.25, $p = .017$, df = 3) was found among the four categories of vaccine.

At the time of diagnosis, 10 patients (13%) had no evidence of thrombocytopenic-related bleeding, while 62 patients (80.5%) exhibited signs of bleeding, and clinical manifestations were not described in the other five cases (6.4%). The most prevalent manifestations were cutaneous involvement, encompassing petechiae, purpura, and ecchymoses, reported in 70.1% of the patients. Mucosal manifestations were seen in 46.7% of the patients. In 22.1% of the cases, internal organ involvements including hemoptysis, hematuria, scleral hemorrhage, gastrointestinal bleeding, vaginal bleeding, and cerebral hemorrhage were reported. Four individuals had intracranial hemorrhage (ICH), one of them had a fatal outcome.[22]

Evans syndrome, a rare condition characterized by the coexistence of autoimmune hemolytic anemia (AIHA) and ITP, was diagnosed in one case after receiving the BNT16B2b2 mRNA vaccine.

3.4 | Laboratory findings

Seventeen patients had available prior-to-vaccination platelet count, which ranged from 126×10^9/L to 429×10^9/L with a median of 220×10^9/L (IQR $172.5–255 \times 10^9$/L). Patients' platelet count at admission had a median of 3×10^9/L (IQR $2–10 \times 10^9$/L) and a mode of 2×10^9/L. The minimum platelet count on the initial day of admission was $<1 \times 10^9$/L, and the maximum count was 66×10^9/L. The median platelet nadir count was 4.5×10^9/L (IQR $1.25–26.75 \times 10^9$/L) in 12 cases with attainable data, ranged from <1 to 59×10^9/L.

TABLE 1 Epidemiologic characteristics of included cases

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
Baba, Y., 2022[42]	90/M	BNT16B2b2 mRNA BNT16B2b2 mRNA	First	7	HTN/DLP/MI	Extensive purpura on the extremities/ICH/ duodenal bleeding/ impaired consciousness/ pallor of palpebral conjunctiva/ tarry stool	3	224	NM	Elevated platelet antibodies-IgG/ negative anti PF4	PSL 40 mg/day/ IVIG/TPO-RA (EPAG)/platelet and RBC transfusion	Yes/67	NM
Sivaramakrishnan, P., 2022[17]	NM/F	ChAdOx1.	First	30	Previously treated pulmonary TB	Hemoptysis/ menorrhagia/ fever/streaked sputum	8	NM	NM	NM	Plt transfusion	Yes/7	NM
	NM/F	ChAdOx1.	Second	11	NM	Hemoptysis/ menorrhagia	10	NM	NM	NM	PSL 80 mg/day	Yes/NM	NM
Chong, K. M., 2022[43]	75/F	mRNA-1273	First	3	Refractory lung adenocarcinoma	Hemoptysis	7	NM	NM	HBV profile compatible with a previous infection	Plt transfusion/PSL 1 mg/kg/day	Yes/5	NM
Shonai, T., 2022[44]	34/F	mRNA-1273	Second	21	NM	Generalized purpura/irregular vaginal bleeding	11	NM	3	NM	At first: followed without treatment At first week of follow up: PSL 1 mg/kg/day TPO-RA (EPAG)	Yes/NM	NM
Chanut, M., 2022[45]	NM/ NM	mRNA-1273	First	7	IgA kappa (MGUS)/obesity/ HTN/hypothyroidism/ corticoid-induced glaucoma/recurrent rheumatic diseases	Extensive bruises/ generalized petechiae/ICH/ epistaxis	2	287	NM	NM	IVIG 1 g/kg for 2 days	Yes/2	310
Al-Ahmad, M., 2022[46]	54/F	ChAdOx1.	First	17	NM	NM	10	NM	NM	NM	PSL 1 mg/kg/day/ IVIG 1 g/kg	Yes/NM	NM
	33/F	ChAdOx1.	First	21	NM	NM	3	NM	NM	NM	PSL 1 mg/kg/day/ IVIG 1 g/kg for 2 days/TPO-RA (Romiplostim)	Yes/NM	NM
	56/F	BNT16B2b2 mRNA	Second	7	NM	NM	2	NM	NM	NM	PSL 1 mg/kg/day/ IVIG 1 g/kg for 2 days/TPO-RA (EPAG)	Yes/NM	NM

(Continues)

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
Battegay, R., 2021[47]	77/M	BNT16B2b2 mRNA	First	8	CAD/AF/HTN/CKD	Wet petechiae	28	126	17	Detectable anti-SARS-CoV2 spike(S1) and anti-RBD specific IgM and IgG Anti-S1-IgG seroconversion confirmed in the ELISA assay at day 25 after vaccination	Oral anticoagulant withdrawal/ oral vitamin K/PSL 1.2 mg/kg/day/ IVIG 0.48 g/kg for 2 days/TPO-RA (EPAG)	Yes/NM	NM
Nakamura, T., 2022[48]	32/F	BNT16B2b2 mRNA	Second	5	NM	Petechiae and purpura on the extremities/ gingival and oral mucosal bleeding/wet purpura	<1	210	NM	Elevated PA-IgG// negative anti PF4	PSL 50 mg/day	Yes/12	NM
Malayala, S. V., 2021[49]	75/F	BNT16B2b2 mRNA	Third/ Booster	NM	Mixed connective tissue disease (RA + scleroderma)/HTN/ osteopenia	Petechiae	13.9	198	9	NM	Dexamethasone 40 mg/day	Yes/NM	NM
Nutalapati, S., 2021[18]	25/F	mRNA-1273	Second	26	well-controlled bronchial asthma	Generalized scattered petechiae/ extensive bruising/ intermittent epistaxis/gross hematuria/ hematochezia/ subconjunctival hemorrhage	1	NL	1	NM	Dexamethasone 40 mg/day/IVIG 2 g/kg for 2 days/ tranexamic acid/plt transfusions Mycophenolate mofetil 1 g/TPO-RA (Romiplostim)	Yes/14	140
Cooper, K. M., 2021[50]	24/F	BNT16B2b2 mRNA	First	10	Dysfunctional uterine bleeding secondary to Etonogestrel implant/mild-controlled asthma/ previous allergic reaction to vaccine	Generalized petechiae/ menorrhagia/ wet petechiae/ cutaneous and mucosal bleeding	NM	NM	1	NM	PSL 0.5–2.0 mg/kg/ IVIG 1 g/kg	Yes/36	NM

TABLE 1 (Continued)

Author, year	Age/gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/L)	Antibody profile	Treatment	Hospital admission/hospital stay (days)	Follow-up Plt ($\times 10^9$/L)
Ogai, A., 2022[51]	73/F	mRNA-1273	First	11	HTN/DLP	Generalized petechiae/oral mucosal bleeding/melena	2	230	<1	NM	PSL/IVIG/TPO-RA (EPAG)	Yes/NM	NM
Hidaka, D., 2022[40]	53/F	BNT16B2b2 mRNA	Second	35	Bronchial asthma/Vogt–Koyanagi–Harada disease/Hashimoto	Evans syndrome/mild anemia/icteric skin and bulbar conjunctiva/pallor of palpebral conjunctiva/wheezing/generalized petechiae/oral mucosal bleeding	3.9	NL	30	Positive lupus coagulant/positive ANA with speckled and nucleolar pattern/positive direct and indirect coombs tests/low level of cold agglutinin	PSL 1 mg/kg	Yes/NM	NM
Gardellini, A., 2021[52]	27/M	BNT16B2b2 mRNA	First	10	NM	Hematoma/epistaxis	1	NM	NM	NM	PSL/IVIG dexamethasone	NM/NM	NM
	63/M	ChAdOx1.	First	14	DM/HTN	Hematoma/epistaxis	2	NM	NM	NM	PSL	Yes/NM	NM
Jasaraj, R. B., 2021[41]	67/F	BNT16B2b2 mRNA	Second	2	HTN/D2M/Hypothyroidism/depression/vitamin B12 deficiency/cluster headaches	Generalized petechiae/oral mucosal bleeding/epistaxis/subconjunctival hemorrhage	3	NL	NM	NM	PSL/IVIG/Plt transfusion/aminocaproic acid/rituximab/TPO-RA (EPAG)	Yes/14 days	200
Kenney, A., 2021[53]	69/F	mRNA-1273	First	7	Hypothyroidism/primary hyperaldosteronism/osteoporosis/migraine headache	Generalized petechiae/minor bruising/gingival mucosal bleeding	4	NM	NM	NM	PSL/IVIG	Yes/3 days	258
Wong, J. S. Y., 2021[54]	86/M	ChAdOx1.	First	2	NM	Gingival mucosal bleeding/wet petechiae/widespread ecchymoses	4	NM	NM	Negative anti PF4	Dexamethasone/IVIG/Plt transfusion/rituximab	Yes/10 days	NL

(Continues)

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
	38/F	ChAdOx1.	First	10	NM	Generalized petechiae and purpura/oral mucosal bleeding	3.2	NM	NM	Negative anti PF4	PSL/IVIG	No/–	430
Bennett, C., 2021[55]	32/F	mRNA-1273	First	11	Negative	Bruising/petechiae	1	268	NM	NM	PSL/IVIG/ dexamethasone	Yes/3 days	303
Akiyama, H., 2021[56]	20/F	BNT16B2b2 mRNA	NM	12	Negative	Generalized subcutaneous hemorrhage/oral mucosal bleeding	16	NL	NM	NM	PSL	Yes/nm	153–343
Koch, M., 2021[57]	41/M	ChAdOx1.	First	10	Negative	Petechiae/mocusal bleeding	<1	189	NM	Negative anti PF4	PSL/IVIG	Yes/4 days	80
Hines, A., 2021[58]	26/F	mRNA-1273	First	7	Irregular menses on OCP	Petechiae/bruising	19	NM	NM	NM	PSL/IVIG/ dexamethasone	Yes/5 days	213
Vaira, L. A., 2022[59]	81/M	BNT16B2b2 mRNA	Second	3	Stage III CKD/hypercholesterolemia	Copious bleeding through the surgical wound/ massive hematoma/ ecchymosis of the right cheek	4	156	NM	Negative anti PF4	Methylprednisolone/ Plt transfusion	Yes/7 days	188
Paulsen, F. O., 2021[60]	72/M	ChAdOx1.	First	11	Autoimmune thyroiditis	Petechiae/ epistaxis/ headache	NM	NM	<5	Negative anti PF4	Glucocorticoid/IVIG	Yes/nm	253
	71/F	ChAdOx1.	First	11	Latent hyperthyroidism/ nodular goiter/breast cancer/stroke	Petechiae/ hyposphagma	NM	NM	<5	Negative anti PF4	Glucocorticoid/IVIG/ TPO-RA	Yes/nm	71
	66/M	ChAdOx1.	First	2	HTN/mild thrombocytopenia	Petechiae	NM	NM	<5	Negative anti PF4	Corticosteroid	Yes/4	89
	64/F	ChAdOx1.	First	15	HTN/COPD/steatosis hepatitis	None	NM	NM	6	Negative anti PF4	Corticosteroid	Yes/6	121
King, E. R., 2021[61]	39/F	BNT16B2b2 mRNA	Second	3	PCOS	Petechiae	1	NL	NM	NM	Plt transfusion/IVIG	Yes/3	243
Shah, S. R. A., 2021[62]	53/M	BNT16B2b2 mRNA	Second	8	Crohn's disease	Episodes of high-grade fever/ diffuse myalgia/ generalized petechiae	2	254	NM	NM	IVIG/Dexamethasone	Yes/4	NM

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/L)
Idogun, P. O., 2021[39]	54/F	BNT16B2b2 mRNA	First	7	Congenital epidermal dysplasia/anxiety/CKD/ HTN/mild cognitive impairment	Rash	NM	NM	NM	NM	No referral to physician	No/NM	NM
	54/F	BNT16B2b2 mRNA	Second	5	Congenital epidermal dysplasia/Anxiety/CKD/ HTN/Mild cognitive impairment	Ecchymosis/ petechiae/oral mucosal bleeding	<1	NM	<1	NM	Dexamethasone IVIG Plt transfusion	Yes/14	114
Fueyo-Rodriguez, O., 2021[63]	41/F	BNT16B2b2 mRNA	First	1	Multiple allergies/ hypothyroidism	Petechiae/gingival mucosal bleeding/fever/ tachycardia/ nausea/malaise/ headache/loose stool	65	NL	38	Elevated anti-dsDNA	Dexamethasone Methyl prednisolone IVIG	Yes/5	629
Julian, J. A., 2021[64]	72/F	mRNA-1273	First	1	Gout/D2M/seasonal contact dermatitis	Petechiae/oral mucosal bleeding/ melena/ headache	12	NM	1	Positive parvovirus IgG	Methylprednisolone/ IVIG/aminocaproic acid/rituximab/Plt transfusion	Yes/NM	NM
Welsh, K. J., 2021[7]	56/M	BNT16B2b2 mRNA	First	2	Negative	Petechiae/ purpura/gingival mucosal bleeding/scleral hemorrhage/ICH	<1	NM	NM	NM	PSL/platelet and RBC transfusion/TPO-RA (EPAG)/ dexamethasone/ cyclosporine/ rituximab/IVIG/ emergent craniotomy/ splenectomy	NM/NM	NM
	22/M	BNT16B2b2 mRNA	First	3	Negative	Petechiae/ Epistaxis/ gingival mucosal bleeding/scleral hemorrhage/ hematuria	2	NM	NM	NM	Dexamethasone/Plt transfusion/IVIG	Yes/NM	NM
	82/F	BNT16B2b2 mRNA	First	NM	NM	Pulmonary embolism/ dyspnea/MI	3	NM	NM	NM	NM	NM/NM	NM
	59/M	BNT16B2b2 mRNA	First	NM	Negative	None	3	NM	NM	NM	NM	NM/NM	NM

(Continues)

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
	39/F	BNT16B2b2 mRNA	First	2	Depression/PCOS	Petechiae/ menorrhagia	1	NM	NM	NM	PSL/IVIG/Plt transfusion/ methylprednisolone	Yes/NM	NM
	80/M	BNT16B2b2 mRNA	First	6	HTN/DM/DLP/aortic stenosis/diverticulosis	GI bleeding	1	NM	NM	NM	RBC and platelet transfusion	NM/NM	NM
	78/F	BNT16B2b2 mRNA	First	6	AF/essential tremor	Petechiae	6	NM	NM	NM	Dexamethasone/ IVIG/Plt transfusion	Yes/NM	NM
	55/F	BNT16B2b2 mRNA	First	4	HTN/DM/arthritis	Petechiae/gingival mucosal bleeding	2	NM	NM	NM	Dexamethasone/ IVIG/Plt transfusion	Yes/NM	NM
	43/F	mRNA-1273	First	8	GERD	Petechiae/bruising	2	NM	NM	NM	PSL/IVIG	Yes/NM	NM
	37/M	mRNA-1273	First	NM	NM	NM	NM	NM	NM	NM	Plt transfusion	NM/NM	NM
	49/F	mRNA-1273	First	1	Migraine/psoriasis	Petechiae/ shortness of breath	66	NM	NM	NM	NM	NM/NM	NM
Candelli, M., 2021[65]	28/M	ChAdOx1.	First	20	Negative	Oral mucosal bleeding/ petechiae/ purpura/fatigue/ fever/headache/ trace hematuria	4	NM	2	Positive lupus anti-coagulant	Dexamethasone	Yes/4	180
Helms, J. M., 2021[66]	74/M	mRNA-1273	First	1	HTN/gout/DLP/Non-ischemic cardiomyopathy	Epistaxis/purpura/ cardiomyopathy/ urinary retention/ constipation/ encephalopathy/ dysarthria/AIDP	10	224	NM	NM	Dexamethasone/PSL /Plt transfusion/IVIG /rituximab/TPO-RA (EPAG) plasma exchange for AIDP	Yes/17	NM
Lee, E. J., 2021[67]	36/F	BNT16B2b2 mRNA	First	5	Negative	Menorrhagia/blood blisters/ petechiae/ epistaxis/ weakness	9	NM	NM	NM	NM	Yes/nm	NM
	25/F	mRNA-1273	First	10	Anxiety	Mucosal bleeding/ bruising	3	NM	NM	NM	Corticosteroids/IVIG	Yes/nm	286
	26/F	mRNA-1273	First	2	Negative	Bruising	2	NM	NM	NM	Corticosteroids/IVIG/ Plt transfusion	Yes/NM	142

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
	73/M	BNT16B2b2 mRNA	First	1	HTN/DLP/DM/ hyperthyroidism	Bruising/petechiae	1	NM	NM	NM	Corticosteroids/IVIG/ Plt transfusion	Yes/2	38
	53/M	BNT16B2b2 mRNA	First	15	Fatty liver	None	10	NM	NM	NM	Plt transfusion/IVIG	Yes/1	47
	72/F	mRNA-1273	First	1	Gout/DM	Bruising/ petechiae/blood blisters	1	NM	NM	NM	Corticosteroids/IVIG/ rituximab/ Aminocaproic acid /vincristine/TPO-RA (Romiplostim)	Yes/NM	71
	50/F	mRNA-1273	First	23	HTN	Petechiae	2	NM	NM	NM	Corticosteroids IVIG Plt transfusion	Yes/NM	20
	36/F	mRNA-1273	First	16	Inherited thrombocytopenia	Headache/ petechiae/ bruising/oral ecchymosis	3	NM	NM	NM	Corticosteroids IVIG	Yes/NM	28
	NM/ NM	mRNA-1273	First	1	NM	Headache/blood blisters	29	NM	NM	NM	Corticosteroids	Yes/NM	45
	41/F	BNT16B2b2 mRNA	First	3	Neuropathy	Chest pain/rash	11	NM	NM	NM	Corticosteroids IVIG	Yes/2	104
	48/F	mRNA-1273	First	13	HTN/Obesity	Heavy vaginal bleeding	1	NL	NM	NM	Corticosteroids IVIG Plt transfusion	Yes/NM	300
	38/F	mRNA-1273	Second	2	NM	Headache/ myalgia/ petechiae	1	NM	NM	Positive antiplatelet antibody	Corticosteroids /IVIG	Yes/NM	60
	53/M	BNT16B2b2 mRNA	First	7	Crohn's disease/HTN/GERD/ prediabetic stage	Petechiae/oral mucosal bleeding	2	NM	NM	NM	Corticosteroids /IVIG	Yes/NM	65
	63/M	mRNA-1273	First	11	DM/HTN/DLP	NM	1	NM	NM	NM	Have not responded to typical ITP therapies	Yes/NM	4
	36/M	mRNA-1273	First	15	Epilepsy	NM	1	NM	NM	NM	NM	Yes/NM	NM
	39/F	BNT16B2b2 mRNA	First	12	NM	ICH	36	NM	NM	NM	Plt transfusion	Yes/NM	NM

(Continues)

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
Tarawneh, O., 2021[68]	22/M	BNT16B2b2 mRNA	First	3	Negative	Petechiae/gingival mucosal bleeding	2	145	NM	Elevated Sjogren's syndrome antibody/ positive for GP IIb/IIIa and Ia/IIa platelet autoantibodies/ low C4	Dexamethasone/IVIG /Plt transfusion	Yes/6	173
Pasin, F., 2022[69]	84/M	BNT16B2b2 mRNA	First	3	Essential tremor/localized bladder cancer/mild CKD/paroxysmal AF	Petechiae/bruising	3	220	NM	Negative anti PF4/positive anti GP IIb/IIIa	Apixaban Discontinued /PSL/IVIG Plt transfusion	Yes/NM	63
Liao, P. W., 2021[70]	79/M	ChAdOx1.	First	7	Ischemic stroke (2 years bedridden)	None	2	NL	2	Negative anti PF4	Hydrocortisone IV 300 mg/day then oral PSL	Yes/12	114
Al-Samkari, H., 2021[71]	71/F	Ad26.COV2. S	First	35	Polymyalgia rheumatica	None	115	429	59	Negative anti PF4/positive for all: anti–GPIIb/ IIIa anti–GPIb/IX anti–GP Ia/IIa	No treatment	NM/–	248
Krajewski, P. K.2021[72]	74/M	BNT16B2b2 mRNA	First	1	HTN	Oral and nasal mucosal bleeding/ purpuraon the extremities/ ecchymosis at injection site	2	NM	NM	NM	Dexamethasone/ Plt transfusion	Yes/NM	NM
Banerjee, S., 2021[73]	63/F	Ad26.COV2. S	First	14	Cervical Cancer/total hysterectomy	Gingival and nasal mucosal bleeding	2	NM	NM	NM	Plt transfusion/ PSL 60 mg/ /Dexamethasone /IVIG	Yes/5	252
Condorelli, A., 2021[74]	52/M	ChAdOx1.	First	3	Negative	Oral mucosal bleeding/diffuse cutaneous purpura	1	NM	NM	Anti-platelet Abs: -	PSL	Yes/7	168
	24/M	BNT16B2b2 mRNA	Second	4	CHD/heart transplant/ Hodgkin lymphoma (complete remission)	None	15	150	NM	NM	PSL 1 mg/kg/day	Yes/30	102

TABLE 1 (Continued)

Author, year	Age/ gender	Vaccine	Dose	REAC. ONSET (days)	PMH/Hematologic PMH	Clinical features	Plt on admission ($\times 10^9$/L)	Plt prior to vaccination ($\times 10^9$/L)	Plt nadir ($\times 10^9$/ L)	Antibody profile	Treatment	Hospital admission/ hospital stay (days)	Follow-up Plt ($\times 10^9$/ L)
	73/M	BNT16B2b2 mRNA	Second	2	HTN/DM/DLP/CABG/IDA	Petechiae/oral mucosal bleeding/diffuse ecchymosis	2	256	NM	Anti-platelet Abs: -	Methylprednisolone/ IVIG 0.4 g/kg/ PSL 1 mg/kg/day	Yes/5	140
Bayas, A., 2021[75]	55/F	ChAdOx1.	First	10	Negative	None	30	NM	NM	Negative anti PF4/elevated platelets antibodies-IgG/ positive PSIFT and MAIPA	Dexamethasone IV 40 mg	Yes/26	NM
Kim, G., 2021[76]	66/F	ChAdOx1.	First	2	Pulmonary TB	Bruising on the extremities/ gingival mucosal bleeding	4	213	NM	Negative anti PF4	Dexamethasone 40 mg/IVIG 1 g/kg for 2 days	Yes/6	100

Abbreviations: AF, atrial fibrillation; AIDP, inflammatory demyelinating polyneuropathy; Anti PF-4, anti-platelet factor 4; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; DLP, dyslipidemia; DM, diabetes mellitus; EPAG, eltrombopag; GERD, gastroesophageal reflux disease; HTN, hypertension; IDA, iron deficiency anemia; IVIG, intravenous immune globulin; MAIPA, monoclonal antibody-specific immobilization of platelet antigen; MGUS, monoclonal gammopathy of undetermined significance; NL, within normal range; NM, not mentioned; OCP, oral contraceptive pills; Plt, platelets; PCOS, poly cystic ovary syndrome; PSL, prednisolone; PSIFT, platelet suspension immunofluorescence test; RA, rheumatoid arthritis; TPO-RA, thrombopoietin receptor agonist.

TABLE 2 Summary of patients' demographics

Variable		Count (% of total)/median (interquartile range)
Age		54 (36–72) years
Gender	Female	46 (59.7%)
	Male	29 (37.7%)
	Not mentioned	2 (2.6%)
Vaccine type	Ad26.COV2.S	2 (2.6%)
	BNT16B2b2 mRNA	35 (45.5%)
	ChAdOx1.	17 (22.1%)
	mRNA-1273	23 (29.9%)
Vaccine dose	First	61 (79.2%)
	Second	14 (18.2%)
	Third/booster dose	1 (1.3%)
	Not mentioned	1 (1.3%)
Positive history of autoimmune disease		8 (10.4%)
ITP disease presentation	Skin manifestation	8 (10.4%)
	Mucosal manifestation	32 (41.6%)
	Internal organs manifestation	17 (22.1%)
Onset of ITP symptoms from vaccination day		7 (3–12) days
Platelets prior to vaccination		220 (172.5–255) $\times 10^9$/L
Platelets on admission		3 (2–10) $\times 10^9$/L
Platelets' nadir		4.5 (1.25–26.75) $\times 10^9$/L
ITP related antibodies	Negative anti-platelet factor 4	16 (20.8%)
	Positive anti-platelet factor 4	0 (0%)
	Positive anti-glycoprotein IIb/IIIa	16 (20.8%)
	Negative anti-glycoprotein IIb/IIIa	16 (20.8%)
	Positive non-specific antibodies against platelets	4 (5.1%)
Management settings of patients	Outpatients	2 (2.5%)
	Inpatients	67 (87%)
	Not Mentioned	8 (10.5%)
Hospital stay of admitted patients		6 (4–13) days
Treatment	Glucocorticoids in total	62 (80.5%)
	Prednisolone or methylprednisolone	34 (44.2%)
	Dexamethasone	19 (24.7%)
	Intravenous immunoglobulin	47 (61%)
	Thrombopoietin receptor agonists in total	12 (15.6%)
	Eltrombopag	8 (10.4%)
	Romiplostim	3 (3.9%)
	Platelet transfusion	30 (39.0%)
Follow-up platelets		140 (71–248) $\times 10^9$/L

Patients underwent various tests based on managing physicians' discretion. In 36 patients (46.7%), antiplatelet antibodies were evaluated. Anti-platelet factor-4 antibody was negative in all 16 tested patients (20.7%). Anti-Glycoprotein IIb/IIIa was assessed in 19 patients (24.6%), it was negative in 16 patients (20.8%) and positive in three (3.9%). In four patients (5.1%), non-specific antibodies against platelets were detected.

Data for the peripheral blood smear (PBS) was available in 21 patients (27.2%); 20 patients had no morphologic changes in leukocytes and red blood cells. In one patient's PBS, rare schistocytes were seen, but other evidence was against the diagnosis of thrombotic thrombocytopenic purpura (TTP). Bone marrow aspiration was performed in 15 patients (19.5%), which showed megakaryocyte proliferation in nine patients (11.7%), and

histopathologic findings in other reports were otherwise negligible.

3.5 | Treatment and clinical outcomes

Management settings of 69 patients were procurable; of them, only two (2.5%) were managed ambulatory. For 67 patients (87%) who were hospitalized, the median length of hospital stay was 6 days (IQR 4–13 days).

Glucocorticoids, alone or in combination, were used in 62 (80.5%) patients. The most frequent corticosteroid choices were prednisolone or methylprednisolone in 34 (44.2%) and dexamethasone in 19 (24.7%) patients. The next frequent medication was intravenous immunoglobulin (IVIg), used in 47 (61%) patients. Thrombopoietin receptor agonists (TPO-RA) were administered in 12 (15.6%) cases, with eltrombopag accounting for 8 (10.4%) and romiplostim accounting for 3 (3.9%) of circumstances. Six (7.8%) patients received rituximab as a rescue treatment, as they had not responded to a combination of treatments at least including corticosteroids and IVIg. Except for one, who had already sustained ICH and was pronounced to death, others improved.

Medications were implemented apart or in various combinations. Thirteen (16.9%) patients received corticosteroids alone, 19 (24.7%) in combination with IVIg, 4 (5.2%) in combination with platelet transfusion, and 14 (18.2%) in combination with both IVIg and platelet transfusion. One patient (1.3%) was given corticosteroids jointly with TPO-RA and platelet transfusion. Five patients (6.5%) received corticosteroids in combination with IVIg, TPO-RA, and platelet transfusion. One patient (1.3%) was managed by IVIg alone, and four patients (5.2%) underwent platelet transfusion as the only management modality. In two patients (2.6%), a combination of IVIg and platelet transfusion was the basis of treatment.

In summary, corticosteroids and IVIg, alone or in combination, were the most common treatment modalities. The various treatment strategies were successful in most circumstances. Nevertheless, platelet counts dropped in two patients after discharge, necessitating readmission.

A follow-up platelet count was available in 39 patients, of whom two achieved normal platelet counts. The included studies adopted different targets of platelet count to define a treatment response. Platelet counts of 30×10^9/L and 50×10^9/L were the most adopted thresholds, and according to those definitions, 38 and 35 patients responded to treatment, respectively.[13,23]

4 | DISCUSSION

There is another systematic review on the COVID-19 vaccine and its association with ITP, which covers both de novo and relapsed ITP. However, we assume induction of de novo ITP following COVID-19 vaccination differs in pathophysiology from relapsed ITP post-COVID-19 vaccination, which primarily occurs due to another cause than COVID-19 vaccination. Accordingly, this is the first study that systematically reviews the medical literature for a specific focus on de novo ITP following COVID-19 immunization.[24] We observed that COVID-19 vaccine-associated ITP was more frequent in the middle-aged population and female gender. Most reported cases developed ITP after the first dose of vaccination. Furthermore, the mRNA-based and adenovirus vector-based COVID-19 vaccines were the most prevalent culprits in order of frequency.

Hemorrhagic mucocutaneous manifestations were the most common presentation, and thrombocytopenia was moderate to severe at the outset in affected patients. The vast majority of patients were managed in an in-patient setting and received various therapeutic regimens that included either glucocorticoids, IVIg, or both. Therapeutic goals were accomplished in most patients who had available follow-up data.

4.1 | COVID-19 vaccine-associated ITP pathophysiology

Scant data elaborates on immunopathogenic mechanisms of vaccine-induced thrombocytopenia.

Before introducing the COVID-19 vaccine, ITP had been known as a rare consequence of various vaccinations. There are reports of vaccine-associated ITP for live measles–mumps–rubella (MMR), varicella, inactivated hepatitis B, diphtheria-tetanus–acellular pertussis (DTaP), pneumococcus, hemophilus influenza B, varicella zoster virus (VZV), human papillomavirus (HPV) and polio vaccines. Amongst them, MMR is the most well-known vaccine that can induce ITP, and its cause-effect relationship has been discussed elsewhere.[25,26]

The etiology of vaccine-associated ITP is perceived immune-related as antibodies can be detected on platelets in roughly 80% of cases following administration of non-COVID-19 vaccines.[7,27] The most accepted hypothesis for platelet autoantibody production after vaccine inoculation is molecular mimicry and cross-reactions between the vaccine antigens and the human molecules. That results in the activation of autoreactive B or T lymphocytes, emergence of antiplatelet antibodies, epitope spreading, polyclonal immune reaction, and the ultimate expression of ITP.[27,28] Our results demonstrated that very few patients tested positive for ITP autoantibodies; we presume this finding ascribes to the very low sensitivity of platelet autoantibody test in ITP patients, and only a few numbers of patients were tested for specific ITP autoantibodies which were from various case reports and probably diverse laboratories.[29]

In addition, COVID-19 infection-associated ITP is well-known.[30,31] Thus, it would not be surprising that ITP risk after COVID-19 immunization increases through a similar mechanism as microbial infections induce antiplatelet autoantibodies with the same antigen utilized in COVID-19 vaccine production (e.g., Spike protein).[26]

The presence of adjuvants in the COVID-19 vaccine could be another trigger of immune cross-reactivity, termed autoimmune/inflammatory syndrome induced by adjuvants; however, there is no

investigation to prove this hypothesis in COVID-19 vaccines and ITP has been linked to different COVID-19 vaccines.[15,16,28]

4.2 | COVID-19 vaccine-associated ITP versus common forms of ITP (unrelated to the COVID-19 vaccines)

4.2.1 | Epidemiologic characteristics

ITP is defined as "Newly diagnosed" within 3 months from diagnosis[32]; given this definition, all of the patients retrieved in this study fell in this duration, thereby we could consider COVID-19 vaccine-associated ITP a sort of newly diagnosed ITP. Interestingly, the time lag between vaccination and ITP presentation was relatively short, and most cases presented within the first week of vaccination. In comparison, this lag time is significantly longer for MMR vaccine-related ITP, ranging from 11 to 38 days with a median of 25 days.[33]

We postulate two hypotheses to justify this observation: Firstly, implicated COVID-19 vaccines that followed ITP in our study were either mRNA or adenoviral based vector vaccines. Both vaccines employ the recipient's cells to reproduce selected epitopes of the COVID-19 spike protein. Thus the mechanisms of antigen production in these novel vaccines are incredibly robust.[34] Data supports that COVID-19 vaccines with novel technology are very potent in inducing favorable neutralizing antibodies against COVID-19. We hypothesize that this may also contribute to an early surge of auto-reactive antibodies against platelets, causing a shorter lag time for ITP presentation. On the other hand, MMR, an attenuated live virus vaccine, induces a more smooth immune reaction and a later onset ITP. Furthermore, our results showed that among COVID-19 vaccines, ITP lag time was even shorter in mRNA than in adenovirus-based vaccines. This observation is again in concert with the current understanding of the potency order of available vaccine choices.[34]

Secondly, the typical recipient of the COVID-19 vaccine is much older than the very young children who receive the MMR vaccine. We postulate that previous exposure to coronaviruses in adults may have already modulated their immune response to vaccination against COVID-19.

The level of thrombocytopenia in COVID-19 vaccine-associated ITP is similar to non-vaccine-associated ITP, and a platelet count below 20×10^9/L was present in 60 (77%) cases. Indeed, in our study, the median of the lowest (nadir) platelet number was 3×10^9/L. In contrast, MMR vaccine-related ITP is associated with milder thrombocytopenia, and a platelet count of more than 20×10^9/L is usual.[27]

The median age of our patients was 54. This figure may not necessarily suggest a particular age susceptibility but may correlate with age-related vaccination policies in the population. Notably, reports show that ITP-associated with COVID-19 infection has a comparable age distribution with the post-vaccinal type, and 70% of patients had an age above 50.[30,31]

Finally, one of the most dreaded complications of ITP is ICH. Hato et al. observed that in the setting of primary ITP, age above 60 and platelet count below 10×10^9/L are two important risk factors for ICH. Noteworthy, the same risk factors were present in our cases who complicated with ICH.[35]

4.2.2 | Clinical presentation and disease course

Except for 10 patients who were asymptomatic at the time of diagnosis, all other cases in our review presented with cutaneous, mucosal, and internal bleeding. These manifestations are typical for thrombocytopenic purpura and present in primary ITP, ITP secondary to COVID-19 infection, MMR vaccine-related ITP, drug-induced ITP, and ITP after wild virus infections or helicobacter pylori.

Most COVID-19 vaccine-associated ITP cases had a benign course, and severe or life-threatening bleeding was rare. Only four patients sustained ICH, all had received mRNA-based vaccines and one led to a fatal outcome despite aggressive immunosuppressive therapy and craniotomy. Like COVID-19 infection-induced ITP, EVANS syndrome was also observed in one case.[27,30,36,37]

Regarding the constitutional symptoms, we noticed a higher prevalence of fever, headache and a lower occurrence of fatigue, compared to primary ITP.[36] Lastly, while no mortality has ever been reported for MMR vaccine-associated ITP, we had a single case of fatality in our data. Of notice, there are also rare reports of fatal outcomes in patients diagnosed with ITP secondary to COVID-19 infection.[15]

4.2.3 | Therapeutic strategy and response

Our series showed that the general treatment pattern in COVID-19 vaccine-associated ITP was analogous to primary ITP. Most patients were hospitalized and received systemic corticosteroids or IVIg, alone or in combination. A minority underwent other treatments, including a TPO-RA drug.

From the advent of TPO-RA drugs, a paradigm shift is proceeding in the management of ITP, and the center of focus is moving from immunosuppression to improving health-related quality of life in the patients. Accordingly, these drugs are making their way into guidelines on ITP management, especially for ITP duration of more than 3 months or refractory cases. Moreover, there has been a recent trend of employing that class of drugs in the acute management of ITP patients, though still, it is an unapproved indication.[13,15,23] Among our series, 12 (15.6%) of COVID-19 vaccine-associated ITP patients received either romiplostim or eltrombopag in combination with other measures. Platelet transfusion, plasmapheresis, rituximab, and tranexamic acid were reserved for rescue treatment or add-on therapy for the most severe cases.

Except for one patient who died of complications of ICH, no other mortality case has been found, and in most cases, the convalescent platelet count was available, which was in the acceptable range. These findings are in line with the Perricone et al. study that claimed most cases of vaccine-associated ITP are mild and treatment-responsive.[38]

Since we had excluded all cases of COVID-19 vaccine-associated ITP if had any prior clinical episode of ITP, we cannot comment on the risk of ITP relapse in case of repeat vaccination. Nevertheless, we noticed three cases in our series who developed purpuric rash after the first dose of the BNT16B2b2 mRNA vaccine, progressed to full-blown thrombocytopenic syndrome following the second vaccine dose. Therefore, despite the appearance of purpura earlier, ITP was diagnosed after the second dose. That limited observation is not surprising from the pathophysiological perspective and may suggest against revaccination by the same brand if thrombocytopenia had already developed after a prior vaccine dose.[39–41]

4.3 | Study limitations

There were some important limitations to this study. First, we only retrieved articles published in the English language in full text. We may have overlooked the inherent differences in population susceptibilities and unequal availability of individual types of COVID-19 vaccines to nations based on local policies.

Second, we could only reach out to ITP cases secondary to four COVID-19 vaccine brands. The lack of data regarding the other brands may be related to under-reporting, the scale of vaccine administration, or their lower chance of inducing ITP.

Third, this was a systematic review based on published cases. Since many patients with ITP can be asymptomatic, the true incidence of significant thrombocytopenia after COVID-19 vaccination is unknown. In our series, only 10 patients (13%) were asymptomatic at the time of diagnosis, a figure that we believe is an underestimation.

Fourth, because the COVID-19 vaccination programs set a priority for the elderly population and patients with underlying comorbidities, it is probable that our sample is not representative of the whole population. This fact can affect the demographic aspects of our study. For instance, the results may underestimate the susceptibility of the young and shift the age of the population at risk to a higher range.

Finally, we made every effort to exclude articles with dubious implications of COVID-19 vaccine-associated ITP. However, because of inadequate data in some circumstances, we were not able to verify the diagnosis independently in a few cases and therefore relied on the authors' discrimination.

5 | CONCLUSION

In essence, our review provided a comprehensive, descriptive compendium of the reported cases of COVID-19 vaccine-associated ITP and highlighted the clinical features and real-world therapeutic interventions in this potentially life-threatening complication of SARS-CoV-2 immunization. We found that clinical manifestations of COVID-19 vaccine-associated ITP were very similar to primary ITP. The disease usually responded to high-dose corticosteroids, IVIg, or both, and fatal complications were rare.

Interestingly, we showed that the lag time for the ITP presentation after vaccination against COVID-19 is shorter than the gap observed in ITP manifestation after routine vaccinations in childhood. The more the COVID-19 vaccine is robust to induce antigenic challenge, the shorter the lag time would be. We also revealed that most cases of post-vaccinal ITP were related to potent COVID-19 vaccine brands, including BNT16B2b2 mRNA and mRNA-1273 vaccine. We postulate that this observation might be related to the broad scale of administration of those vaccines in developed countries where vaccine surveillance, case finding, and case reports are typically more reliable. Still, we could not exclude the notion that potent vaccines are more prone to induce cross-immunity.

It merits consideration that further large-scale prospective studies are required to establish the features and risk factors of COVID-19 vaccine-associated ITP. Furthermore, we need basic research to explore the causality role of the COVID-19 vaccines in developing ITP via investigating epitope similarities between platelets and vaccine-driven antigens. The possible disparity between the brands of COVID-19 vaccines to induce ITP needs further investigation and may help manufacturing vaccines with less chance of induction of autoimmunity.

AUTHOR CONTRIBUTIONS

Ali Bidari, Sara Asgarian, and Milad Gholizadeh Mesgarha were responsible for conceptualization. Arash Pour Mohammad performed systematic search and analysis, tabulated data and prepared figure. Sara Asgarian, Delaram Naderi, Milad Gholizadeh Mesgarha, Shiva Rahimipour Anaraki, Mahya Naderkhani carried out study screening and data extraction. All authors participated in composing the inital draft, finalizing the manuscript, applying revisions, and approved of the final version.

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The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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