EXPERT REVIEW OF HEMATOLOGY
https://doi.org/10.1080/17474086.2022.2029699

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META-ANALYSIS

COVID-19 associated with immune thrombocytopenia: a systematic review and meta-analysis

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ABSTRACT

Background: Immune thrombocytopenia, also known as immune thrombocytopenic purpura (ITP), has emerged as a significant COVID-19-associated complication. This study analyzes the published literature of case reports and case series regarding COVID-19 infection associated with ITP.

Methodology: In this systematic review and meta-analysis, a systematic search was conducted through PubMed, Web of Science, and Medline through Clarivate and EBSCO to include the eligible studies. The authors utilized Review Manager 5.4 to conduct quantitative data synthesis for the condition of interest analysis.

Results: A total of 13 eligible case reports and case series with 42 patients were included in this study; 54.8% of them were male. The pooled mean age of all participants was (59.5 ± 19) years with a median age of 63 years. The estimated mean time from diagnosis with COVID-19 to ITP development was 18.1 ± 21 days and the mean time to recovery from ITP was 5.8 ± 4.8 days. The pooled random effect of mean platelet count in the included six studies was 14.52, CI [8.79, 20.25].

Conclusion: Our analysis shows that ITP secondary to COVID-19 infection is slightly more prevalent among males (54.8%). Elderly patients were more vulnerable to the disease. Most cases developed ITP within 2–3 weeks after COVID-19 infection and recovered in less than one week from ITP.

ARTICLE HISTORY
Received 9 October 2021
Accepted 12 January 2022

KEYWORDS
COVID-19; immune thrombocytopenic purpura; ITP; platelet count

1. Introduction

By the end of 2019, a series of lower respiratory tract infection cases of unknown cause emerged in Wuhan, China [1]. A few weeks later, deep sequencing of lower respiratory tract samples identified a novel virus as the culprit, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease was named 'coronavirus infectious disease-19' (COVID-19). The infection relentlessly spread throughout the world and was designated a pandemic by the World Health Organization (WHO) in March 2020 [2].

Coronaviruses, initially characterized in 1966, are enclosed single-stranded large RNA viruses that infect humans and a variety of animals [3]. As of July 2021, the COVID-19 pandemic has affected 223 countries, with more than 185 million confirmed cases and more than 4 million confirmed deaths worldwide [4].

Acute respiratory distress syndrome (ARDS), cardiac problems, and thromboembolic complications are the major causes of COVID-19-related deaths. Hyperinflammatory states resembling hemophagocytic lymphohistiocytosis (HLH) and coagulopathy resembling the hypercoagulable stage of disseminated intravascular coagulation (DIC) have been reported with this infection [5].

Thrombocytopenia was seen during the severe acute respiratory syndrome (SARS) caused by another coronavirus in 2002–2003, and its presence was linked to the severity of the infection [6,7]. Thrombocytopenia is a well-known complication of many viral infections, with many underlying mechanisms causing the drop in platelet count. Immune-mediated thrombocytopenia is one of these mechanisms (ITP) [8]. With the current SARS-CoV-2 pandemic, thrombocytopenia was reported in up to 36% of patients 9.[9–11]

The proposed mechanisms of hematopoietic dysfunction with the SARS-CoV-2 infection are many, including but not limited to changes in megakaryocytic differentiation and maturation resulting from infection of hematopoietic stem cells and megakaryocytes, changes in the bone marrow microenvironment caused by inflammation, a decline in TPO production by liver cells and by the lung damage caused by SARS-CoV-2 infection that may alter megakaryocyte fragmentation, and platelet production in pulmonary vessels [12].

ITP is characterized by a platelet count of $< 100 \times 10^9$/L and often manifests as petechial or purpuric rashes [13]. ITP has been reported following many viral infections, including but not limited to hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), varicella-zoster virus (VZV), and zika viruses [14]. Thrombocytopenia can

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result from other factors including some commonly associated with COVID-19 infections as the high incidence of hypercoagulability, thrombosis, and eventually DIC [12].

In this systematic review and meta-analysis, we aimed to collect and analyze the published case reports and case series of COVID-19 infections associated with ITP.

2. Methodology

2.1. Search strategy

An electronic systematic literature search of three major databases, PubMed, Web of Science and Medline through Clarivate, and EBSCO, was conducted to include relevant and eligible study articles. The search was limited to the English language. The relevant literature was searched using the following keywords, which corresponded to Mesh terms in PubMed or subject terms in EBSCO; 'COVID-19,' 'severe acute respiratory syndrome coronavirus-2,' 'SARS-CoV-2,' 'immune thrombocytopenia,' 'immune thrombocytopenic purpura,' 'immune cytopenia,' 'petechiae,' 'bleeding,' and 'hemorrhage.' Boolean operators such as 'OR' and 'AND' were used in combination with the appropriate keywords. The search results included full texts, openly available publications, human trials, and the English language.

2.2. Selection criteria

Inclusion criteria:

- Case reports and case series that investigate the association between COVID-19 infection and ITP.
- The condition will be considered ITP as reported in the literature, after excluding other possible causes or types of thrombocytopenia.
- No age or sex restrictions were set.

Exclusion criteria:

- Studies not conducted in the English language.
- Studies reporting other types or causes of thrombocytopenia than ITP.

2.3. Data extraction

Rayyan (QCRI) [15] was used to identify the duplicate records of the search strategy results. The reviewers screened titles and abstracts for convenience by investigating the pooled search results utilizing a set of inclusion/exclusion criteria. The researchers evaluated the full text of the study articles that met the inclusion criteria. They overcame any disagreements or conflicts through debate and discussion. To comprise the eligible articles, a data extraction sheet was created. The reviewers extracted data of the study titles, authors, study year, study design, study population, participants' age, and gender, the case presentation, medical history, diagnosis, and the laboratory investigations of the selected cases.

2.4. Strategy for data synthesis

To produce a qualitative overview of the included research characteristics and result data, summary tables containing the collected details from the eligible studies were presented. After the data processing was evaluated, the extent of the proposed pooled analyses was investigated. Following the conclusion of data extraction in this meta-analysis, decisions were made on how to improve the use of case and control data and the numerical data of the included case reports. A qualitative synthesis of the determined data was performed regardless of the feasibility of the pooled meta-analyses. Studies that fulfilled the full-text inclusion criteria but did not present numerical data on ITP among COVID-19 patients were excluded.

To conduct quantitative data synthesis for the condition of interest analysis, the authors utilized Review Manager 5.4 [16]. A random-effects meta-analysis was used to investigate the association between COVID-19 infection and ITP. An I-square statistic was used to measure heterogeneity as part of the pooled meta-analysis. To evaluate publication bias, the funnel plot and funnel plot symmetry measures were obtained.

3. Results

3.1. Search results

The initial systematic search came out with a total of 466 studies. Rayyan (QCRI) identified and removed 84 duplicates from these studies. After the title and abstract screening, 224 studies were removed because of irrelevant findings and inappropriate research type or design, followed by the full-text screening and removal of an additional 145 studies due to irrelevant analysis or wrong outcome. This analysis eventually resulted in a total of 13 eligible case reports and case series. The selection process and identification are shown in Figure 1.

3.2. Characteristics of the included literature

The included case reports and series comprised a total of 42 participants; 23 (54.8%) of them were male. The pooled mean age of all participants was (59.5 ± 19) years with a median age of 63 years.

This study included a total of 7 case reports, two of them were reported from the United States [17,18], one from Canada [19], one from Italy [20], one from Turkey [21], and one from Greece [22]. The lowest platelet count ranged from 1×10^9/L in **Clerici *et al.*** [20] to 23×10^9/L in **Lévesque *et al.*** [19]. These characteristics are presented in Table 1.

Lévesque *et al.* reported a 53-year-old male patient who presented with a three-day history of dyspnea, dry cough, fever, and a preexisting medical history of hypertension, dyslipidemia, type 2 diabetes (T2DM), and a body mass index (BMI) of 24. The patient recovered after being diagnosed with ITP that manifested late after the COVID-related classic clinical

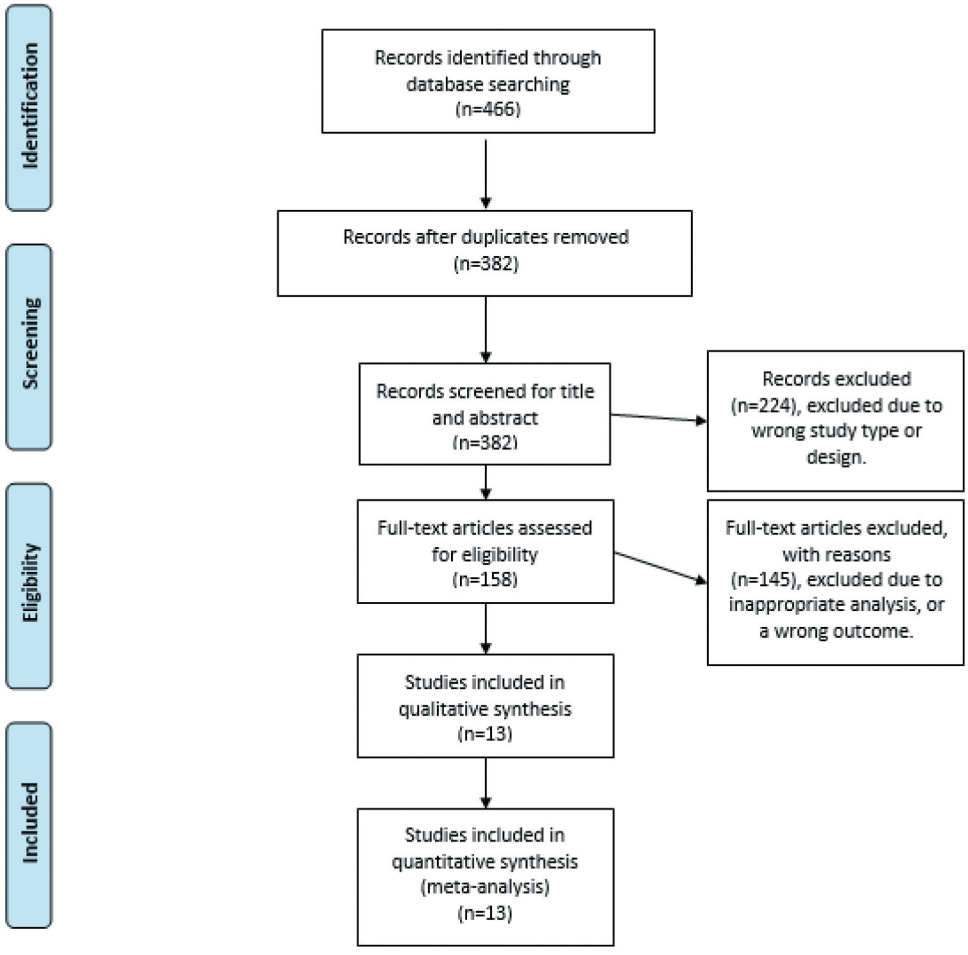

Figure 1. PRISMA flowchart presenting the selection process of the included literature.

symptoms started. He had no cutaneous manifestations of ITP nor severe hemorrhage [19].

Bennett *et al.* reported a case of a 73-year-old female patient who presented with fever, shortness of breath, and diarrhea and a preexisting medical history of hypertension and hyperlipidemia. The patient suffered from a sharp decrease in the platelet count without response on transfusion of platelet units, so ITP was suspected. The patient recovered after being diagnosed with COVID-19 infection-associated ITP [17].

Clerici *et al.* reported a 64-year-old male patient presenting with unexplained fever following contact with a known SARS-CoV-2 positive subject, and traumatic epistaxis and mucocutaneous petechiae were reported. The patient recovered after being diagnosed with COVID-19 infection and ITP [20].

Martincic *et al.* reported a 48-year-old male patient who presented with dyspnea, cough, fever, headache, and muscle ache and a preexisting medical history of T2DM, obesity, and obstructive sleep apnea. Later, on the 9th day after admission, the patient had non-traumatic macroscopic hematuria, minor bleeding in the oral mucosa, and blood clots in the gastric residual volume, and complete blood count indicated the incidence of thrombocytopenia. The patient recovered after being diagnosed with COVID-19 associated with ITP [23].

Hindilerden *et al.* reported a case of an 86-year-old male patient who presented with a one-week history of excessive bruising, fatigue, fever, and dry cough and a preexisting medical history of hypertension and T2DM. After being diagnosed with ITP associated with COVID-19 with purpuric eruptions all over the skin and hemorrhagic bullae in the oral cavity, the patient recovered well [21].

Metallidis *et al.* reported a 33-year-old female patient who presented with a two-day history of mild muscle ache, pharyngula, low-grade fever, and a preexisting medical history of diabetes mellitus type 1 (T1DM). Platelet count markedly dropped on the 6th day of admission, so ITP was suspected. The patient recovered after being diagnosed with COVID-19 induced immune thrombocytopenia [22].

Ayesh *et al.* reported a case of a 76-year-old female patient who presented with a 5-day history of skin rash, fatigue, mouth pain, visual disturbances, and arthralgia and a preexisting medical history of insulin-dependent T2DM essential hypertension, cerebrovascular accident, and hyperlipidemia. The patient recovered after being diagnosed with secondary ITP associated with COVID-19 [18].

A total of 6 case series with 35 patients were included in this study. One study was conducted in Turkey [24], one in Greece [25], one in the Netherlands [26], one in the USA [27], and one in France [28]. The participants' ages ranged from a 3-year-old female patient who presented with a low-grade fever for one day, epistaxis, and melena and was diagnosed with ITP

Table 1. The characteristics of the included case reports.

Study	Study design	Age	Sex	Presentation/ signs	Preexisting medical history	Diagnosis	Country	The lowest platelet count recorded	Platelet count at discharge	Outcomes
Lévesque et al., 2020 [19]	Case report	53	Male	Three-day history of dyspnea, dry cough, and fever	Hypertension, dyslipidemia, type 2 diabetes (T2DM), and a BMI of 24.	ITP manifested late after the COVID-related classic clinical symptoms started, was not accompanied by any cutaneous manifestations of ITP, and had no severe hemorrhages.	Canada	23×10^9/L	178×10^9/L	Recovery
Bennett et al., 2020 [17]	Case report	73	Female	Fever, shortness of breath, and diarrhea	Hypertension and hyperlipidemia	COVID-19 infection caused by ITP	USA	8 K/μL	146 K/μL	Recovery
Clerici et al., 2020 [20]	Case report	64	Male	Unexplained fever following contact with a known SARS-CoV-2-positive subject, atraumatic epistaxis, and appearance of mucocutaneous petechiae	Diabetes mellitus and arterial hypertension	COVID-19 infection and persistent ITP	Italy	1×10^9/L	118×10^9/L	Recovery
Martincic et al., 2020 [23]	Case report	48	Male	Dyspnea, cough, fever with the highest temperature of 38.5°C, headache, and muscle ache	T2DM, obesity, and obstructive sleep apnea	COVID-19 associated with ITP and supported by an isolated thrombocytopenia	Slovenia	4,000/ mm^3	9,000/mm^3	Recovery
Hindilerden et al., 2020 [21]	Case report	86	Male	A 1-week history of excessive bruising, fatigue, fever, and dry cough	Hypertension and T2DM	ITP associated with COVID-19 at first presentation, along with purpuric eruptions all over the skin and hemorrhagic bullae in the oral cavity	Turkey	10,000/ mm^3	150,000/ mm^3	Recovery
Metallidis et al., 2020 [22]	Case report	33	Female	2-day history of mild muscle ache, pharyngula, and low-grade fever	Diabetes mellitus type 1 (T1DM) under insulin pump	COVID-19-induced immune thrombocytopenia	Greece	18×10^9/ μL	~445×10^9/ μL	Recovery
Ayesh et al., 2021 [18]	Case report	76	Female	Five-day history of skin rash, fatigue, mouth pain, visual disturbances, and arthralgia	Insulin-dependent T2DM, essential hypertension, cerebrovascular accident, and hyperlipidemia	Secondary ITP associated with COVID-19	USA	3×10^9/L,	> 80×10^9/ L	Recovery

Table 2. The characteristics of the included case series.

Author	Study design	Patients number	Age	Sex	Presentation/ signs	Preexisting medical history	Diagnosis	Country
Aydın et al., 2021 [24]	Case series	2	42	Female	Nasal bleeding and extensive petechiae	Epilepsy	COVID-19-associated ITP	Turkey
			33	Female	Cough and fever	Chronic hepatitis B virus infection		
Behlivani et al., 2021 [25]	Case series	2	15	Male	Epistaxis, petechiae, and bruises	*	ITP is possibly related to SARS- CoV-2	Greece
			3	Female	Low-grade fever for 24 h, epistaxis, and melena	*		
Bomhof et al., 2020 [26]	Case series	3	59	Male	Oral mucosal petechiae, spontaneous skin hematomas, cough, and fever	Stage IV neuroendocrine tumor (NET) of the small bowel	COVID-19-associated ITP	Netherlands
			66	Female	Petechiae, spontaneous epistaxis, and increased blood loss from hemorrhoids	Hypertension		
			67	Male	Fever, coughing, and dyspnea	Hypertension and DM		
Kewan et al., 2021 [27]	Case series	11	89	Male	Fever, cough, SOB, and GI symptoms	Hypertension, atrial fibrillation, DM, and CKD	ITP secondary to COVID-19	USA
			58	Male	SOB	Hypertension, atrial fibrillation, DM, and CKD		
			53	Male	Cough and SOB	Prostate cancer		
			26	Female	*	Pregnancy (third trimester) and hypertension		
			65	Male	Cough and GI symptom	Hypertension, lung cancer, and CKD		
			95	Male	Fever, cough, and SOB	Hypertension and atrial fibrillation		
			70	Female	No symptoms	SLE and CKD		
			68	Male	Fever, cough, and SOB	No medical disease		
			35	Female	GI symptoms	Hypertension, lung cancer, and CKD		
			60	Female	Cough and SOB	Hypertension, diabetes, and vitiligo		
			63	Male	No symptoms	Hypertension		
Mahévas et al., 2020 [28]	Case series	14	58	Female	Fever and cough	*	COVID-19 associated with ITP	France
			66	Male	Fever, cough, anosmia, dyspnea, hypoxemia, and moderate pneumonia on CT scan	*		
			62	Female	Fever, cough, and moderate pneumonia on CT scan	*		
			62	Male	Dyspnea and minor pneumonia on CT scan	*		
			74	Male	Fever, and cough pneumonia on CT scan	*		
			63	Male	Fever, cough, dyspnea, hypoxemia, and moderate pneumonia on CT scan	*		
			65	Male	Fever and minor pneumonia on CT scan	*		
			66	Female	Fever, cough, dyspnea, hypoxemia, and moderate pneumonia on CT scan	*		
			79	Female	Fever, cough, dyspnea, hypoxemia, and moderate pneumonia on CT scan	*		
			59	Female	Fever, cough, dyspnea, and moderate pneumonia on CT scan	*		
			61	Female	Fever, cough, anosmia, dysgeusia, and moderate pneumonia on CT scan	*		
			69	Female	Fever, cough, dyspnea, hypoxemia, and moderate pneumonia on CT scan	*		
			53	Male	Fever, cough, dyspnea, and moderate pneumonia on CT scan	*		
			72	Male	Fever, cough, dyspnea, hypoxemia, diarrhea, and moderate pneumonia on CT scan	*		
Pascolini et al., 2020 [29]	Case series	3	69	Female	Respiratory distress without hemorrhagic complications	Cerebral lymphoma	COVID-19 associated with ITP	Italy
			88	Male	Respiratory failure resulting from COVID-associated interstitial pneumonia, without hemorrhagic complications	Coronary artery disease and recent hip replacement		
			31	Male	High fever, dyspnea, and respiratory distress due to interstitial pneumonia without hemorrhagic complications	*		

related to SARS- CoV-2 [25] to an 89-year-old male patient who presented with fever, cough, shortness of breath (SOB), and gastrointestinal (GI) symptoms and a preexisting medical history of hypertension, atrial fibrillation, DM, and chronic kidney disease (CKD) [27]. All of the 35 included patients were diagnosed with COVID-19 associated ITP. Their characteristics are presented in Table 2.

4. Clinical characteristics of the included studies

Table 3 presents the clinical characteristics of the included case reports and case series. The majority of cases were treated with intravenous immunoglobulin (IVIG) and intravenous dexamethasone, with good response and complete resolution of ITP. Most patients who received platelet transfusion alone did not improve. Two patients received romiplostim in combination with IVIG and showed complete response [19,20]. Methylprednisolone only [25], or in combination with IVIG [19,26,27], Romiplostim [20], and eltrombopag [27] lead to complete response. Response to the administered treatment and then relapse occurred in the following cases; a patient who received dexamethasone 40 mg (D1–D4), IVIG (D1–D2), eltrombopag (D5–D28) [26], prednisone, dexamethasone, and prednisone with IVIG [27]. The estimated mean time from diagnosis with COVID-19 to ITP development was (18.1 ± 21) days and ranged from diagnosing ITP at the same time of diagnosis of COVID-19 infection to 125 days. The estimated mean time to recovery from ITP was (5.8 ± 4.8) days and ranged from 2 to 22 days.

5. Platelet count among patients with COVID-19associated ITP and interstudy heterogeneity

The forest plot through random effect analysis shows that the mean platelet count in the included six studies was 14.52, CI [8.79, 20.25] with significant ($P < 0.000$) overall effect analysis. There was significant heterogeneity among the studies ($I^2 = 97\%$, $P < 0.000$) (Figure 2). Visual inspection of the funnel plot reveals publication bias due to some asymmetry (Figure 3).

6. Discussion

Immune thrombocytopenia is typically diagnosed retrospectively after eliminating other potential causes of thrombocytopenia and after assessing the response to therapy [30]. A spectrum of severity characterizes the COVID-19 infection, ranging from asymptomatic to critical [31]. The diagnosis of COVID-19-associated ITP is challenging because of many confounding variables in these patients. This systematic review and meta-analysis summarized the published relevant literature of case reports and case series about COVID-19 infection associated with ITP.

This study found that the incidence of ITP secondary to COVID-19 infection is slightly more common among males (54.8%) than females; moreover, it was more prevalent among the elderly with mean age of (59.5 ± 19) years and a median age of 63 years. A similar systematic review conducted by **Bhattacharjee *et al.*** has also reported that most ITP cases (71%) were found to be elderly with a median age > 60 years [15].

Two cases were diagnosed with ITP at the same time as COVID-19 diagnosis and many other cases within the first week; this may be attributable to patients' failure to report the development of the initial COVID-19 symptom. Regarding management of ITP in COVID-19 patients, observation alone is advised in such conditions; nevertheless, treatment with glucocorticoids might be considered for people with comorbidities, age > 60 years, or on anticoagulation according to contemporary therapy guidelines. Most cases in this study were treated with IVIG in different doses (400 mg/kg/day for 5 days or 1 g/kg for 1–3 days) and dexamethasone. This could be due to concerns about the use of glucocorticoids in COVID-19 patients with the severe acute respiratory disease [5]. Nonetheless, IVIG is recommended for individuals at risk of serious bleeding since it can cause a platelet count increase in 12–48 h, whereas glucocorticoids generally result in a 2–5 day improvement in platelet count [32]. According to the American Society of Hematology, dexamethasone (40 mg/day for 4 days) or prednisolone (1 mg/kg/day) with tapering (depending on response and for a maximum length of 6 weeks) is recommended. Dexamethasone may be favored over prednisolone in studies on people with ITP due to a higher response rate at 7 days [30]. Relapse and lack of sustained response in monotherapy of IVIG were also reported [26]. It is hypothesized that this relative resistance to IVIG therapy was caused by high antibody load owing to underlying severe COVID-19 and enhanced platelet consumption or loss of IVIG due to active bleeding [19]. Thrombopoietin receptor agonists (TP-RA), which can cause a sustained increase in platelet count 1–2 weeks after treatment, can also assist in avoiding severe thrombocytopenia recurrences [32]. Because of the increased risk of thrombotic events and hepatotoxicity, recommendations suggest using TP-RA only as a second-line treatment in COVID-19 patients with no evidence of severe disseminated intravascular coagulation (DIC) [33].

To offer a clear viewpoint indicating the predictive significance of platelet count in this new infection, we presented a pooled mean platelet count in 6 included studies (14.52, CI [8.79, 20.25]) which implies that COVID-19 patients are more likely to develop thrombocytopenia. This was also consistent with **Bashash *et al.***, who reported that low platelet count was found to be related to an increased risk of severe COVID-19 illness, with a pooled mean difference of (−21.5, 95% CI [−31.57, −11.43]).

Mean time (±SD) of recovery from ITP was 5.8 ± 4.8 days. This is similar to the findings of a retrospective study that included 3255 patients that found that the median time of recovery was 4 days [27].

7. Limitations

Our main limitations are the low number of included cases, the heterogeneity of data reported, the absence of a confirmatory test to confirm SARS-CoV-2-associated ITP, the absence of a standard definition for SARS-CoV-2-associated ITP, the absence of information regarding time points (time from COVID-19 to ITP, duration of thrombocytopenia, etc.), and treatment response. Additionally, there is an inherent

Table 3. The clinical characteristics of the included studies.

Study	Time from diagnosis with COVID to ITP development	Time to recovery from ITP	Treatment strategies
Lévesque et al., 2020 [19]	20 days	14 days	On ITP days 1 and 2, they provided 1 g of IVIG per kilogram of body weight daily, and on days 3–6, they administered 40 mg of intravenous dexamethasone daily. They also gave him a platelet, and they subsequently chose to use second-line treatments, giving romiplostim daily from ITP days 5–14 and vincristine on ITP day 9. From ITP days 10–13, they additionally gave 500 mg of intravenous methylprednisolone in pulses.
Bennett et al., 2020 [17]	NA	5 days	The patient received one unit of platelets, but his platelet count did not improve. ITP was suspected; therefore, IVIG was given at 1 g/kg/day for two doses. She came to the hematology clinic 28 days following discharge with a platelet count of 8 K/L.
Clerici et al., 2020 [20]	NA	10 days following the initial dosage of romiplostim	The patient had a platelet pool transfusion with no significant change in platelet count after 45 minutes, as well as methylprednisolone 1 mg/kg. Because the platelet count remained extremely low, IVIG (400 mg/kg/day for 5 days) was administered. Rituximab was avoided, and romiplostim at a dose of 1 g/kg was used instead. One week and ten days following the initial dosage of romiplostim, the platelet count has developed.
Martincic et al., 2020 [23]	9 days	3 days	Due to the bleeding, the patient received one unit (325 ml) of pooled platelet concentrate with a one-hour post-transfusion platelet increase of 5,000/mm^3 (from 4,000/mm^3 to 9,000/mm^3). The patient was started on IVIG for a total of 1 g per kilogram of adjusted body weight (100 g), divided into two daily doses (50 g/day), and administered alongside intravenous dexamethasone 40 mg daily. On the third day of therapy, the platelet count started to rise.
Hindilerden et al., 2020 [21]	NA	10 days	For two days, IVIG was given at a rate of 1 g/kg body weight. His platelet count was 25,000/mm^3 three days after starting IVIG. As a result, oral prednisolone at a dosage of 1 mg/kg/day was initiated. On the tenth day of his hospitalization, the purpura had gone away, and his oxygen saturation in ambient air was 96%. His platelet count had risen to 100,000/mm^3.
Metallidis et al., 2020 [22]	7 days	4 days	A short course of dexamethasone and IVIG was started. Thus, 24 mg of dexamethasone was given daily for four days, and 1 g/kg/day of IVIG was given for two days in a row. During the hospitalization, the platelet count recovered sufficiently.
Ayesh et al., 2021 [18]	NA	After 2 days of IVIG and five days of dexamethasone	Following initial stabilization, she had two units of platelet transfusions, as well as aspirin and clopidogrel. After consulting with hematology, they decided to start her on weight-based IVIG and dexamethasone burst treatment. After two days of IVIG and five days of dexamethasone 20 mg, her platelet count improved. The patient was discharged with a stable medical state, given a vitamin K supplement and prednisone.
Aydın et al., 2021 [24]	NA	Within 2–4 days	IVIG was administered (1 g/kg).
	NA	Within 2–4 days	IVIG was administered (1 g/kg).
Behlivani et al., 2021 [25]	7 days	NA	Dexamethasone 16 mg daily. The patient showed a response to the treatment.
	NA	NA	Methylprednisolone 1 mg/kg/day. The patient showed a complete response to the treatment.
	NA	NA	Prednisone 1 mg/kg/day. The patient showed a response to the treatment.
Bomhof et al., 2020 [26]	12 days	4 days	Dexamethasone 40 mg (D1–D4), IVIG (D1–D2). The patient showed a complete response to the treatment.
	5 days	6 days	Dexamethasone 40 mg (D1–D4). The patient showed a complete response to the treatment.
	19 days	3 days	Dexamethasone 40 mg (D1–D4) and eltrombopag (D5–D30). The patient showed a response to the treatment.
	125 days	3 days	Dexamethasone 40 mg (D1–D4) and IVIG (D1–D3). The patient showed a complete response to the treatment.
	7 days	5 days	Methylprednisolone 125 mg (D1–D2) and IVIG (D1–D2). The patient showed a complete response to the treatment.
	10 days	7 days	IVIG (D1–D3). The patient showed a response to the treatment.
	4 days	NA	Dexamethasone 6 mg (D1–D6), methylprednisolone 1000 mg (D7), and eltrombopag (D7). The patient showed no response to the treatment.
	31 days	NA	Dexamethasone 6 mg (D1–D10). The patient showed no response to the treatment.
	At time of diagnosis	2 days	Dexamethasone 40 mg (D1–D4). The patient showed a complete response to the treatment.
	At time of diagnosis	4 days	Methylprednisolone 250 mg (D1–D5) and IVIG (D1–D5). The patient showed a complete response to the treatment.
	30 days	6 days	Dexamethasone 40 mg (D1–D4), IVIG (D1–D2), and eltrombopag (D5–D28). The patient showed complete response then relapse.

(*Continued*)

Table 3. (Continued).

Study	Time from diagnosis with COVID to ITP development	Time to recovery from ITP	Treatment strategies
Kewan et al., 2021 [27]	9	NA	IVIg (D1 and D5) andthen eltrombopag until D28 with complete response
	13 days	NA	IVIg (D1 and D3) then eltrombopag until D15 with complete response
	5 days	NA	Prednisone 5 days with a response and then relapse
	2 days	NA	Prednisone 3 days with complete response
	12 days	NA	Prednisone 10 days with complete response
	23 days	NA	Prednisone 3 weeks with complete response
	22 days	NA	Dexamethasone (D1–D4) with a complete response and then relapse
	8 days	NA	Methylprednisolone + IVIg (D1–D3) + eltrombopag until D15 with complete response
	16 days	NA	IVIg (D1–D3) with response
	30 days	NA	IVIg (D1–D3) with response
	25 days	NA	IVIg (D1–D3) with response
	14 days	NA	IVIg (D1–D2)
	27 days	NA	Prednisone 3 weeks IVIg (D1–D3) with a complete response then relapse.
	15 days	NA	IVIg (D1–D3) with complete response
Mahévas et al., 2020 [28]	NA	2 days	IVIG was administered (1 g/kg).
	At the time of diagnosis	22 days	Dexamethasone 40 mg daily for four days. Without any response on day, 6 patients received IVIG, resulting in a platelet count of 32 9 109/l on day 22.
	12 days	NA	Anticoagulant therapy and IVIG.
Pascolini et al., 2020 [29]	21 days	7 days	Treatment with prednisolone (1 mg/kg/day) and IVIG 1 g/kg) was initiated.
	4 days	2 days	The patient received two units of apheresis platelet transfusion. Two courses of IVIG (1 g/kg) were administered.
Mean ± SD	18.1 ± 21.9	5.8 ± 4.8	

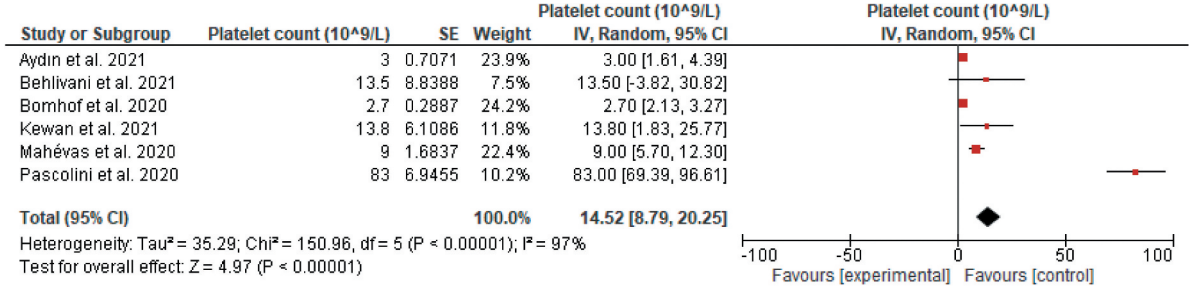

Figure 2. Forest Plot of the platelet count among COVID-19 patients associated with ITP.

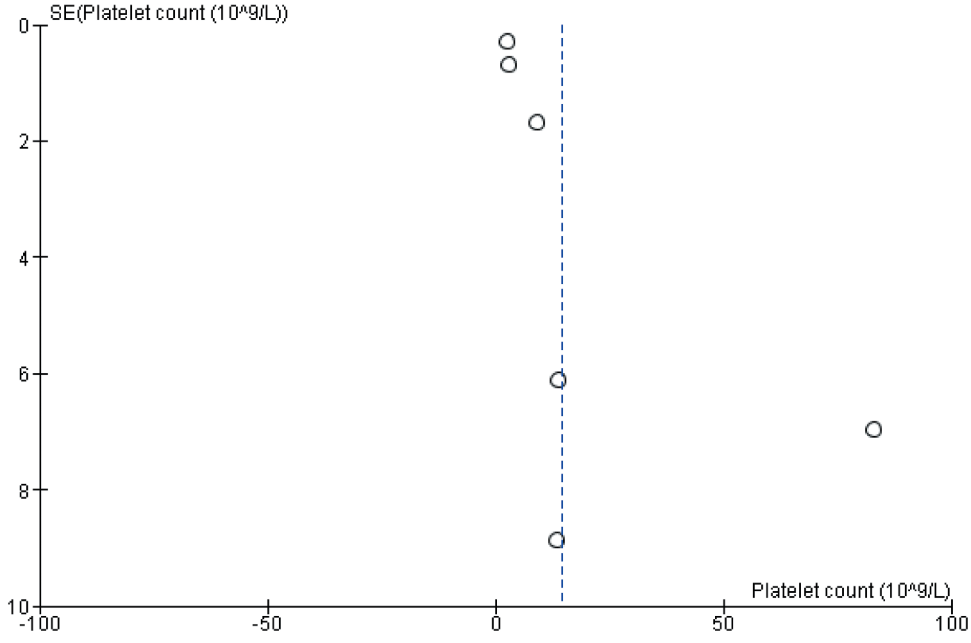

Figure 3. Funnel plot for visual detection of publication bias.

possibility of bias in reporting mild cases with a focus on reporting cases with a severe drop in platelet count.

8. Conclusion

This systematic review and meta-analysis have demonstrated that ITP secondary to COVID-19 infection was slightly more prevalent among males (54.8%) than females. The elderly population was more vulnerable to the disease as most of the cases were older than 50 years with a median age of 63 years. We also found that most cases developed ITP after COVID-19 infection within 2–3 weeks with an estimated mean time of 18.1 ± 21 days, and the estimated mean time to recovery from ITP was less than one week (5.8 ± 4.8). Most patients in this study were treated with IVIG in variable doses, and dexamethasone and platelet unit transfusion usually failed. We also recorded a low mean platelet count in thrombocytopenic COVID-19 patients, which exposes them to a higher risk of complications. After excluding many concomitant causes or illnesses that can induce thrombocytopenia in COVID-19, the authors believe that a systematic approach is required to diagnose new-onset ITP. Clinicians should also be aware of multiple instances of ITP in COVID-19 patients in the post-recovery phase.

Funding

Funding This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Review disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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