bjh short report

Incidence, characteristics and clinical profile of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with pre-existing primary immune thrombocytopenia (ITP) in Spain

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Summary

Infections are one of the well-known precipitating factors for relapses in patients with immune thrombocytopenia (ITP). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can sometimes lead to or be associated with thrombocytopenia due to an increase in peripheral platelet destruction from inflammatory hyperactivation. Currently, we do not know if SARS-CoV-2 infection modifies the natural evolution of chronic or persistent ITP or if previous immunosuppression of patients with ITP influences the incidence and severity of coronavirus disease 2019 (COVID-19) in this group. The present study was an observational, multicentre, national series of 32 adult patients with pre-existing ITP and subsequent SARS-CoV-2 infection, collected by the Spanish ITP Group [Grupo Español de Trombocitopenia Inmune (GEPTI)].

Keywords: ITP, COVID-19, steroids, chronic, persistent, treatment.

Introduction

Primary immune thrombocytopenia (ITP) produces a decrease in the number of platelets increasing the risk of bleeding. Among its pathophysiological mechanisms, we find an increase in platelet destruction basically mediated by antibodies against platelet membrane glycoproteins and cytotoxicity lysis.[1]

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Infections are among the precipitating factors for relapses in patients with ITP.[1,2] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection induces thrombocytopenia in some patients by different mechanisms.[3] In most cases, it is a moderate thrombocytopenia, but 20% of them are severe and related with a poor clinical course of coronavirus disease 2019 (COVID-19).[4] Among the mechanisms of SARS-CoV-2-induced thrombocytopenia, there is an increase in peripheral platelet destruction due to inflammatory hyperactivation cytokine storm syndrome in 36% of cases.[5]

To date, only a few cases of newly diagnosed ITP associated with SARS-CoV-2 infection have been published.[6,7] However, no series of patients with pre-existing ITP who subsequently present with COVID-19 have been reported. It is not known if this infection modifies the natural history of ITP, or if previous use of immunosuppressive drugs for ITP influences the incidence and severity of the COVID-19 in this group. To try to answer these questions, we present an observational, multicentre, national series of patients with ITP according to the American Society of Hematology (ASH) 2019 criteria,[8] aged >18 years with subsequent SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR), collected by the Spanish ITP Group [Grupo Español de Trombocitopenia Inmune (GEPTI)] of the Spanish Society of Haematology and Haemotherapy [Sociedad Española de Hematología y Hemoterapia (SEHH)].

Between March and December 2020, we recruited 32 patients with COVID-19 and pre-existing ITP. It is a small series, but it could give us a valuable insight of this group of patients assuming an estimated prevalence of ITP in Spain of four per 100 000 inhabitants[9] and the COVID-19 accumulated incidence of 7·6% by 30 December 2020.[10] The main characteristics of the series are described in Table I. The median [interquartile range (IQR)] age was 65 [51–79] years and 62% of them were female. Comorbidities were present in 78% of the series. Only four patients were under angiotensin-converting-enzyme inhibitors (ACEI) and one patient required home oxygen.

Most of the series comprised patients with chronic ITP (cITP), with a median (IQR) time from ITP diagnosis to COVID-19 confirmation of 39·5 (8–148·6) months. Only 60% of the patients required ITP treatment throughout the disease, with a median (IQR) of treatment lines of 1 (0–2). As second line, seven patients were treated with thrombopoietin analogues (TPOa) and one with rituximab. At the time of COVID-19 diagnosis, only one patient was on active treatment with low-dose prednisone in a descending regimen and seven of them were on treatment with TPOa (four romiplostim and three eltrombopag).

The most frequent symptoms of COVID-19 were cough (72%), fever (69%), asthenia (63%), myalgia (47%), dyspnoea (41%) and headache (34%). The median (IQR) time from the suspicion of COVID-19 to confirmation by PCR was 6 (2–9) days. More than half of the patients required hospitalisation assistance (18/32), three of them in the Intensive Care Unit (ICU). Ventilatory support was indicated in 38% of the total series, including three patients with non-invasive mechanical ventilation. COVID-19 was treated with chloroquine (58%) and azithromycin (32%). Only one patient required tocilizumab. The median (IQR) time of hospitalisation was 15 (12–25·5) days.

Regarding the evolution of ITP, the median (IQR) platelet count at the time of confirmation of COVID-19 was 47 (5–94) $\times 10^9$/l. In all, 47% of the series presented with a decrease in the number of platelets requiring treatment, with a median (IQR) time from the onset of COVID-19 symptoms to the relapse of ITP of 9 (4–12·5) days. The ITP relapse treatment regimens are described in Table I. Of the two patients who did not receive steroids, one was treated with immunoglobulin (Ig; 1 g/kg $\times$ 2 days) and in the other the baseline romiplostim dose was increased. Figure 1 describes the change in platelets counts during COVID-19 infection in the present series. With a median follow-up of 267 days, no new relapses of ITP have been evidenced. Figure S1 describes the evolution of the laboratory analytical parameters at COVID-19 diagnosis and at ITP recovery. We did not find statistically significant differences between the clinical characteristics of the patients that would allow for the prediction of relapse of ITP.

An important issue in hospitalised patients with COVID-19 is thromboembolic prophylaxis. In the present series, 35% of the patients received low-molecular-weight heparin, 11 patients as primary prophylaxis at high intermediate-risk doses and in one patient as secondary prophylaxis using therapeutic doses. In all cases, prophylaxis was started with platelet counts $>30 \times 10^9$/l. No thrombosis or ischaemia have been described, but an incidence of 17% of World Health Organization (WHO) Grade ≥1 bleeding in the anticoagulated patients. The median (IQR) duration of prophylactic anticoagulant treatment was 11 (6·5–26) days.

Regarding morbidity and mortality, four patients developed nosocomial bacterial infections, three of them with criteria of sepsis. These three patients were admitted to ICU due to adult respiratory distress syndrome and died from progression of respiratory failure. The overall mortality of the series was 9·4%. According to age, it was 33% in patients aged >80 years and 7% in those under that age.

We only have a SARS-CoV-2 PCR test to define recovery in 18 patients, as the rest were labelled as non-contagious by determination of IgG against the virus 14 days after COVID-19 diagnosis. The median (IQR) time from the onset of COVID-19 symptoms to a negative PCR result was 21 (15·5–35·5) days. The present series is short but we found no difference in time to SARS-CoV-2 PCR negativity depending on steroids use, at a median (IQR) of 29·5 (13·5–48·5) days with no steroids *versus* 19·5 (13·5–27) days with steroids (Figure S2).

The ITP relapse rate was higher in the group of patients who required hospitalisation (74% vs. 15%, $P = 0·006$). Of the 19 patients with admission criteria, 14 had ITP relapse but only 12 started steroid treatments. Among these patients,

Table I. Description of the patients' and ITP characteristics of the present series.

Patient no.	Age, years	Sex	ITP status	ITP treatment lines before COVID-19	CCI	Platelet count at the time of COVID-19 diagnosis, × 10^9/l	Relapse	Relapse ITP treatment	Response to ITP treatment	Platelet count after COVD-19 resolution, × 10^9/l
1	92	F	cITP	1	7	7	Yes	Metilprednisolone 1 mg/kg/d	CR	120
4	79	F	cITP	2	3	1	Yes	Dexamethasone 40 mg/d ×4 d and Ig 1 g/kg/d × 2 d	R	44
5	53	F	cITP	2	2	2	Yes	Dexamethasone 40 mg/d × 4 d, Ig 1 g/kg/d × 2 d, danazol 400 mg/d	CR	170
7	79	M	pITP	1	12	12	Yes	Dexamethasone 40 mg/d ×4 d and Ig 0.4 g/kg/d × 5 d	R	Death day 25 32
8	88	F	nITP	1	8	5	Yes	Dexamethasone 40 mg/d × 4 d and Ig 1 g/kg/d × 2 d	NR	12
10	82	F	cITP	0	7	5	Yes	Prednisone 1 mg/kg/d and i.v. Ig 1 g/kg/d × 2 d	NR	Death day 8 19
11	40	M	cITP	2	2	69	Yes	Dexamethasone 40 mg/d × 4 d	CR	Death day 14 165
12	65	M	nITP	1	5	23	Yes	Increase romiplostim dose	CR	240
14	81	M	nITP	0	5	5	Yes	Metilprednisolone 1 g/kg/d and i.v. Ig 0·4 g/kg/d ×5 d	R	72
15	51	M	cITP	1	1	5	Yes	Dexamethasone 40 mg/d × 4 d and Ig 1 g/kg/d ×2d	CR	206
16	57	F	cITP	2	1	8	Yes	Dexamethasone 40 mg/d × 4 d plus Ig 1 g/kg/d ×2d plus eltrombopag 50 mg/d	R	39
18	89	M	nITP	0	5	18	Yes	Dexamethasone 40 mg/d ×4 d, follow by prednisone 0·5 mg/kg/d	R	84
23	64	F	cITP	1	2	15	Yes	Metilprednisolone 2 mg/kg/d, follow by prednisone 0·5 mg/kg/d	R	57
31	66	M	nITP	1	3	3	Yes	Prednisone 1 mg/kg	R	53
32	57	F	cITP	1	2	6	Yes	i.v. Ig 1 g/kg/d ×2 d	R	54
3	65	F	cITP	1	2	120	No	NA	NA	94
6	52	F	pITP	1	1	212	No	NA	NA	167
9	60	F	cITP	3	2	102	No	NA	NA	98
13	49	M	cITP	1	0	98	No	NA	NA	134
17	43	F	nITP	0	0	68	No	NA	NA	72
19	67	F	cITP	2	2	120	No	NA	NA	110
20	26	F	cITP	2	0	88	No	NA	NA	90
21	74	F	cITP	1	3	95	No	NA	NA	75
22	84	M	cITP	0	8	62	No	NA	NA	57
24	63	M	cITP	4	5	78	Yes	NA	CR	475
25	44	F	cITP	2	0	124	No	NA	NA	132
26	77	M	cITP	4	6	64	No	NA	NA	78
27	36	F	cITP	3	1	59	No	NA	NA	75
28	45	F	cITP	4	4	94	No	NA	NA	143
29	58	F	cITP	4	2	27	No	NA	NA	35
30	79	F	pITP	3	6	47	No	NA	NA	41

CCI, Charlson Comorbidity Index; CR, complete response; d, day; F, female; Ig, immunoglobulins; i.v., intravenous; (c)(n)(p)ITP, (chronic) (newly diagnosed) (persistent) immune thrombocytopenia; M, male; NA, not available; NR, no response; R, response.

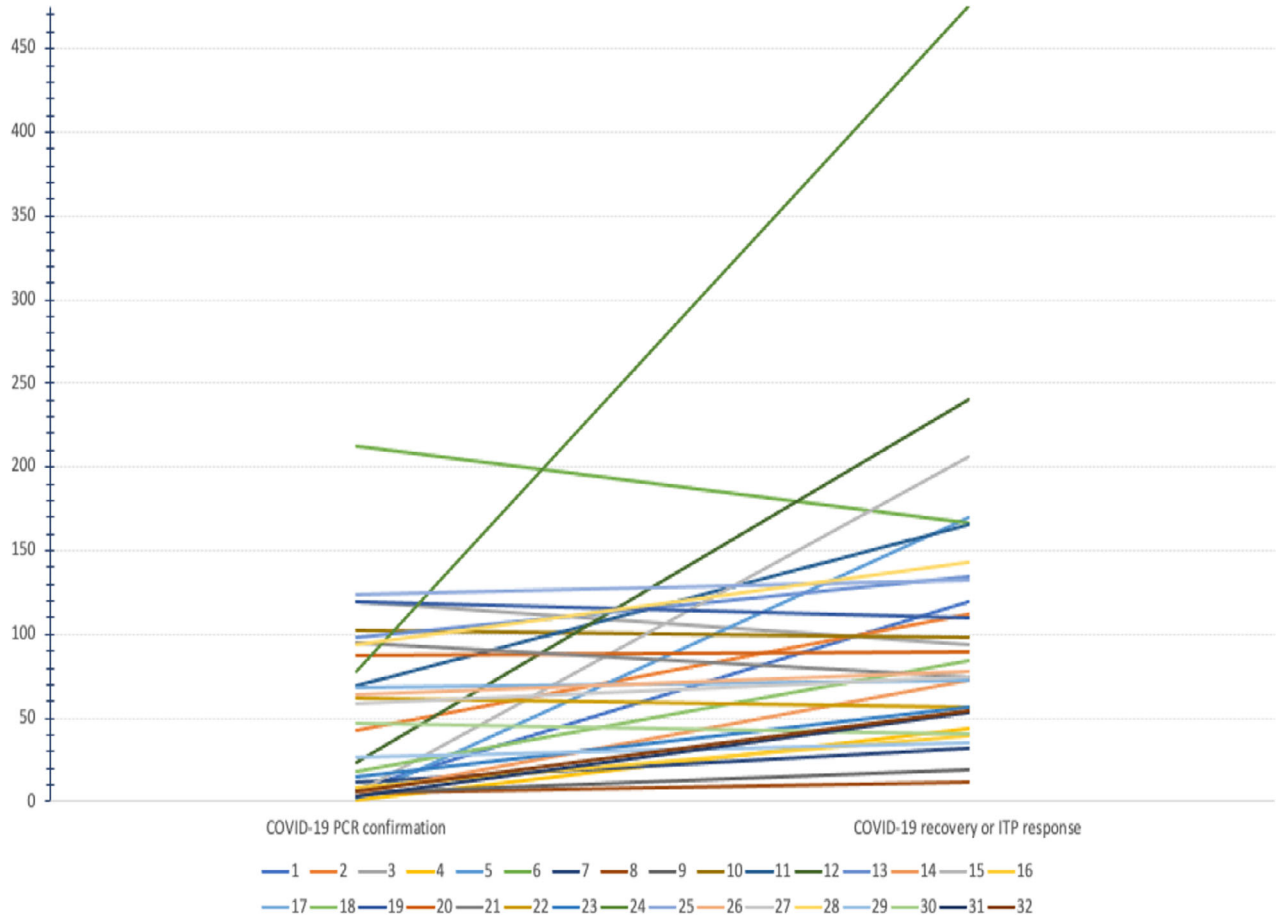

Fig 1. Evolution of platelet count of all the patients since COVID-19 confirmation to their ITP response and/or COVID-19 recovery. The figure describes the evolution of all the patients since COVID-19 PCR confirmation until ITP response in case of relapse or COVID-19 recovery (PCR negative or IgG against SARS-CoV-2 positive). COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; IgG, immunoglobulin G; ITP, immune thrombocytopenia; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2. [Colour figure can be viewed at wileyonlinelibrary.com]

we found the three who developed nosocomial infections with severe pneumonia and ultimately died. In the hospitalised patients, there was no difference between patients treated with or without steroids with regard to hospitalisation duration, at a median (IQR) of 15 (13–17) days with no steroids *versus* 14 (10–34·5) days with steroids.

There are several limitations and possible bias in the present study. A significant number of patients with ITP have been followed using telemedicine care systems and they may have had COVID-19 without biological confirmation limiting recruitment. In addition, patients with ITP, especially those treated with immunosuppressive drugs and splenectomised patients, have avoided going to hospitals due to the risk of infection, limiting the exposure to SARS-CoV-2. Finally, the patients included in the present study were mainly those who required medical assistant and came to hospital or the emergency room. This could select those with especially severe COVID-19 and underestimate the real incidence.

Based on the present results, the relapse rate in patients with pre-existing ITP affected by COVID-19 seems high. In our present series, as in a French cohort of patients with COVID-19-induced thrombocytopenia in patients without previous ITP, time from a PCR-positive result to thrombocytopenia is around 3–13 days.[7] This leads us in the current scenario, to consider the usefulness of requesting screening for SARS-CoV-2 infection in ITP patients relapse and in new thrombocytopenia cases. In addition, we must consider the possibility of a closer clinical monitoring in this group, whether physical or with telemedicine care systems, to identify haemorrhagic symptoms and the possible need for early ITP treatment adjustment. A possible justification for the high relapse rate in patients with ITP could be the trigger effect of SARS-CoV-2, as with other infections.[2,9,12] Following the infection, the immune responses raised against SARS-CoV-2 may cross-react with human proteins that share peptide sequences with the virus, in this way leading to autoimmune pathological sequelae.[2] On the other hand, by the same mechanism, several proteins could be blocked as interleukin-7 that plays a critical role in the regulation of the immune

system and associates with severe lymphopenia when deficient.[2,13]

Regarding treatment, we observed that patients who need hospitalisation because of COVID-19 severity have higher rates of ITP relapse and use of steroids to improve platelet counts. The three deaths that occurred were in this group of patients, but in these patients steroids had not only been used because of ITP relapse but due to the severity of COVID-19. Time to a SARS-CoV-2-negative PCR was similar to the rest of population at ~30 days,[14] despite the use or not of steroids. Despite the recommendations to restrict the use of high doses of steroids,[15] we did not find differences in ITP or COVID-19 evolution in hospitalised patients treated with or without steroids according to ITP guidelines.[11,12]

To conclude, in our experience COVID-19 infection can affect the platelet counts in patients with a pre-existing ITP, so they should be carefully followed. Most patients with ITP with criteria of moderate or severe COVID-19 will relapse. Morbidity and mortality seem to be related to COVID-19 severity and patients' comorbidity. We found no difference in ITP and COVID-19 outcomes between patients treated with or without standard steroids schemes of treatment. These results should be validated by other series.

Author contributions

María E. Mingot-Castellano and Patricia Alcalde-Mellado designed and performed the research and analysed the data. María E. Mingot-Castellano wrote the paper. María E. Mingot-Castellano, Cristina P. Izquierdo, Gloria P. Rus, Aida C. Pérez, María P. Martinez, Francisco J. López-Jaime, Lorena A. Perez, José R. Gonzalez-Porras, Fernanda L. Fernández, Isabel S. C. Miranda, Tomás J. González-López, María E. M. Beltrán, Rebeca R. Escuin, Reyes J. Bárcenas reported clinical data and review the final version.

Supporting Information

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

Fig S1. (A). COVID-19 laboratory severity parameters.

Fig S1. (B). COVID-19 laboratory severity parameters.

Fig S2. Time to SARS-CoV-2-negative PCR since COVID-19 first symptoms Kaplan–Meyer analysis between patients with ITP with COVID-19 infection hospitalised treated with *versus* without steroids.

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