Pentoxifylline in patients with COVID-19 and with liver cirrhosis or metabolic dysfunction-associated steatotic liver disease: Emerging insights

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Abstract. Coronavirus (CoV) disease 2019 (COVID-19) deteriorates existing hepatopathies, such as liver cirrhosis and metabolic-associated syndrome liver disease (MASLD), which in turn increases the risk of serious complications. The pathophysiology of COVID-19 includes inflammation, proinflammatory cytokine storms, oxidative stress and fibrosis. Notably, pentoxifylline (PTX) blocks nuclear factor-κB activity, thus inhibiting the secretion of proinflammatory cytokines, and is an antioxidant and antifibrotic agent. The present study reported on the use of PTX in 20 patients with liver cirrhosis (13 men, 7 women) of different etiologies and in 25 patients with MASLD (16 women, 9 men) infected with severe acute respiratory syndrome-CoV-2; age range of all patients, 29-83 years. Firstly, the detection of CoV-2 was confirmed by PCR. All patients received PTX (400 mg twice daily; *per os*) for 8 weeks, alongside standard care provided for COVID-19 symptoms and for their liver condition. In all patients, the following inflammatory markers were assessed at the beginning and at the end of the study: C-reactive protein, D-dimer, ferritin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), platelet count and oxygen saturation. Statistical analysis was performed using the Wilcoxon signed-rank test. At the end of the study, no patient required admission to the intensive care unit and no patient fatalities were noted. Notable improvement was noted in seven of the eight inflammatory markers in both liver pathologies, and the only sole parameter that worsened was LDH. Notably, no serious adverse events were observed in these patients. In conclusion, PTX treatment was associated with favorable clinical outcomes and improved inflammatory marker levels in patients with liver cirrhosis and MASLD with COVID-19.

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Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; COVID-19, coronavirus disease 2019; ACLF, acute-on-chronic liver failure; PTX, pentoxifylline

Key words: COVID-19, hepatic cirrhosis, MASLD, PTX

Introduction

According to the World Health Organization, coronavirus (CoV) disease 2019 (COVID-19) was responsible for ~15 million deaths worldwide in 2020 (1). This disease remains capable of progressing to acute respiratory distress syndrome (ARDS), multiple organ failure or respiratory failure, and death, particularly in patients with advanced age or underlying comorbidities, including obesity, hypertension, diabetes, chronic kidney disease, cardiovascular conditions, cancer, liver cirrhosis, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) (2). These hepatic pathologies have a high prevalence worldwide. In particular, liver cirrhosis causes >2 million deaths annually worldwide (3). When associated with COVID-19 or severe acute respiratory syndrome (SARS)-CoV-2 variants, mortality increases by >50% and in decompensated patients it can reach

63%, increasing the risk of acute-on-chronic liver failure (ACLF). Even 28 days after the virus has been cleared from the body, these patients continue to have a high risk of mortality (4). SARS-CoV-2 infection has an incubation period of 1-3 days, which is shorter than that of the initial strain (5-6 days; range, 1-14 days) (5,6). The main symptoms of COVID-19 include rhinorrhea, fever, sore throat, headache, fatigue, chest pain, dyspnea, and a loss of smell and taste (7). According to the literature, certain patients hospitalized for COVID-19 experience various degrees of liver damage, as shown by increased levels of liver enzymes such as aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) (6). SARS-CoV-2 primarily spreads through droplet infection via the respiratory tract, and liver damage caused by this virus has been identified as one of the main factors contributing to ACLF and systemic inflammation in patients with pre-existing cirrhosis (6).

Decompensated patients with cirrhosis with COVID-19 are highly susceptible to severe pulmonary infections, with 72% of these patients presenting an increased risk of microvascular thrombosis, cardiac arrhythmias and complications of cirrhosis, such as hepatic encephalopathy, variceal bleeding, ascites and spontaneous peritonitis (8). In addition, pre-existing liver damage is aggravated by the cytopathic effect of the virus and the damage due to the large number of medications administered to these patients, including anti-inflammatory drugs, antibiotics and antivirals (lopinavir, favipiravir, ribavirin, remdesivir), as well as chloroquine, steroids and immunomodulators (tocilizumab) (9). COVID-19-associated MASLD and MASH displayed a higher risk of severe progression (60%) and hospitalization (75%) during the pandemic (2020-2023), as well as a higher risk of intensive care unit (ICU) admissions, with mortality affecting 40% of cases (10).

COVID-19 initially presents a high viral load; after ~2 weeks (average, 11 days), the viral infection elevates cytokine levels, resulting in a hyperinflammatory cytokine storm. A cytokine storm with the participation of nuclear factor (NF)-κB is characterized by heightened levels of interferon-α, tumor necrosis factor, interleukin (IL)-6, IL-1, IL-18 and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10) (11). In COVID-19, an uncontrolled immune response can lead to acute inflammatory processes, fibrosis, a hypercoagulable state associated with thrombosis and disseminated intravascular coagulation, culminating in multiple organ failures and death (12,13). Concomitantly, elevated inflammatory markers, including D-dimer, ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP) and lactate dehydrogenase (LDH), are frequently reported in COVID-19 (14). In addition, leukopenia, thrombocytopenia, hypoalbuminemia, elevated AST and ALT levels, lymphopenia or lymphocytosis (notably in patients with severe disease) and, to a lesser extent, altered creatine kinase levels are noted in COVID-19 (9,15).

Once inflammation sets in, antiviral treatment alone is insufficient to control disease severity, and anti-inflammatory or immunomodulatory drugs are subsequently required. These include lopinavir, favipiravir, ribavirin and remdesivir, the corticosteroid chloroquine, and immunomodulators such as tocilizumab, as well as broad-spectrum antibiotics (9). However, therapeutic schemes may have contradictory results in patients with cirrhosis and those with COVID-19. The hepatotoxic effects of therapeutic drugs, when added to the direct cytopathic effects of the virus and hepatic damage, are most likely the underlying mechanisms for liver damage in patients with COVID-19 (16). In addition, it has been reported that patients with liver disease often respond poorly in an ICU setting during SARS-CoV-2 infection (17). Therefore, it has been suggested that the use of pentoxifylline (PTX) could benefit patients with cirrhosis undergoing a cytokine storm. PTX, which was first discovered >50 years ago, is a methylxanthine derivative (18), the main mechanism-of-action of which lies in the inhibition of phosphodiesterase 4, which in turn leads to an increase in intracellular levels of cyclic adenosine monophosphate (19). The latter results in an inhibition of the phosphorylation of NF-κB, thereby decreasing the levels for proinflammatory cytokines (20,21); this drug has been reported to possess anti-inflammatory, antithrombotic, antiviral, antifibrotic and antitumor properties and effects (22). Notably, PTX also downmodulates the synthesis of prostaglandin E2, a lipid mediator with proinflammatory effects (23). Furthermore, PTX has been shown to reduce the expression of endothelial adhesion molecules, such as ICAM-1 and VCAM-1, thereby decreasing leukocyte migration and adhesion to blood vessels and reducing endothelial damage (24). PTX also exerts an antioxidant effect by inhibiting the production of reactive oxygen species, which serve a key role in the amplification of inflammation and cellular damage (25). Within the context of infectious diseases, this drug has been described as having beneficial effects in septic and viral processes (26); due to its ability to modulate the replication of RNA and DNA viruses, including hepatitis C virus (HCV) and hepatitis B virus, it can reduce their replication and spread (27,28). Notably, the use of PTX in patients with HCV treated with ribavirin and pegylated interferon, the rate of sustained viral response has been reported to be markedly increased (27).

PTX has also been postulated for use in other viral infections characterized by elevated oxidative stress, such as infectious encephalitis caused by Japanese encephalitis virus, in which antioxidants have a key role in mitigating cellular damage (29). Several pre-clinical and clinical studies have confirmed that PTX possesses potent bronchodilator, antifibrotic and anti-inflammatory properties. It has been reported that PTX decreases pulmonary fibrosis in patients with breast and head and neck cancer treated with chemotherapy and radiotherapy (30). Furthermore, it has been shown that PTX improves survival rates among patients with compensated cirrhosis (31), exhibits encouraging results and can effectively treat MASLD (32) and fulminant hepatitis (33), and exerts antitumor effects on patients with hepatocellular carcinoma (34). These findings suggest that PTX could be used to treat chronic inflammatory diseases and viral infections with a high inflammatory burden. Studies have supported the idea of utilizing PTX in patients with COVID-19. Previous studies have reported its inhibitory activity against SARS-CoV-2, suggesting an antiviral mechanism-of-action mediated by modulation of the inflammatory response and cellular oxidative stress (35,36). Given these multifaceted mechanisms, PTX is hypothesized to mitigate several key pathological pathways, including systemic inflammation, oxidative stress and endothelial dysfunction, which are markedly exacerbated in patients with COVID-19 and underlying chronic liver disease. The aim of the present study was to evaluate the effects of PTX in patients with liver cirrhosis or steatohepatitis who are also infected with SARS-CoV-2.

Materials and methods

Study design. The present study is a descriptive, retrospective, observational study of patients infected with SARS-CoV-2 who also had chronic liver disease, specifically MASLD or liver cirrhosis. The patients received PTX and conventional treatment. The present study included patients admitted to the Gastroenterology and Hepatology Service, Institute for Security and Social Services for State Workers (ISSSTE), Valentín Gómez Farías General Hospital (Zapopan, México) between February 1 and September 30, 2020. Retrospective data were collected from the medical records of these patients between April 16 to June 16, 2022, for subsequent analysis. The present study was approved by the Biomedical Research Ethics Committee of Valentín Gómez Farías General Hospital (ISSSTE; approval nos. ISSSTE/CEI/816/2025 and RPI. HVGF.055.2025). Due to the retrospective nature of the study, the patient consent exemption was approved.

Study population. A total of 71 patients were diagnosed with SARS-CoV-2 infection, which was confirmed by PCR. Among these patients, 45 patients were included in the present study, 51% of whom were men and 48% women, with an age range of 29-83 years and a mean age of 56.2±12.3 years. A total of 20 patients had a previous diagnosis of liver cirrhosis (13 men, 7 women) of different etiologies and stages according to the Child-Pugh classification (37), whereas 25 patients exhibited MASLD (17 women, 8 men), as diagnosed by biochemical and imaging studies (ultrasound and FibroScan) (Table I).

Inclusion criteria. The following inclusion criteria were adhered to: Adult patients of both sexes; >18 years of age; confirmed diagnosis of SARS-CoV-2 infection via a positive PCR test; a previous diagnosis of liver cirrhosis or MASLD; and moderate-to-severe clinical manifestations of SARS-CoV-2.

Exclusion criteria. The following exclusion criteria were adhered to: Patients with deterioration of general condition, loss of consciousness, arrhythmia, acute kidney damage, dehydration, severe hypoxemia or ACLF requiring urgent admission; and patients with comorbidities such as cancer, chronic infections or bleeding from the digestive tract.

Intervention. Patients were treated with PTX (400 mg; *per os*) every 12 h. The antipyretic drugs paracetamol (1-2 g/day; *per os*) or celecoxib (100-200 mg/day; *per os*) were administered in case of fever and oxygen support was administered in case of hypoxemia (oxygen saturation of <92%). For the management of liver disease, propranolol (40 mg every 12 h; *per os*) was administered for primary prophylaxis of portal hypertension. Esophageal variceal ligation was also performed when there was a risk of bleeding; antioxidants, vitamin E (400 mg every 12 h; *per os*) and silymarin (1 g every 24 h; *per os*) were administered, in addition to a diet low in refined carbohydrates and saturated fats favoring vegetal protein, fiber and unsaturated fats.

Outcome assessment. The following variables were assessed at the start of treatment and after 8 weeks: i) For biochemical determinations, serum was obtained via peripheral venipuncture. Liver enzymes and inflammatory markers were quantified using a Roche Cobas C311 automated clinical chemistry analyser (Roche Diagnostics GmbH), with various kits purchased from Roche Diagnostics GmbH: AST (ASTL, aspartate aminotransferase; reagent cat. no. 20764949322), ALT (ALTL, alanine aminotransferase acc. to IFCC without pyridoxal phosphate activation; cat. no. 20764957322), LDH (cat. no. 03004732122), CRP (cat. no. 07876033190) and ferritin (FERR4, Tina-quant Ferritin Gen.4; cat. no. 04885317190). Platelet counts were determined using a CBC-Line kit for the Sysmex XN Series (cat. no. CL018;

Table I. Demographic and clinical characteristics of patients with liver cirrhosis or MASLD infected with severe acute respiratory syndrome-coronavirus-2.

A, Liver cirrhosis group (n=20)	
Variable	Value
Mean ± SD age, years	53.5±12.6
Age range, years	29-82
Sex, n (%)	
Male	13 (65)
Female	7 (35)
Etiology, n (%)	
AI	3 (15)
AUD	8 (40)
HCV	1 (5)
OB	3 (15)
OB + DM	2 (10)
OB + DM + AUD	3 (15)
Child-Pugh classification, n (%)	
A	14 (70)
B	4 (20)
C	2 (10)
Mean ± SD oxygen saturation levels, %	85.2±4.4
B, MASLD group (n=25)	
Mean ± SD age, years	53.5±11.6
Age range, years	30-83
Sex, n (%)	
Male	8 (32)
Female	17 (68)
Etiology, n (%)	
OB	15 (60)
DM	1 (4)
OB + DM	6 (24)
OB + AI	2 (8)
OB + DM + HT	1 (4)
Mean ± SD oxygen saturation levels, %	86.0±5.3

AI, autoimmune; AUD, alcohol use disorder; DM, diabetes mellitus; HT, hypothyroidism; HCV, hepatitis C virus, MASLD, metabolic-associated syndrome liver disease; OB, obesity; SD, standard deviation.

R&D Systems, Inc.) and measured on a Sysmex XE-5000 hematology analyser (Sysmex Corporation). D-dimer levels (Werfen HemosIL D-Dimer HS; cat. no. 0020007700; Instrumentation Laboratory; Werfen) and oxygen saturation levels were measured using a Rad-57® handheld pulse CO-oximeter (McKesson cat. no. 787597; Masimo Corporation). All kits were used according to the manufacturer's instructions. ii) Clinical manifestations, including cough, dyspnea, fever, chills, headache, anosmia, ageusia, arthralgia and diarrhea. iii) Clinical outcomes, including hospitalization, ICU admission and mortality.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation. All statistical analyses were performed using SPSS version 27.0.1 (IBM Corp.). The Wilcoxon signed-rank test for paired samples was used to compare the differences between pre-treatment and post-treatment measurements (at 8 weeks) for all biochemical and clinical parameters (CRP, D-dimer, ferritin, AST, ALT, LDH, platelet count and oxygen saturation). Two-tailed P<0.05 was considered to indicate a statistically significant difference. The percentage change (Δ%) for each variable was calculated using the following formula: [(post-treatment value-pre-treatment value)/pre-treatment value] x100.

Results

Patient and clinical characteristics. During the study period, 71 patients were diagnosed with SARS-CoV-2 infection; of this population, 45 patients met the inclusion criteria, including 20 patients with hepatic cirrhosis [7 women (35%) and 13 men (65%); average age, 53.5±12.6 years; age range, 29-82 years] (Table I). The remaining 25 patients presented with MASLD, 17 of whom were women (68%) and 8 of whom were men (32%), with an average age of 53.5±11.6 years and an age range of 30-83 years.

COVID-19 symptoms. In the entire population, the most frequent SARS-CoV-2-associated symptoms were cough in 60% of patients, followed by dyspnea in 49% of patients, fever in 48% of patients, central nervous system symptoms in 46% of patients (headache, anosmia, ageusia, insomnia, irritability and depression) and pneumonia in 22% of patients, while symptoms of lesser clinical relevance included chills and arthralgia in 6% of patients and diarrhea in 4% of patients (Table II). No hospitalizations were required during the 4-8-week recovery period following clinical viremia (data not shown).

Biochemical characteristics of patients with hepatic cirrhosis and MASLD. The patients with liver cirrhosis were classified according to the Child-Pugh score as follows: A total of 14 patients were categorized as class A, 4 as class B and 2 as class C. No modifications in the Child-Pugh score were observed at the end of the study.

The levels of several inflammatory markers were evaluated, as well as those of hepatic enzymes, platelets and the degree of oxygen saturation (Table III). It was noted that CRP in patients with hepatic cirrhosis exhibited a mean of 29.6±9.5 mg/l at the start of the study, whereas this was reduced to 17.3±4.2 mg/l at the end, representing Δ%=-41% (P<0.001). In patients with MASLD, the initial mean CRP level was 32.4±12.7 mg/l, which was reduced to 16.9±5.7 mg/l, with Δ%=-47% (P<0.001), following treatment. D-dimer is another important inflammatory marker that exhibited similar behavior; the blood levels in patients with hepatic cirrhosis indicated Δ%=-63% (initial, 1,123.0±720.0 ng/ml; final, 415.0±86.8 ng/ml; P<0.001) and in MASLD Δ%=-37% (initial, 543.5±428.5 ng/ml vs. final, 340.1±121.3 ng/ml; P<0.04). With regard to the levels of ferritin in patients with hepatic cirrhosis following treatment, an improvement was also observed with Δ%=-60% (initial, 625.3±241.2 ng/ml; final, 249.2±72.4 ng/ml; P<0.006). For MASLD, the Δ% between the initial value and the final value was-55% (499.0±187.9 ng/ml vs. 224.0±72.9 ng/ml; P<0.001).

Table II. Clinical manifestations in patients with liver cirrhosis and metabolic-associated syndrome liver disease infected with severe acute respiratory syndrome-coronavirus-2.

Manifestation	Percentage
Cough	60
Dyspnea	49
Fever	48
CNS symptoms[a]	46
Pneumonia	22
Chills	6
Arthralgia	6
Diarrhea	4

[a]Headache, anosmia, ageusia, insomnia, irritability, depression. CNS, central nervous system.

In patients with hepatic cirrhosis, the plasma levels of AST, ALT and LDH at the beginning of the study were as follows: 93.6±105.9, 351.0±139.6 and 295.6±90.2 IU/l, respectively. Following PTX treatment AST and ALT were reduced to the following: AST, 50.1±34.9 IU/l and ALT, 41.5±16.9 IU/l, representing Δ%=-46 and -86%, respectively (P<0.001). By contrast, the concentration of LDH was increased to 417.0±93.4 IU/l, representing Δ%=57% (P<0.001). In addition, improvements were noted in the patients with MASLD following PTX treatment; the initial plasma levels of AST and ALT were 46.4±16.2 and 351.0±139.6 IU/l, respectively, and they were reduced to 38.0±15.5 IU/l (P=0.144) and 41.5±16.1 IU/l (P<0.001), respectively (Δ%=-18 and -88%, respectively). By contrast, the levels of LDH were initially considered normal (174.4±90.2 IU/l), whereas at the end of the study they were increased to 268.8±97.7 IU/l (Δ%=53; P<0.001). The number of platelets was also reported; a similar number was found prior to and following treatment. In the case of patients with hepatic cirrhosis, the number of platelets was 98.1±31.2/10^3/μl, which was similar to the number detected at the end of the study (100.4±21.3/10^3/μl; Δ%=2). However, in MASLD, an improvement was observed; initially the number of platelets was 180.0±52.8/10^3/μl, whereas at the end of the study, it was 229.9±72.9/10^3/μl (Δ%=27%; P<0.03). Oxygen saturation is a parameter that is markedly affected during SARS-CoV-2 infection; initially, it was strongly diminished in hepatic cirrhosis and in MASLD (85.2±4.4 and 86.0±5.3%, respectively) compared with the normal reference value (≥95%). However, an improvement was observed at the end of the study,

Table III. Biochemical results in patients with liver cirrhosis or MASLD infected with severe acute respiratory syndrome-coronavirus-2 treated with pentoxifylline.

	Liver cirrhosis				MASLD				
Variable	Initial	Final	Δ%	P-value[a]	Initial	Final	Δ%	P-value[a]	Reference level
CRP	29.6±9.5 mg/l	17.3±4.2 mg/l	-41	<0.001	32.4±12 7 mg/l	16.9±5.7 mg/l	-47	<0.001	<10 mg/l
D-dimer	1,123.0±720.0 ng/ml	415.0±86.8 ng/ml	-63	<0.001	543.5±428.5 ng/ml	340.1±121.3 ng/ml	-37	0.04	<100 ng/ml
Ferritin	625.3±241.2 ng/ml	249.2±72.4 ng/ml	-60	<0.006	499.0±187.9 ng/ml	224.0±72.9 ng/ml	-55	<0.001	24-336 ng/ml
AST	93.6±105.9 IU/l	50.1±34.9 IU/l	-46	<0.001	46.4±16.2 IU/l	38.0±15.5 IU/l	-18	0.144	0-38 IU/l
ALT	351.0±139.6 IU/l	41.5±16.9 IU/l	-86	<0.001	351.0±139.6 IU/l	41.5±16.1 IU/l	-88	<0.001	10-40 IU/l
LDH	295.6±90.2 IU/l	417.0±93.47 IU/l	57	<0.001	174.4±90.2 IU/l	268.8±97.7 IU/l	53	<0.001	140-248 IU/l
Platelets	98.1±31.2 $10^3/\mu l$	100.4±21.3 $10^3/\mu l$	2	0.881	180.0±52.8 $10^3/\mu l$	229.9±72.9 $10^3/\mu l$	27	<0.03	150-400 $10^3/\mu l$
Oxygen saturation	85.2±4.4%	92.6±2.1%	9	<0.001	86.0±5.3%	92.5±2.5%	7.5	<0.001	95-100%

[a]Wilcoxon signed-rank test. CRP, C reactive protein; LDH, lactate dehydrogenase; MASLD, metabolic-associated syndrome liver disease; AST, aspartate aminotransferase; ALT, serum alanine aminotransferase.

with oxygen saturation increasing to 92.6±2.1% in patients with hepatic cirrhosis (Δ%=9) and 92.5±2.5 in patients with MASLD (Δ%=7.5%) (P<0.001).

Discussion

PTX has been used to treat patients with hepatopathies with encouraging results, and has also been utilized with similar results in patients with COVID-19 (38-40). Notably, it is well known that the coexistence of chronic liver diseases and COVID-19 increases the likelihood of ICU admission and death (4,7). The fact that no ICU admissions or deaths were noted in the present study may be partly explained by the fact that the exclusion criteria selected a lower risk cohort. However, it is important to consider that although the observations prevent the possibility of causality, in a cohort of 45 cases with chronic liver disease and COVID-19 no deaths or ICU admissions were noted. In similar contemporary cohorts, one could expect a mortality rate of 13-18% and an ICU admission rate of 20-25%, which suggests in improvement associated with PTX (4,8).

All patients in the present study were symptomatic and were positive for SARS-CoV-2. At week 8, PTX treatment significantly improved seven of eight parameters: CRP, D-dimer, ferritin, liver enzymes (AST and ALT), platelet count and oxygen saturation. In all of these cases, the improvements were significant, with the exception of the number of platelets in patients with cirrhosis, which exhibited no significant variation, and serum AST concentrations in patients with MASLD, which indicated a slight non-significant decrease (Δ=-18%). However, the mean AST levels were improved to within the normal range (0-38 IU/l). Notably, the only parameter in both patient groups that did not exhibit an improvement and was worsened in response to PTX, was LDH.

The paradoxical elevation of LDH levels following treatment, despite improvements in the seven other inflammatory and hepatic parameters, requires specific interpretation. LDH is a marker of cellular injury and hypoxia (13), and its sustained increase may reflect persistent tissue damage (pulmonary or muscular) or unresolved metabolic stress. In COVID-19, elevated LDH is a recognized indicator of disease severity, lung injury and multi-organ involvement (2). In the present cohort, it was suggested that while PTX effectively attenuated the systemic inflammatory response, as demonstrated by sharp declines in the levels of CRP, D-dimer and ferritin, it may not have fully resolved the underlying cellular injury within the 8-week study period. This may represent a component of post-COVID sequelae or indicate that tissue repair lags behind improvements in circulating biomarkers. Consequently, this finding indicates that the beneficial effects of PTX on systemic inflammation may be incomplete or may require more time to influence all markers of tissue stress. In relation to COVID-19, PTX has been consistently associated with amelioration of disease severity, ARDS, myocardial involvement and microvascular thrombosis due to its anti-inflammatory, immunomodulatory, hemorheological and antithrombotic properties (35). This suggests that the used treatment does not have an overall protective effect and/or that the studied parameters require different recovery times.

Another possibility is that these effects are rare side effects of the drug. Furthermore, no modification was noted in the

number of platelets in patients with cirrhosis. PTX acts at the molecular/cellular level (anti-inflammatory), but does not reverse underlying pathologies such as portal hypertension, which is responsible for hypersplenism, resulting in sequestration of up to 90% of platelets by the spleen (40) or decreases in their number (41). However, PTX did not increase the risk of bleeding suggesting that it may possess selective anti-inflammatory activity. PTX has been used with promising results in fulminant hepatitis (33), which is in agreement with the results reported in the present study. Furthermore, it has been shown to markedly improve sustained virological response to chronic hepatitis C virus infection (27), has been employed in combination with celecoxib in hepatocellular carcinoma (34) and has increased the life expectancy of patients with compensated hepatic cirrhosis (31).

Taking into account all the properties of PTX, it is possible that the results obtained in the present study are related to PTX-induced protection against liver injury and viral damage. This effect may be mainly due the inhibition of the NF-κB pathway, and the antioxidant and antifibrotic effects of PTX (20,21,31,42).

Notably, the present study has several fundamental limitations, including a relatively small sample size and a retrospective, uncontrolled design that involved patient follow-up without a control group, and the exclusion of the most critically ill patients, and thus lack of assessment of the effects of concomitant supportive therapies and the natural variation of the disease, all of which preclude potential causal attribution. Nevertheless, the marked contrast between the observed results and published epidemiological observations is striking and hypothetically consistent with a likely beneficial effect of PTX (4,8). While epidemiological data typically report high rates of disease progression and mortality in patients with underlying liver disease and COVID-19 (43,44), in the present study, PTX treatment was associated with improvements in seven of the eight parameters assessed at 8 weeks. Therefore, this marked discrepancy underscores the potential therapeutic promise of PTX in this context, and strongly justifies the initiation of prospective, randomized, controlled clinical trials with a comparative group without PTX, with the aim of definitively evaluating its efficacy and safety in patients with chronic liver disease and COVID-19 (38).

Furthermore, the treatment with PTX was well-tolerated without notable adverse reactions leading to treatment discontinuation. Notably, PTX has been used at this point in children with other pathologies, also without serious side effects, as well as in adults (45). Another advantage in addition to its optimal tolerance is its low cost.

In conclusion, PTX, a drug with >40 years of use, has demonstrated anti-inflammatory, antioxidant and antiviral properties (36). In the present study, its use in patients with chronic liver disease infected with SARS-CoV-2 was associated with an improvement in the majority of clinical and biochemical parameters, with optimal tolerance and a lack of notable adverse effects. Given its accessibility and low cost, multicenter, randomized studies are recommended to evaluate its effectiveness in larger populations, and to assess its molecular targets, such as signaling pathways and inflammatory cytokines. *In vitro* studies with hepatocytes are also recommended.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MAJL, AEJP, RFDH and MAJP conceptualized and designed the study, and reviewed the manuscript. ABH and MMVG developed the methodology for extracting and analyzing data. GHF, MMVG and ABH acquired data and wrote, reviewed and edited the manuscript. ABC used software, carried out data analysis and edited the manuscript. MAJL and ABC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Biomedical Research Ethics Committee of Dr. Valentín Gómez Farías General Hospital (Institute for Security and Social Services for State Workers, Zapopan, Mexico; approval nos. ISSSTE/CEI/816/2025 and RPI.HVGF.055.2025). Because of the retrospective nature of the study, the patient informed consent exemption was approved.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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