Original paper

Evaluation of the effects of the pandemic period on cirrhosis patients

Rezan Karaali[1], Ejder Saylav Bora[2], Firdevs Topal[3]

[1]Department of Emergency Medicine, Faculty of Medicine, Izmir Democracy University, Izmir, Turkey
[2]Department of Emergency Medicine, Izmir Ataturk Research and Training Hospital, Izmir, Turkey
[3]Department of Gastroenterology, Faculty of Medicine, Izmir Katip Çelebi University, Izmir, Turkey

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Address for correspondence: Ejder Saylav Bora MD, PhD, Department of Emergency Medicine, Izmir Ataturk Research and Training Hospital, Izmir, Turkey, e-mail: ejdersaylav@gmail.com

Abstract

Introduction: Cirrhosis is a common liver disease, which is characterized by life-limiting complications. In cirrhosis, liver ACE2 mRNA levels were 34-times upregulated, ACE2 protein 97-times upregulated, and ACE2 receptors increased in 80% of hepatocytes. Increased ACE2 receptor sensitizes hepatocytes to COVID-19.

Aim: To evaluate the applications of cirrhosis patients to the Emergency Department before and after the pandemic.

Material and methods: The study was conducted retrospectively in a single centre on cirrhotic patients who applied to the Emergency Department in a 2-year period. The obtained data were compared with the laboratory values of the patients: the severity of cirrhosis, the reasons for applying to the Emergency Department, hospitalization/discharge status, and pre-pandemic and pandemic period values. The mortality of the patients was recorded.

Results: The biochemical values, CTP score, and complications of cirrhosis patients deteriorated during the pandemic period, which contributed to the increase in mortality and that the CTP score and its complications worsened, which contributed to the increase in mortality. COVID-19 positivity contributes to the progression of the CTP score, but it is not directly associated with mortality.

Conclusions: We think that new treatment protocols should be included in the guidelines to minimize the effects of this type of viral infection on the liver.

Introduction

Cirrhosis is a common liver disease [1, 2] that is characterized by life-limiting complications such as variceal haemorrhage, ascites, hepatic encephalopathy, and hepatocellular carcinoma (HCC). It is known to be the cause of 2 million deaths per year around the world [1, 3].

Hepatocytes and cholangiocytes activate to repair the liver damage in cirrhosis patients, and during the repair, these cells increase their expression of ACE receptors. The ACE protein is detectable at low levels mostly in endothelial cells, rarely in bile duct cells, and seldom in centrilobular hepatocytes in healthy livers [4–6]. In the human cirrhotic liver, it has been observed that ACE2 mRNA levels and ACE2 protein are upregulated 34-fold and 97-fold, respectively, while ACE2 receptors increase in 80% of hepatocytes [6].

The ACE2 is the receptor to which SARS-CoV-2 binds to enter cells, and so an increased expression of ACE2 receptors can lead hepatocytes to become susceptible to COVID-19. The liver damage associated with COVID-19 may be partly due to direct injury to cholangiocytes, and impaired regeneration due to existing cirrhosis leads to impaired liver function. In cirrhosis, the immune system is suppressed and the coagulation system is impaired, and so cirrhosis is a high-risk comorbidity for severe COVID-19 [7–9].

Up to 62% of severe COVID-19 patients without liver disease have elevated transaminase levels, hypoalbuminaemia, and elevated γ-glutamyl transferase. In post-mortem cases, the endothelial dysfunction caused by SARS-CoV-2 and platelet-fibrin microthrombi due to

coagulopathy have been identified in hepatic sinusoids [6, 10].

Aim

The present study investigates the effects of both the pandemic and COVID-19 on cirrhosis patients through an assessment of the emergency admissions of cirrhosis patients before and after the pandemic.

Material and methods

This single-centre retrospective study was conducted in a tertiary, university-affiliated training and research hospital with a gastroenterology unit serving 24/7. Patients previously diagnosed with cirrhosis, those over the age of 18 years, those who were not pregnant, and those with no history of trauma and no symptoms were included in the study. Patients without emergency admission in either period (the pandemic and pre-pandemic periods), those with organ transplants, human immunodeficiency virus and unclear diagnoses of cirrhosis/COVID-19, and those with insufficient data were excluded from the study.

Cirrhosis patients who presented to the Emergency Department between 10 March 2019 (the date the first case of COVID-19 was reported in our country) and 31 December 2021 were searched using the ICD-10 code (K47) within the hospital automation system. Among the identified patients, those who presented to the Emergency Department in the pre-pandemic 2-year period (10 March 2017–10 March 2019) were included in the study.

The age and gender of the patients were recorded, along with pre-pandemic and post-pandemic laboratory findings, including white blood cell (WBC), neutrophil/lymphocyte ratio (NLR), haemoglobin (Hb), platelets (PLT), international normalized ratio (INR), glucose (GLU), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (BIL), albumin (ALB), and C-reactive protein (CRP) levels.

The cirrhosis classification of the patients was made based on the Child-Turcotte-Pugh (CTP) score using information obtained from the patient files. Accordingly, the score was calculated using the bilirubin, albumin, and INR levels in the blood samples recorded at the time of emergency admission, the presence of ascites detected on abdominal ultrasound, and the presence of clinically documented encephalopathy [11]. The CTP scores of the patients were calculated and recorded separately for the pre-pandemic and pandemic periods.

Cirrhosis-related complications before and during the pandemic were recorded, assessed as variceal haemorrhage, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy [12]. The reasons for the emergency admission, hospitalization status (intensive care unit/ward), and discharge status were recorded separately for the pre-pandemic and pandemic periods.

COVID-19 diagnoses were made based on the results of Real-Time Reverse Transcription Polymerase Chain Reaction tests (Biospeedy® RT-PCR test) of nasopharyngeal swab specimens, as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Fifth Version for Trial) [13]. Patients with 2 negative tests were considered negative. Based on the RT-PCR test results, the patients were divided into COVID-19-positive and COVID-19-negative groups. In those with COVID-19 pneumonia, the thoracic computed tomography (TCT) findings were assessed according to the Radiological Society of North America (RSNA) criteria [14], and patients reported as type 1 and type 2 were considered COVID-19 compatible (Group 1), while those reported as type 3 and type 4 were considered COVID-19 incompatible (Group 2).

The obtained data were compared with the laboratory values of the patients, the severity of cirrhosis, the reasons for emergency admission, hospitalization/discharge status, and the pre-pandemic and pandemic period values. Mortality among the patients was recorded. The impact of the pandemic and COVID-19 on these situations was evaluated.

Statistical analysis

The study data were assessed using IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp.). The frequency and percentage distributions were calculated for descriptive statistics, and mean, standard deviation, and minimum and maximum values for continuous variables. The normality of continuous variables was analysed with Kolmogorov-Smirnov and Shapiro-Wilk ($p < 0.05$) tests, steering the decision to use either parametric or non-parametric tests.

χ^2 test statistics were used to compare categorical variables between groups, while Mann-Whitney *U* statistical analyses were used for comparisons between the 2 groups due to the non-normal distribution of the continuous data.

A Binary Logistic Regression model was used to examine the effect of the variables on cirrhosis, i.e. the cause-effect relationship between the dependent variable and independent variables.

Results

A total of 161 patients diagnosed with cirrhosis were admitted to our Emergency Department between the specified dates, among which 78 who presented to

the Emergency Department in both the pre-pandemic and pandemic periods, who had sufficient data in their files, and who met the study criteria, were included in the study. Of these patients, 48 (61.5%) were male, and the mean age was 62.24 years – 63.52 years in male patients and 62.33 years in female patients.

A statistically significant difference was noted in the NLR, AST, BIL, ALB, CRP, and INR values in the laboratory data of the patients at the time of emergency admission between the pre-pandemic and pandemic periods. The reasons for the emergency admission of the patients in the pre-pandemic and pandemic periods, complications due to cirrhosis, and the classification of cirrhosis according to CTP are presented in Table I.

The admission data of the non-surviving and surviving patients in the pandemic period were compared, revealing a statistically significant difference in NLR, Hb, GLU, AST, ALT, BIL, ALB, and INR levels from the laboratory findings between non-surviving and surviving patients. Encephalitis and liver failure, as complications of cirrhosis that developed in the post-pandemic period, were significantly associated with mortality. The thoracic CT findings of COVID-19-compatible pneumonia, PCR positivity, and the CTP score calculated at the time of admission in the pandemic period were also associated with mortality (Table II).

The status of CTP scores in the pre-pandemic and pandemic periods and the relationship with COVID-19 positivity were evaluated and are presented in Table III. Accordingly, 30 of 42 patients who were CTP class A in the pre-pandemic period were COVID-19 positive in the pandemic period. Of these patients, the CTP class progressed to Class B in 33% and to Class C in 19%.

Table I. Laboratory and anamnesis information before and after the pandemic

Variables	Before the pandemic (*n* = 78)	After the pandemic (*n* = 78)	*P*-value
Data, mean ± standard deviation (min.–max.):			
WBC	7.64 ±3.78 (1.57–15.87)	8.61 ±4.31 (1.18–19.85)	0.14
NLR	5.34 ±3.74 (0.61–15.74)	8.37 ±5.28 (1–20)	< 0.001
Hb	10.15 ±2.25 (4.9–15.1)	10.17 ±2.66 (5.1–15.3)	0.87
PLT	161.36 ±77.38 (37–361)	145.74 ±83.85 (20–376)	0.16
GLU	159.13 ±86.51 (77–529)	148.87 ±70.82 (82–415)	0.47
AST	44.59 ±36.39 (16–182)	91.28 ±161.68 (14–913)	0.05
ALT	35.03 ±47.59 (10–300)	63.47 ±158.65 (6–985)	0.57
BİL	2.6 ±3.58 (0.12–18.67)	5.85 ±8.86 (0.3–38.92)	0.01
ALB	30.69 ±4.73 (22–42)	28.44 ±5.92 (17–42)	< 0.001
CRP	24.92 ±36.55 (0.3–163.28)	51.19 ±54.86 (0.46–290)	< 0.001
INR	1.29 ±0.25 (0.93–1.93)	1.55 ±0.56 (0.93–4.08)	< 0.001
Complaint, *N* (%):			
Dyspnoea	10 (12.8)	14 (18)	< 0.001
GIS bleeding	14 (17.90)	36 (46.2)	
Abdominal pain	40 (51.4)	8 (10.30)	
Icterus	8 (10.3)	2 (2.6)	
SBP	6 (7.7)	2(2.6)	
Coma	0 (0)	16 (20.7)	
Complications, *N* (%):			
Pleural effusion	14 (17.90)	14 (17.90)	0.593
Ascites	28 (35.90)	28 (35.90)	0.63
Varices	18 (23.10)	36 (46.2)	0.04
PVT	12 (15.40)	8 (10.30)	< 0.001
SBP	6 (7.70)	28 (35.90)	< 0.001
Encephalopaty	4 (5.10)	22 (28.20)	< 0.001
Liver failure	2 (2.60)	12 (15.40)	< 0.001

PVT – portal vein thrombosis, GIS – gastrointestinal system, SBP – spontaneous bacterial peritonitis.

Furthermore, 22 of the 36 patients who were Class B in the pre-pandemic period were COVID-19 positive in the pandemic period. Of the CTP Class B patients in the pre-pandemic period, 28% progressed to Class C after COVID-19 positivity. The CTP score fell into a higher group in 15.3% of the patients in the pandemic period, despite COVID-19 negativity.

An examination of the effects of the presence of COVID-19-compatible pneumonia on the mortality of patients and the severity of cirrhosis revealed that 36.4% of patients with TCT findings of COVID-19-compatible pneumonia died, while the mortality rate was 14.3% in patients without TCT findings of COVID-19-compatible pneumonia. There was a statistical difference in the presence of COVID-19-compatible pneumonia on TCT between the non-surviving and surviving patients ($p < 0.05$). While 54.5% of the patients with TCT findings of COVID-19-compatible pneumonia were CTP Class C, 50% of those without TCT findings of COVID-19-compatible pneumonia were CTP Class B.

Table II. Pandemic period comparison between deceased and living patients

Variables		Alive	Ex	*P*-value
Complications, *n* (%):				
After the pandemic	Pleural effusion	11 (78.6)	3 (21.4)	0.073
	ASCİT	24 (85.7)	4 (14.3)	0.523
	VARİS	32 (88.9)	4 (11.1)	0.131
	PVT	6 (75.0)	2 (25.0)	0.901
	SBP	20 (71.4)	8 (28.6)	0.245
	Encephalopathy	10 (44.6)	12 (54.4)	< 0.001
	Liver failure	4 (33.3)	8 (66.6)	0.02
COVID BT	Covid compatible	14 (63.3)	8 (36.6)	0.030
	No signs of COVID	48 (96.0)	8 (4.0)	
COVID PCR	Positive	38 (73.0)	14 (27.0)	0.047
	Negative	24 (92.3)	2 (7.7)	
Post-pandemic CTP classification	A	16 (100)	0 (0)	0.001
	B	30 (88.2)	4 (11.8)	
	C	16 (57.1)	12 (48.9)	
Gender	Woman	26 (85)	4 (15)	0.26
	Man	36 (81)	12 (19)	
Data, mean ± standard deviation:				
Age	Woman	65.23 ±16.94 (30–93)	63.83 ±20.05 (31–88)	0.646
	Man	63.41 ±16.94 (40–86)	66.00 ±10.39 (57–75)	
	General	64.2 ±15.4 (30–93)	64.38 ±17.8 (31–88)	
WBC		8.28 ±4.44 (19.85–1.18)	9.88 ±3.89 (5.08–16.85)	0.166
NLR		7.41 ±5 (1–18.89)	12.07 ±5.14 (5.2–20)	0.003
Hb		9.68 ±2.71 (5.1–13.9)	12.05 ±1.48 (10.2–15.3)	0.002
PLT		148.97 ±79.67 (20–300)	133.25 ±106.03 (20–376)	0.322
GLU		155.55 ±75.95 (82–415)	123 ±43.56 (86–215)	0.075
AST		58.1 ±63.57 (14–276)	219.88 ±320.44 (30–913)	0.002
ALT		36.76 ±52.21 (6–295)	167 ±333.68 (17–985)	0.004
BİL		4.79 ±8.42 (0.3–38.92)	9.94 ±10.16 (1.68–30.46)	0.001
ALB		29.9 ±5.76 (17–42)	22.75 ±1.98 (21–26)	0
CRP		49.51 ±59.19 (0.46–290)	57.73 ±38.43 (13.3–126.59)	0.119
INR		1.43 ±0.32 (1.07–2.46)	2 ±1.01 (0.93–4.08)	0.026

PVT – portal vein thrombosis, GIS – gastrointestinal system, SBP – spontaneous bacterial peritonitis.

Table III. The status of CTP scores in the pre-pandemic and pandemic periods and the relationship with COVID-19 positivity

Variable	CTP Classification of Post-Pandemic Cirrhosis							
	Class	PCR positive			PCR negative			Grand total
		A	B	C	A	B	C	
		Count (%)	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)
CTP Classification of Pre-Pandemic Cirrhosis	A	8 (19)	14 (33)	8 (19)	8 (19)	2 (19)	2 (5)	42 (100)
	B	0 (0)	12 (33)	10 (28)	0 (0)	6 (17)	8 (22)	36 (100)
Total		8 (10.3)	26 (33.3)	18 (23.1)	8 (10.3)	8 (10.3)	10 (12.8)	78 (100)

CTP – Child-Turcotte-Pugh score.

Table IV. Evaluation of effects of the presence of COVID-19-compatible pneumonia on the mortality of patients and the severity of cirrhosis

Variable		Thoracic CT				*P*-value
		COVID-19 compatible		COVID-19 non-compatible		
		Count	Column *N* %	Count	Row *N* %	
Mortality	Live	14	63.6	48	85.7	0.03
	Deceased	8	36.4	8	14.3	
Pre-pandemic CTP classification	A	16	72.7	26	46.4	0.04
	B	6	27.3	30	53.6	
Post-pandemic CTP classification	A	4	18.2	12	21.4	0.03
	B	6	27.3	28	50.0	
	C	12	54.5	16	28.6	

There was a statistical difference in the presence of COVID-19-compatible pneumonia on TCT between the CTO scores for cirrhosis ($p < 0.05$) (Table IV).

Discussion

Since the identification of the first case of COVID-19, the disease has been a matter of concern for the entire healthcare community, with many unknown factors. Previous studies have mostly focused on lung involvement, given the direct association with mortality, while there remains a lack of data on the damage inflicted on other organs. Hepatocyte involvement in COVID-19 via the ACE2 receptor has been overlooked, especially in patients with known liver failure [15]. Cirrhosis is a disease that causes severe liver damage and is a risk factor for COVID-19, and the COVID-19 positivity rate of 66.7% among our study patients can be considered an indicator of the susceptibility of cirrhosis patients to the disease. Our hospital is the only healthcare facility in the region with a gastroenterology unit providing 24/7 care, and so cirrhosis patients requiring immediate medical attention are regularly referred to our Emergency Department, while more stable patients are treated in the hospitals to which they present. We believe that the high rate can be attributed also to the treatment of patients with cirrhosis and diagnosed with COVID-19 in our hospital.

Because the CTP score used to assess the severity of cirrhosis is calculated based on few parameters and is easily obtainable in emergency department conditions, we used this score in our study to assess cirrhosis severity [11]. We found that the CTP score progressed to a higher level in 42% of the patients in the pandemic period. While there were no CTP-C patients in the pre-pandemic period, CTP-C patients in the pandemic period accounted for 23.1% of the COVID-19-positive and 12.8% of the COVID-19-negative patients. Both the COVID-19 positivity and the pandemic period led to the progression of the disease, although the progression of the disease in PCR-negative patients may have been a result of the expected natural course of cirrhosis due to the prolonged period of our study. We attributed the higher rate of progression to CTP-C in PCR-positive patients than in PCR-negative patients to the effect of COVID-19. Similar to our findings, in their study comparing COVID-19-positive and -negative patients, An *et al.* reported higher CTP scores in COVID-19-positive cirrhosis patients than in COVID-19-negative cirrhosis patients [9]. The multicentre study by Qi *et al.*, in turn, evaluated 21 patients who were previously diagnosed with cirrhosis and positive

for COVID-19, and identified 16 patients as CTP-A, 3 patients as CTP-B, and 2 patients as CTP-C after identifying COVID-19 positivity [16]. Similarly to our study, Iavarone *et al.* examined COVID-19-positive patients with a previous diagnosis of cirrhosis and reported that patients who were Class A and B before the pandemic progressed to Class C, and that the number of Class C patients increased with COVID-19 positivity [17]. Unlike in the present study, in which we assessed the changes in the CTP score from the patient scores from before the pandemic, the 3 studies above provided no information about the CTP classification of patients before COVID-19 positivity. By including patient data from both the pre-pandemic and pandemic periods, the effects of COVID-19 on the severity of cirrhosis were more clearly revealed than in previous studies.

In addition to these findings, we found that 54.5% of the patients with TCT findings of COVID-19-compatible pneumonia were CTP Class C, while 50% of the patients without TCT findings of COVID-19-compatible pneumonia were CTP Class B. The most common symptoms in the patients presenting to the Emergency Department in the pandemic period were oesophageal variceal oesophageal variceal hemorrhage, clouding of consciousness, and dyspnoea. We believe that hypoxia induced by respiratory distress secondary to pneumonia caused by COVID-19, increased breathing effort, and increased cytokine storm in response to pulmonary involvement led to multiple organ dysfunction, including the liver. In conclusion, it can be suggested that COVID-19 and COVID-19 pneumonia contribute to the increased severity of cirrhosis.

Another factor contributing to the increased severity of cirrhosis was the increased incidence of complications in our patients in the pandemic period. Our findings showed that the severity of disease in patients who were hepatically compensated before the pandemic increased in the pandemic period, which may be attributed to the higher incidence of encephalopathy – one of the parameters in CTP scoring – and liver failure in the pandemic period. The increase in the incidence of encephalopathy may be attributed to the liver damage caused directly by SARS-CoV-2, as well as multiple organ dysfunction through respiratory distress, hypoxia, and cytokine storm. Considering the fact that our study patients most frequently presented to the Emergency Department with oesophageal variceal hemorrhage, clouding of consciousness, and dyspnea in the pandemic period, we believe COVID-19 to be involved also in the increased severity of cirrhosis.

Similar to our findings, Iavarone *et al.* reported an increased rate of encephalopathy in cirrhosis patients after COVID-19 positivity [17]. After evaluating admissions of cirrhosis patients in the pre-pandemic and pandemic periods, Gaspar *et al.* reported encephalopathy (55%) to be the most common reason for admission during the pandemic [18]. Assessing encephalopathy and other complications related to cirrhosis, Jeon *et al.* reported a severe complication rate of 26.9% in COVID-19-positive patients with cirrhosis, and 16.3% in COVID-19-negative patients with cirrhosis. In their study comparing patients with cirrhosis before the pandemic and those with cirrhosis who were positive for COVID-19 during the pandemic, Shalimar *et al.* reported that cirrhosis-related complications occurred in 12 (46.2%) and respiratory complications in 3 (11.5%) of the patients with COVID-19 and cirrhosis [15]. Considering the overall complications, we found oesophageal variceal haemorrhage, SBP, encephalopathy, and acute liver failure to be more common in our patients in the pandemic period. It is likely that complications increased during the pandemic because cirrhosis patients were unable to attend their routine follow-up visits and presented to the Emergency Department only when their disease progressed or when conditions such as bleeding, clouding of consciousness, or shortness of breath developed. Reporting findings in support of our hypothesis, An *et al.* suggested that COVID-19-positive cirrhosis patients were better able to access healthcare than COVID-19-negative patients, who did not present to hospital unless they there was a worsening in their condition, resulting in more complications [9].

Unlike these studies, the present study assessed complications in terms of their presence in the pre-pandemic and pandemic periods, and we did not differentiate between patients who were COVID-19 negative and positive. We found that complications with an increased incidence in the pandemic period were also influential on mortality. The presence of encephalopathy and liver failure was statistically different between the non-surviving and surviving patients. Similar to our findings, Iavarone *et al.* reported that 34% of patients with cirrhosis and COVID-19 died, with deaths attributable to liver failure (25%) and respiratory failure (12%) [17]. In a similar study, Qi *et al.* reported that 5 of 21 patients with cirrhosis and COVID-19 died, with the deaths being mostly due to respiratory failure [16]. Low lymphocyte and platelet counts, ARDS, and gastrointestinal bleeding were identified as factors influencing mortality. Bajaj *et al.* reported a mortality rate in COVID-19-positive patients with cirrhosis of 40%, with mortality occurring due to liver failure resulting from respiratory failure [19]. Similar to these studies, we found a high mortality rate in COVID-19-positive patients, and as mentioned in the above studies, we also found that the presence of COVID-19-compatible pneumonia identified on TCT increased mortality. We can thus conclude that the increase in complications and CTP

score in COVID-19-positive patients in the pandemic period also contributed to the increased mortality.

Another parameter that we identified as contributing to mortality was the laboratory findings of the patients, with NLR, HB, GLU, AST, ALT, BIL, ALB, and INR values all playing a role. Similar to our findings, Citu *et al.* and Mao *et al.* found that changes in the blood biochemistry in the presence of cirrhosis and COVID-19 affected mortality [20, 21]. Citu *et al.* reported that NLR, in particular, served as a marker of the severity of the inflammatory response and was associated with mortality [20]. Mao *et al.* reported a decrease in lymphocyte and platelet percentages and an increase in CRP, D-dimer, AST, and ALT to be indicators of progression in COVID-19 [21].

Conclusions

As in all patients with chronic diseases, there were failures and interruptions in the follow-up and treatment of cirrhosis patients during the pandemic. Our study found that the biochemical values, CTP score, and complications of cirrhosis patients deteriorated during the pandemic, which contributed to the increase in mortality. It was further noted that PCR positivity and the presence of COVID-19-compatible pneumonia increased the mortality and disease severity in those with cirrhosis, and led to a worsening of biochemical values, CTP score, and complications, all of which contributed to an increase in mortality in the pandemic period. Considering that the state of cirrhosis patients without COVID-19 may also deteriorate, we believe that new treatment protocols should be included in the guidelines to avoid interruptions to the follow-up and treatment of cirrhosis patients, and to minimize the effect of this type of viral infection on the liver. Further studies and case series will clarify the issue.

Conflict of interest

The authors declare no conflict of interest.

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