

Influence of COVID-19 on Patients with Esophageal Varices under Prophylactic Endoscopic Band Ligation Therapy

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Keywords

COVID-19 · Endoscopic band ligation · Liver cirrhosis · Variceal eradication

Abstract

Background and Objectives: Endoscopic band ligation (EBL) plays a critical role in patients with clinically significant portal hypertension, as variceal eradication (VE) is essential to prevent further variceal upper gastrointestinal bleeding (GI). The emergence of COVID-19 has led to a dramatic reduction in endoscopic activity. Our study aimed to evaluate the effect of COVID-19 on VE, GI, and 6-month mortality of patients treated with prophylactic EBL therapy. In addition, our goal was to identify the risk factors for our proposed outcomes. **Methods:** A single-center retrospective cohort study included patients with esophageal varices treated with prophylactic EBL therapy between 2017 and 2021. To demonstrate the impact of COVID-19 on two independent groups on prophylactic EBL therapy with 1 year of follow-up, March 2019 was selected as the cut-off date. Clinical, laboratory, and endoscopic data were recovered from electronic reports. **Results:** Ninety-seven patients underwent 398 prophylactic EBL sessions, 75 men (77.3%) with mean age 59 ± 12 years. Most achieved VE (60.8%), 14.4% had GI bleeding

post-therapy, and 15.5% died at 6 months. The rate of variceal obliteration was significantly lower in the pandemic group (40.9% vs. 77.4% in the pre-pandemic group, $p = 0.001$). Mean number of EBL sessions and pandemic group were independently associated with incomplete VE, while MELD-Na, portal vein thrombosis and failed VE were identified as risk factors associated with mortality at 6 months. **Conclusions:** Almost 60% of patients in the pandemic group failed to eradicate esophageal varices. Failure to achieve this result conferred a higher risk of GI bleeding and death at 6 months, the latter also significantly associated with the MELD-Na score and portal vein thrombosis. Our study is among the first to demonstrate the impact of COVID-19 in patients receiving prophylactic EBL therapy.

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Influência da COVID-19 nos doentes com varizes esofágicas submetidos a laqueação elástica profilática

Palavras Chave

Cirrose hepática · COVID-19 · Erradicação de varizes esofágicas · Laqueação elástica endoscópica

Resumo

Introdução e objetivos: A laqueação elástica endoscópica (LEE) é crucial nos doentes com hipertensão portal clinicamente significativa, uma vez que permite a erradicação das varizes esofágicas (EVE) que, por sua vez, previne a hemorragia digestiva varicosa. Com o início da pandemia COVID-19, a atividade endoscópica foi drasticamente reduzida. Com este estudo pretendemos avaliar a influência da COVID-19 na EVE, hemorragia gastrointestinal (GI) e mortalidade aos 6 meses dos doentes sob LEE profilática, assim como identificar os seus fatores de risco. **Métodos:** Estudo de coorte monocêntrico e retrospectivo que incluiu doentes com varizes esofágicas sob LEE profilática entre 2017 e 2021. Para demonstrar o impacto da pandemia COVID-19 em dois grupos independentes sob LEE profilática durante um ano de follow-up, a escolha da data-limite foi Março de 2019. Os dados clínicos, laboratoriais e endoscópicos foram obtidos a partir dos relatórios eletrónicos. **Resultados:** Noventa e sete doentes cumpriram 398 sessões de LEE, 75 homens (77,3%), com idade média de 59 ± 12 anos. A maioria dos doentes obteve EVE (60,8%), 14,4% desenvolveu hemorragia GI e 15,5% faleceu nos primeiros 6 meses pós-terapêutica. A taxa de EVE foi significativamente inferior no grupo pandémico (40,9% vs. 77,4% no grupo pré-pandémico, $p = 0.001$). O número médio de sessões de LEE e o grupo pandémico foram independentemente associados à EVE incompleta; enquanto MELD-NA, trombose da veia porta e falha na EVE foram identificados como fatores de risco associados à mortalidade aos 6 meses. **Conclusão:** Cerca de 60% dos doentes no grupo pandémico não conseguiu erradicar as varizes esofágicas. A EVE incompleta aumenta o risco de hemorragia GI e mortalidade aos 6 meses, esta última também associada de forma significativa ao score MELD-Na e TVP. O nosso estudo foi pioneiro na demonstração do impacto da pandemia COVID-19 nos doentes sob LEE profilática.

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Introduction

Patients with compensated cirrhosis or compensated advanced chronic liver disease and clinically significant portal hypertension have guided diagnostic and therapeutic orientations in variceal bleeding prophylaxis, as they are at increased risk of decompensation. Accordingly, nonselective beta-blocker (NSBB) treatment should

be considered in primary prophylaxis, preferably carvedilol, as it is more effective in decreasing the hepatic venous pressure gradient and improves survival. Child-Pugh C patients or patients with high-risk varices (large varices [≥ 5 mm]) or signs of red spots, who have intolerance or contraindications to NSBB, should undergo endoscopic band ligation (EBL) to prevent first variceal bleeding [1].

Regarding the prevention of recurrent variceal bleeding (secondary prophylaxis), first-line therapy is the combination of NSBBs and EBL. In patients without access or who cannot tolerate NSBBs or EBL, any of these therapies can be maintained alone [1–3]. A recent individual patient meta-analysis has shown that pharmacological therapy with NSBB is the most important part of combination therapy and should be used as monotherapy in patients who are unable or unwilling to be treated with EBL [4]. EBL is performed every 3–4 weeks until eradication is achieved. Varices are eradicated usually after a mean of 2–3 sessions, but there is high variability ranging from 1 to more than 10 sessions [2]. The American Association for the Study of Liver Disease recommends esophagogastroduodenoscopy (EGD) 3–6 months after eradication and every 6–12 months thereafter. Variceal recurrence occurs frequently, with 20–75% of patients requiring repeated EBL sessions [5].

Taking into account the importance of variceal eradication (VE) as a preventive measure for further decompensation in cirrhosis, the emergence of COVID-19 as a global pandemic in March 2020 led to the cessation of endoscopic activity and liver cancer management throughout the world [6–9]. Most guidelines during the pandemic recommended the decision to perform EBL therapy on a case-by-case basis [10]. Our department delayed EBL therapy during 3 months after lockdown. The restart of endoscopic activity required negative polymerase chain reaction test 72 h before procedure. All this led to endoscopic activity reduction from 4,725 gastroscopies in 2018 to 2,651 procedures in 2020. In United Kingdom, COVID-19 pandemic reflected in a 58% reduction in missing cancer cases per week, ranging from 19% (biliopancreatic) to 72% (colorectal) [9]. An European multinational cross-sectional survey of patients with neoplastic GI lesions and feasible endoscopic resection revealed that in 2020, 55% of scheduled procedures were postponed, with 3% of cases requiring surgery [8]. Concerning liver cancer, an international survey from March to June 2020 showed that 87% of the centers modified their clinical practice, 80.9% in the screening program, 50% cancelled curative and/or palliative treatments, and 41.7% modified the liver transplantation program [6]. Our study aimed to evaluate the effect of COVID-19 on the outcomes of

patients with esophageal varices under prophylactic EBL therapy in a tertiary hospital, namely VE and bleeding after the first EBL therapy during a year of follow-up, and death at 6 months after the last session.

Materials and Methods

Study Design and Patient Selection

We conducted a single-center retrospective cohort study between 2017 and 2021. All patients with esophageal varices under primary or secondary prophylactic EBL therapy were consecutively included based on the endoscopic reports extracted from our data between March 2018 and March 2021. However, in case patients started EBL therapy before March 2018, the total number of EBL sessions was recorded since the first procedure, with some of them having started in 2017. In order to demonstrate the impact of COVID-19 on two independent groups on prophylactic EBL therapy with 1 year of follow-up, March 2019 was selected as the cut-off date. The exclusion criteria were previous placement of a transjugular intrahepatic portosystemic shunt, liver transplantation, and patients with acute variceal gastric bleeding.

Definitions

EBL therapy was performed under sedation using Multiband Ligator[®] (Wilson-Cook Medical), starting with the first band from the gastroesophageal junction. The mean number of ligation bands applied per session was six. In our institution, EBL session was performed each 4 weeks, until the varices were obliterated at the discretion of the endoscopist. Prophylactic EBL was defined as therapy for prophylaxis of variceal bleeding in patients without active bleeding at the time of EGD. Primary prophylaxis referred to the prevention of the first variceal bleed, while secondary referred to the prevention of its recurrence. The medium-large varices were defined as not collapsing with insufflation at EGD, in contrast to the small ones [3]. The diagnosis of portal hypertensive gastropathy (PHG) was made endoscopically by showing a snake-skin mosaic pattern (mild subtype), which could have superimposed red signs (severe PHG), usually located in the proximal stomach (fundus and body) [2].

Liver cirrhosis was defined based on the diagnosis of electronic reports, laboratory and radiological findings, liver transient elastography values, and histological reports, if available. Portal vein thrombosis (PVT) was diagnosed based on computed tomography scanning and/or magnetic resonance.

Etiological factor suppression was defined as the elimination of liver cirrhosis cause at least 1 year before the first EBL session, such as alcohol abstinence, sustained virological response in HCV, or undetectable viral load in HBV. Post-EBL bleeding was defined according to EGD reports as bleeding related to gastroesophageal varices or ligation ulcers, or even as blood detected in the upper GI tract without other evident cause.

Demographic, Clinical, and Endoscopic Variables

The characteristics of the patients, the relevant medical history, the laboratory data, and the date of death were recovered from the electronic reports. Endoscopic data: indication; type of varices; presence of PHG; total number of EBL sessions per patient as its first and last registered date; endoscopic report of VE achievement and bleeding after EBL therapy. National electronic health records

were assessed to detect EBL therapy in other institutions and all post-EBL bleeding admissions. The access was restricted in case patients deceased in other institution.

Outcomes

Our primary endpoint was to compare the two groups (pre-pandemic and pandemic) regarding the outcomes defined as VE and bleeding after the first EBL therapy during 1 year of follow-up, and death at 6 months after the last session. In case patient lost follow-up and VE was unknown, we assumed as incomplete VE for our outcomes. Our secondary objectives were to evaluate the influence of other variables on our results, including sex, age, eradication of cirrhosis etiology, liver reserve defined by Child-Pugh classification and MELD-Na score, hepatocellular carcinoma, PVT, as well as the role of INR, platelets, use of anticoagulants, periprocedural proton pump inhibitors (PPIs), and NSBB on GI bleeding after EBL therapy.

Data and Statistical Analysis

Continuous variables were reported as mean \pm standard deviation or median \pm range, according to their distribution. Categorical variables were reported as absolute and relative frequencies. Continuous variables were compared between 2 groups using Student's *t* test if normal variance distribution and homogeneity were verified, or Mann-Whitney U test in the absence of these conditions. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Univariate and multivariate analysis using a logistic regression model was performed to determine factors associated with our defined outcomes. Covariates with a *p* value <0.1 in the univariate analysis were included in the multivariate analysis. All hypotheses were 2-tailed and a *p* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v27 (SPSS Inc., Chicago, IL, USA).

Results

We included 97 patients with 398 prophylactic EBL sessions, 75 men (77.3%) with mean age 59 ± 12 years. Cirrhosis was the predominant cause of portal hypertension in 85 cases (87.6%), with alcohol and virus as the main etiologies (76.5%). Etiology eradication was observed in 54 of 78 cases (55.7%). The majority were Child-Pugh A (63.9%) with a median MELD-Na score of 11 (9.0–14.0). Twenty-two patients presented PVT (22.7%) and 9 hepatocellular carcinoma (9.3%). Regarding their medication, most were using periprocedural PPI (68.0%) and NSBB (63.9%): carvedilol (43.3%) and propranolol (20.6%). Fourteen patients (14.4%) were on anticoagulation: warfarin 7.2%, direct oral anticoagulants (DOACs) 4.1%, and enoxaparin 3.1%. Only a minority were on antiplatelet therapy (4.1%). The median results of the laboratory tests were INR 1.2 (1.1–1.4), platelets $85.0 \times 10^9/L$ (58.5–138.5), and bilirubin 0.9 mg/dL (0.7–1.7).

Regarding the total number of 389 prophylactic EBL sessions in 97 patients, most of them underwent EBL as a secondary prophylaxis (68.0%). At the first session of EBL,

almost all esophageal varices were medium-large, with only 3.1% small varices with red signs. Additionally, PHG was present in 87.6% of the cases, 47.4% mild and 40.2% severe. The mean EBL sessions per patient were 4.1 ± 2.0 . Considering our results, most patients managed to eradicate esophageal varices (60.8%), 20.6% lost follow-up, and 18.6% did not eradicate it. Fourteen patients (14.4%) had GI bleeding after EBL therapy. We observed 15 cases (15.5%) of death at 6 months after the last session, with 5 cases occurring at 6-week mortality.

Taking into account our main endpoint (Table 1), 53 patients underwent 223 sessions (56%) in the pre-pandemic group and 44 underwent 175 (44%) in the latter, with no statistical significance in the mean number of sessions between them ($p = 0.577$). VE was the only outcome with significant difference between the two groups ($p = 0.001$). In fact, 40.9% of the pandemic group reached variceal obliteration, in contrast to the pre-pandemic, whose patients were almost double (77.4%) (Fig. 1).

Regarding our secondary objectives, the variables associated with incomplete VE (Table 2) in univariate analysis were PVT, EBL therapy as secondary prophylaxis, mean number of EBL sessions and pandemic group. In multivariate analysis, the last two remained independently associated with incomplete variceal obliteration: EBL sessions (odds ratio [OR] 0.8; 95% confidence interval [CI] 0.6–0.9) and pandemic group (OR: 4.9; 95% CI: 1.8–13.2). Mean number of EBL sessions and incomplete VE were associated with bleeding after EBL therapy (Table 3) in univariate analysis. However, male gender (OR: 5.0; 95% CI: 1.2–21.3), EBL sessions (OR: 1.4; 95% CI: 1.1–2.0), and incomplete VE (OR: 4.9; 95% CI: 1.1–21.4) were independently associated in multivariate analysis. There was no statistically significant association of peri-interventional use of PPIs, NSBBs, anticoagulants, and coagulation test results with bleeding incidence after EBL. Univariate analysis found that Child-Pugh B/C, MELD-Na score, PVT, and incomplete VE were associated with 6-month mortality (Table 4). After multivariate adjustment, the association remained significant with all except Child-Pugh B/C: MELD-Na (OR: 1.3; 95% CI: 1.1–1.6); PVT (OR: 10.5; 95% CI: 1.4–79.4); and incomplete VE (OR: 23.4; 95% CI: 2.6–211.9).

Discussion

Our study showed that our pre-pandemic group achieved VE in almost 80% of cases, consistent with published data rates between 58% and 100% [11].

However, the pandemic COVID-19 reduced the total number of EBL prophylactic sessions by 12 percentage points, therefore variceal obliteration was significantly affected. Almost 60% of the patients lost follow-up or did not eradicate the varices, in particular the secondary prophylaxis group, where EBL plays a crucial role in combination with NSBB in preventing recurrent GI bleeding [4]. Several meta-analyses have demonstrated that combination therapy (EBL and NSBB) is significantly more effective than either alone in preventing a new episode of GI hemorrhage, although pharmacological therapy with NSBB is the fundamental part [1, 12]. Regarding the complication rates of GI bleeding after EBL therapy and mortality at 6 months, there were no significant differences between the two groups ($p = 0.760$ and $p = 0.500$, respectively).

Incomplete VE was associated with PVT, secondary prophylaxis indication, mean number of EBL sessions, and pandemic group. In multivariate analysis, only the last two remained independently associated. There is little evidence on risk factors for incomplete variceal obliteration, with the majority focusing on bleeding and death complications. A plausible explanation for the association between the identified variables (except the pandemic group) and incomplete VE is the continued increase in portal hypertension by PVT, which was not measured by splenic elastography, nor invasively. A retrospective Italian study evaluated the role of PVT in EBL efficacy, concluding that it is a predictor of longer time to achieve VE, with no difference in eradication rates or in median sessions of EBL between cirrhotic patients with or without PVT [13].

The bleeding rate after EBL therapy was 14.4% at 1 year of follow-up, consistent with the results of several studies [11, 12, 14], where the mean rates were 9% (0–25%) for primary prophylaxis and 14% (6–26%) for secondary prophylaxis, partly explained by the significant heterogeneity regarding variceal treatment, definitions of recurrent bleeding, follow-up time, and presence of risk factors [11]. As such, several causes have been associated with the occurrence of variceal bleeding, including the severity of portal hypertension, poor liver reserve, variceal sizes, endoscopic treatment modality of acute bleeding, infection, and PVT [15, 16]. In our study, the mean number of EBL sessions and incomplete VE were associated with bleeding complication in the univariate analysis. However, in multivariate analysis, besides these two variables, male gender was also independently associated to the outcome (OR: 5.0; 95% CI: 1.2–21.3). EBL sessions (OR: 1.4; 95% CI: 1.1–2.0) and incomplete VE (OR: 4.9; 95% CI:

Table 1. Patients characterization

Variables	Pre-pandemic (n = 53)	Pandemic (n = 44)	p value
Sex male (%)	39 (73.6)	36 (81.8)	0.466
Age, years	57.3±12.6	61.9±11.8	0.068
Cirrhosis (%)	47 (88.7)	38 (86.4)	0.765
Child-Pugh A	37 (69.8)	25 (56.8)	
Child-Pugh B	8 (15.1)	10 (22.7)	0.404
Child-Pugh C	2 (3.8)	3 (6.8)	
Etiology (%)			
Alcohol	19 (40.4)	21 (55.3)	0.054
Viral	10 (21.3)	5 (13.2)	
Alcohol + viral	6 (12.8)	4 (10.5)	
Other	12 (25.5)	8 (21.1)	
Etiology eradication (%)	31/43 (72.1)	23/35 (65.7)	0.544
Portal vein thrombosis (%)	9 (17.0)	13 (29.5)	0.141
HCC (%)	7 (13.2)	2 (4.5)	0.143
NSBBs (%)	32 (60.4)	30 (69.8)	0.339
MELD-Na score, median (IQR)	11.0 (8.8–14.0)	11.0 (9.00–14.0)	0.966
Platelets 10 ⁹ /L, median (IQR)	96.0 (60.0–150.0)	74.5 (55.8–128.0)	0.264
INR, median (IQR)	1.2 (1.1–1.4)	1.3 (1.1–1.4)	0.377
Primary prophylaxis (%)	21 (39.6)	10 (22.7)	0.076
Secondary prophylaxis (%)	32 (60.4)	34 (77.3)	0.076
Total EBL sessions (%)	223 (56)	175 (44)	0.577
Mean EBL sessions	4.2±1.7	4.0±2.3	
Variceal eradication (%)	41 (77.4)	18 (40.9)	0.001
GI bleeding (%)	7 (13.2)	7 (15.9)	0.706
6-month mortality (%)	7 (13.2)	8 (18.2)	0.500

HCC, hepatocellular carcinoma; NSBBs, nonselective β -blockers; MELD, model of end-stage liver disease; IQR, interquartile range; INR, international normalized ratio; EBL, endoscopic band ligation; GI, gastrointestinal.

1.1–21.4) might be related to more severe portal hypertension and therefore the necessity for more EBL sessions.

As secondary objectives, there was no statistically significant association of coagulation test results with bleeding incidence following EBL. As changes are common in advanced liver disease, several studies have already shown that standard coagulation tests are a poor indicator of bleeding [16]. Moreover, administration of blood products or factor concentrates in patients with stable cirrhosis did not reduce the frequency of these episodes or procedure-associated mortality [16, 17]; therefore, it is not recommended [18]. Also, we did not observe an association between anticoagulants, the use of periprocedural PPIs, and bleeding complications. In cirrhotic patients, anticoagulant therapy can confer a higher risk of bleeding due to their susceptible rebalanced hemostasis [18]. However, its use in two studies did not increase secondary GI bleeding [19, 20]. Regarding PPI use, our findings were consistent with a recent study that also did not identify it as a risk factor [16]. Nonetheless,

there are several data [21–23], including a meta-analysis study, suggesting that short-term acid suppression may be considered in patients undergoing prophylactic EBL, as it significantly decreases bleeding incidence [23].

The 6-month mortality rate of our study (15.5%) was within the values of published studies [12], a reflection of end-stage liver disease [11]. In this regard, we identified an association between our outcome and Child-Pugh B or C, median MELD-Na score, PVT, and incomplete VE in the univariate analysis. After multivariate adjustment, the association remained independent with all except Child-Pugh B/C. A study by Ray G. also showed that Child-Pugh class C and alcohol consumption were independent risk factors that affected mortality [11].

Regarding the interpretation of our results, we need to consider several limitations of the present study. First, this is a single-center retrospective study with a small sample size, whose design implies some limitations as well as potential selection and recall biases. Second, the percentage of follow-up loss in pandemic group was significantly higher compared to pre-pandemic (29.5% vs. 13.2%, respectively).

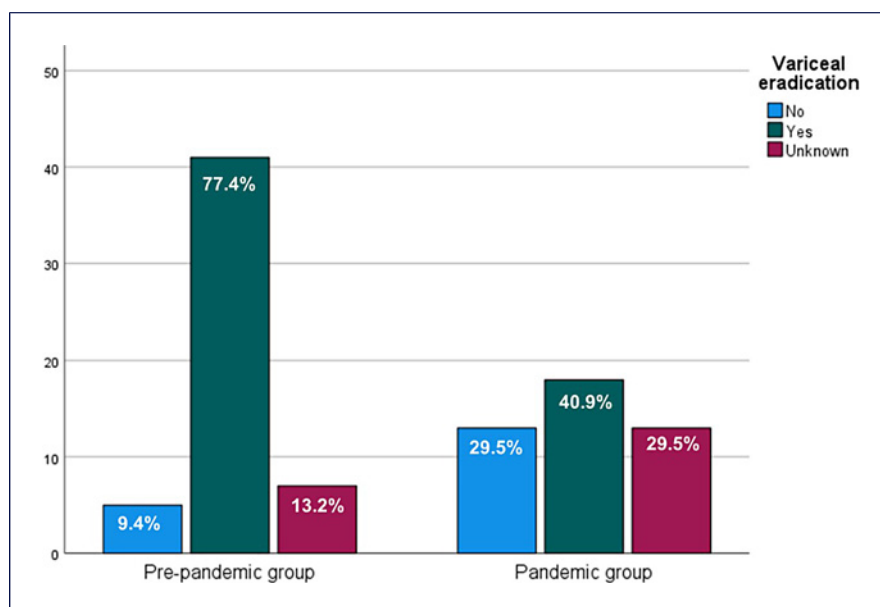


Fig. 1. Variceal eradication.

Table 2. Analysis of risk factors associated with variceal eradication

Risk factors	Variceal eradication complete (n = 59)	Variceal eradication incomplete (n = 38)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Male gender (%)	47 (79.7)	28 (73.7)	0.7	0.3–1.9	0.493			
Age (mean±SD), years	58.7±11.5	60.5±13.8			0.491			
Etiology eradication (%)	33/49 (67.3)	21/29 (72.4)	1.3	0.5–3.5	0.639			
Child-Pugh B/C (%)	14/53 (26.4)	9/32 (28.1)	1.1	0.4–2.9	0.863			
MELD-Na, median (IQR)	11.0 (8.3–14.0)	11.0 (9.75–15.0)			0.348			
PVT (%)	9 (15.2)	13 (34.2)	0.3	0.1–0.9	0.030	2.9	0.9–9.4	0.077
HCC (%)	5 (8.5)	4 (10.5)	0.8	0.2–3.1	0.734			
NSBBs (%)	35 (59.3)	27/37 (73.0)	0.5	0.2–1.3	0.173			
Platelets 10 ⁹ /L, median (IQR)	82.0 (57.0–144.0)	90.5 (66.0–133.5)			0.779			
Nr.EBL sessions (mean±SD)	3.7±1.4	4.7±2.6			0.028	0.8	0.6–0.9	0.048
Secondary prophylaxis (%)	34 (57.6)	32 (84.2)	0.3	0.1–0.7	0.006	3.0	0.9–9.7	0.068
Severe PHG (%)	25 (42.4)	14 (36.8)	1.3	0.5–2.9	0.588			
Pandemic group (%)	18 (30.5)	26 (68.4)	0.2	0.08–0.5	<0.001	4.9	1.8–13.3	0.002

SD, standard deviation; MELD, model of end-stage liver disease; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β -blockers; EBL, endoscopic band ligation; IQR, interquartile range; PHG, portal hypertensive gastropathy.

Several reasons may explain this increase, namely endoscopic activity reduction during pandemic period, requirement for SARS-CoV-2 swab before procedure, as patients' denial to perform gastroscopy due to fear of enhanced risk

of COVID-19 infection in hospitals [24]. Third, VE at the discretion of the endoscopist enabled a high interobserver variability. Also, post-EBL bleeding definition englobed all possible causes, as varices, ligation ulcers, or even as blood

Table 3. Analysis of risk factors associated with gastrointestinal (GI) bleeding

Risk factors	Control (n = 83)	GI bleeding (n = 14)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Male gender (%)	67 (80.7)	8 (57.1)	3.1	0.9–10.3	0.080	5.0	1.2–21.3	0.030
Age (mean±SD), years	59.5±11.5	58.5±17.1			0.780			
Etiology eradication (%)	50/69 (72.5)	4/9 (44.4)	3.3	0.8–13.6	0.124			
Child-Pugh B/C (%)	21/74 (28.4)	2/11 (18.2)	1.7	0.4–8.9	0.719			
MELD-Na, median (IQR)	11.0 (9.0–14.0)	12.0 (10.0–14.0)			0.516			
PVT (%)	20 (24.1)	2 (14.3)	0.5	0.1–2.5	0.513			
HCC (%)	8 (9.7)	1 (7.1)	0.7	0.8–6.3	1.000			
NSBBs (%)	53/82 (64.6)	9 (64.3)	0.9	0.3–3.2	0.980			
PPIs (%)	56/82 (68.3)	10 (71.4)	1.2	0.3–4.0	1.000			
Anticoagulants (%)	11 (13.3)	3 (21.4)	1.8	0.4–7.4	0.420			
Platelets 10 ⁹ /L, median (IQR)	82.0 (58.0–138.0)	108.0 (72.5–184.5)			0.257			
INR, median (IQR)	1.3 (1.1–1.4)	1.2 (1.1–1.4)			0.383			
Nr.EBL sessions (mean±SD)	3.9±1.9	5.6±2.3			0.003	1.4	1.1–2.0	0.025
Incomplete VE (%)	27 (32.5)	11 (78.6)	0.1	0.03–0.5	0.001	4.9	1.1–21.4	0.036
Severe PHG (%)	33 (39.8)	6 (42.9)	1.1	0.4–3.6	0.827			
Pandemic group (%)	37 (44.6)	7 (50.0)	1.2	0.4–3.9	0.706			

SD, standard deviation; MELD, Model of End-Stage Liver Disease; IQR, interquartile range; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β -blockers; PPIs, proton pump inhibitors; INR, international normalized ratio; EBL, endoscopic band ligation; PHG, portal hypertensive gastropathy.

Table 4. Analysis of risk factors associated with mortality at 6 months

Risk factors	Control (n = 82)	Death at 6 months (n = 15)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Male gender (%)	65 (79.3)	10 (66.7)	1.9	0.6–6.3	0.319			
Age (mean±SD), years	58.8±11.8	62.6±15.1			0.273			
Etiology eradication (%)	47/67 (70.1)	7/11 (63.6)	1.3	0.4–5.1	0.729			
Child-Pugh B/C (%)	16/72 (22.2)	7/13 (53.8)	4.1	1.2–13.9	0.037	2.7	0.4–20.3	0.336
MELD-Na, median (IQR)	11.0 (8.5–14.0)	15.0 (10.0–22.0)			0.016	1.3	1.1–1.6	0.016
PVT (%)	15 (18.3)	7 (46.7)	3.9	1.2–12.4	0.038	10.5	1.4–79.4	0.023
HCC (%)	6 (7.3)	3 (20.0)	3.2	0.7–14.4	0.142			
NSBBs (%)	52 (63.4)	10/14 (71.4)	1.4	0.4–5.0	0.764			
Nr.EBL sessions (mean±SD)	4.2±2.0	3.7±1.9			0.363			
Incomplete VE (%)	26 (31.7)	12 (80.0)	0.1	0.03–0.5	< 0.001	23.4	2.6–211.9	0.005
Severe PHG (%)	32 (39.0)	7 (46.7)	1.4	0.5–4.1	0.579			
Pandemic group (%)	36 (43.9)	8 (53.3)	1.5	0.5–4.4	0.500			

SD, standard deviation; MELD, model of end-stage liver disease; IQR, interquartile range; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β -blockers; INR, EBL, endoscopic band ligation; VE, variceal eradication; PHG, portal hypertensive gastropathy.

detected without other evident cause. Thus, its rate might have been underestimated, as national electronic health records could not be accessed in 7 patients (7.2%) who deceased in other institutions. Fourth, regarding the risk factors for our outcomes, even though almost all varices were large (96.9%), we did not register the risk factors for

esophageal varices, in particular presence of red marks or spots, nor the number of bands applied. However, in several studies, there was no significant association between them and the risk of bleeding [14, 25]. Finally, no portal hypertension measurement was performed in our patients. Therefore, our explanations related to variceal obliteration are

hypothetical and need further investigation. Nevertheless, despite these limitations, the present study reflects the importance of EBL therapy in these patients, for whom no data are available about the impact of pandemic COVID-19 on gastroesophageal varices treatment.

In conclusion, our study is among the first to demonstrate the impact of pandemic COVID-19 on patients receiving prophylactic EBL therapy, namely in achieving VE during this period. Our results also showed that patients with incomplete VE were at higher risk for GI bleeding and death at 6 months. Incomplete VE was associated with PVT, secondary prophylaxis indication, mean number of EBL sessions, and pandemic group, perhaps explained by a further increase in portal hypertension and therefore the need for more EBL sessions. However, we need to consider the limitations mentioned above in order to interpret our conclusions with caution. Thus, the impact of COVID-19 on the management of these patients requires further validation by multicentric studies.

Statement of Ethics

This study was approved by the Ethical Review Board of the Medical Academic Center of Lisbon on March 17, 2022 (reference number 02/22). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki of 1975, as reflected in a priori approval by the institution's human research committee.

References

- 1 de Franchis R, Bosch J, Garcia-tsoo G, Reiberger T. *Seminar Baveno VII: renewing consensus in portal hypertension*. Vol. 76; 2022. p. 959–74.
- 2 Berzigotti A, Gines père, and durand françois “EASL POSTGRADUATE COURSE”. 2019. Accessed: Feb. 21, 2021. [Online]. Available: www.ilc-congress.eu.
- 3 European Association for the Study of the Liver Electronic address easloffice@easlofficeeuEuropean Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69(2):406–60.
- 4 Albillos A, Zamora J, Martínez J, Arroyo D, Ahmad I, De-la-Peña J, et al. Stratifying risk in the prevention of recurrent variceal hemorrhage: results of an individual patient meta-analysis. *Hepatology*. 2017;66(4):1219–31.
- 5 Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. Jan. 2017;65(1):310–35.
- 6 Muñoz-Martínez S, Sapena V, Forner A, Nault JC, Sapisochin G, Rimassa L, et al. Assessing the impact of COVID-19 on liver cancer management (CERO-19). *JHEP Rep*. 2021;3(3):100260.
- 7 Longcroft-Wheaton G, Tolfree N, Gangi A, Beable R, Bhandari P. Data from a large Western centre exploring the impact of COVID-19 pandemic on endoscopy services and cancer diagnosis. *Frontline Gastroenterol*. 2021;12(3):193–9.
- 8 Rodríguez-Carrasco M, Albéniz E, Bhandari P, Beyna T, Bourke MJ, Min A, et al. COVID-19 and endoscopic management of superficial gastrointestinal neoplastic lesions: a multinational cross-sectional survey. *Endoscopy*. 2021;53(2):173–7.
- 9 Rutter MD, Brookes M, Lee TJ, Rogers P, Sharp L. Impact of the COVID-19 pandemic on UK endoscopic activity and cancer detection: a National Endoscopy Database Analysis. *Gut*. 2021;70(3):537–43.
- 10 Libânio D, Bastos P, Pimentel-Nunes P. Safe and valuable endoscopy in the COVID era. *GE Port J Gastroenterol*. 2020;27(4):219–23.
- 11 Ray G. Long-term outcome of endoscopic variceal band ligation of esophageal varices in patients with chronic liver disease. *Indian J Gastroenterol*. 2019;38(1):69–76.
- 12 Ko SY, Kim JH, Choe WH, Kwon SY, Lee CH. Pharmacotherapy alone vs endoscopic variceal ligation combination for secondary prevention of oesophageal variceal bleeding: meta-analysis. *Liver Int*. May 2012;32(5):867–9.
- 13 Dell A. *Impact of portal vein thrombosis on the efficacy of endoscopic variceal band ligation*. Vol. 46; 2014. p. 152–6.
- 14 Petrasch F, Grothaus J, Mössner J, Schiefke I, Hoffmeister A. Differences in bleeding behavior after endoscopic band ligation: a retrospective analysis. *BMC Gastroenterol*. 2010;10(2–11):5.
- 15 Lo GH. The role of endoscopy in secondary prophylaxis of esophageal varices. *Clin Liver Dis*. 2010;14(2):307–23.
- 16 Drolz A, Schramm C, Seiz O, Groth S, Vettorazzi E, Horvatits T, et al. Risk factors associated with bleeding after prophylactic endoscopic variceal ligation in cirrhosis. *Endoscopy*. 2021;53(3):226–34.

Considering the retrospective observational character of the study, the Local Ethics Committee waived the need for individual informed consent.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Data gathering, literature review, and manuscript writing: Ana Craciun and Inês Botto. Manuscript revision for important intellectual content: João Lopes, Miguel Moura, Sofia Carvalhana, Helena Cortez-Pinto, and Rui Tato Marinho.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

- 17 Blasi A, Machlab S, Risco R, Costa-Freixas JP, Hernández-Cely G, Horta D, et al. A multicenter analysis of the role of prophylactic transfusion of blood products in patients with cirrhosis and esophageal varices undergoing endoscopic band ligation. *JHEP Rep*. 2021;3(6):100363.
- 18 European Association for the Study of the Liver Electronic address easloffice@easloffice.eu European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. *J Hepatol*. 2022;76(5):1151–84.
- 19 Bianchini M, Cavani G, Bonaccorso A, Turco L, Vizzutti F, Sartini A, et al. Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients. *Liver Int*. 2018;38(7):1253–62.
- 20 Ponthus S, Spahr L, Casini A, Berney T, Frossard JL, Majno P, et al. Safety of variceal band ligation in patients with cirrhosis and portal vein thrombosis treated with anticoagulant therapy: a retrospective study. *Eur J Gastroenterol Hepatol*. Mar. 2020;32(3):395–400.
- 21 Ghazizadeh H, Patel P, Stancampiano F, Patel S, Fox EA, Yousaf MB, et al. Proton-pump-inhibitor use associated with lower short-term rebleeding and mortality in patients receiving esophageal variceal band ligation: a retrospective cohort study. *Eur J Gastroenterol Hepatol*. 2020;32(12):1571–8.
- 22 Hidaka H, Nakazawa T, Wang G, Kokubu S, Minamino T, Takada J, et al. Long-term administration of PPI reduces treatment failures after esophageal variceal band ligation: a randomized, controlled trial. *J Gastroenterol*. 2012;47(2):118–26.
- 23 Zhu J, Qi X, Yu H, Su C, Guo X. Acid suppression in patients treated with endoscopic therapy for the management of gastroesophageal varices: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2018;12(6):617–24.
- 24 Schmiderer A, Schwaighofer H, Niederreiter L, Profanter C, Steinle H, Ziachehabi A, et al. Decline in acute upper gastrointestinal bleeding during COVID-19 pandemic after initiation of lockdown in Austria. *Endoscopy*. 2020;52(11):1036–8.
- 25 Harewood GC, Baron TH, Song LMWK. Factors predicting success of endoscopic variceal ligation for secondary prophylaxis of esophageal variceal bleeding. *J Gastroenterol Hepatol*. 2006; 21(1 Pt 2):237–41.