Original research

Endoscopic variceal ligation versus propranolol for the primary prevention of oesophageal variceal bleeding in patients with hepatocellular carcinoma: an open-label, two-centre, randomised controlled trial

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ABSTRACT

Objective This randomised trial aimed to address whether endoscopic variceal ligation (EVL) or propranolol (PPL) is more effective at preventing initial oesophageal variceal bleeding (EVB) in patients with hepatocellular carcinoma (HCC).

Design Patients with HCC and medium-to-large oesophageal varices (EVs) but without previous EVB were randomised to receive EVL (every 3–4 weeks until variceal eradication) or PPL (up to 320 mg daily) at a 1:1 ratio. Long-term follow-up data on EVB, other upper gastrointestinal bleeding (UGIB), non-bleeding liver decompensation, overall survival (OS) and adverse events (AEs) were analysed using competing risk regression.

Results Between June 2011 and April 2021, 144 patients were randomised to receive EVL (n=72) or PPL (n=72). In the EVL group, 7 patients experienced EVB, and 30 died; in the PPL group, 19 patients had EVB, and 40 died. The EVL group had a lower cumulative incidence of EVB (Gray's test, p=0.009) than its counterpart, with no mortality difference (Gray's test, p=0.085). For patients with Barcelona Clinic Liver Cancer (BCLC) stage A/B, EVL was better than PPL in reducing EVB (p<0.001) and mortality (p=0.003). For patients beyond BCLC stage B, between-group outcomes were similar. Other UGIB, non-bleeding liver decompensation and AEs did not differ between groups. A competing risk regression model confirmed the prognostic value of EVL.

Conclusion EVL is superior to PPL in preventing initial EVB in patients with HCC. The benefits of EVL on EVB and OS may be limited to patients with BCLC stage A/B and not to those with BCLC stage C/D.

Trial registration number NCT01970748.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ According to the Baveno VII consensus, treatment with non-selective beta-blockers (NSBBs) should be used to prevent decompensation in patients with clinically significant portal hypertension.
⇒ Endoscopic variceal ligation (EVL) is recommended for compensated patients with high-risk oesophageal varices (EVs) who have contraindications or an intolerance to NSBBs.
⇒ However, no randomised trials have directly compared the efficacy of EVL and NSBBs in the primary prevention of oesophageal variceal bleeding (EVB) in patients with hepatocellular carcinoma (HCC).

WHAT THIS STUDY ADDS

⇒ This two-centre randomised controlled trial is the first to demonstrate the superiority of EVL over propranolol (PPL) as a primary prevention strategy in patients with HCC with medium-to-large EVs.
⇒ EVL was better than PPL at preventing initial EVB in patients with HCC.
⇒ In the subgroup analysis, EVL reduced EVB and improved overall survival (OS) in patients with Barcelona Clinic Liver Cancer (BCLC) stage A/B but not in those with BCLC stage C/D.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ EVL is superior to PPL in preventing initial EVB in patients with HCC.
⇒ The EVB and OS benefits of EVL may be limited to patients with BCLC stage A/B and not to those with BCLC stage C/D.
⇒ Our findings may have a major impact on the treatment and outcomes of patients with HCC.

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INTRODUCTION

Gastro-oesophageal variceal bleeding, a major complication of portal hypertension (PHT), is associated with high rebleeding and mortality rates.[1] Hepatocellular carcinoma (HCC), a subgroup of PHT, is the third leading cause of cancer death worldwide.[2] More than half of patients with HCC have oesophageal varices (EVs), which are associated with poorer survival.[3 4] In addition, nearly half of these patients experience oesophageal variceal bleeding (EVB) if primary prevention strategies are not implemented.[5–7] The prognosis of patients with HCC and EVB is extremely poor, with rebleeding

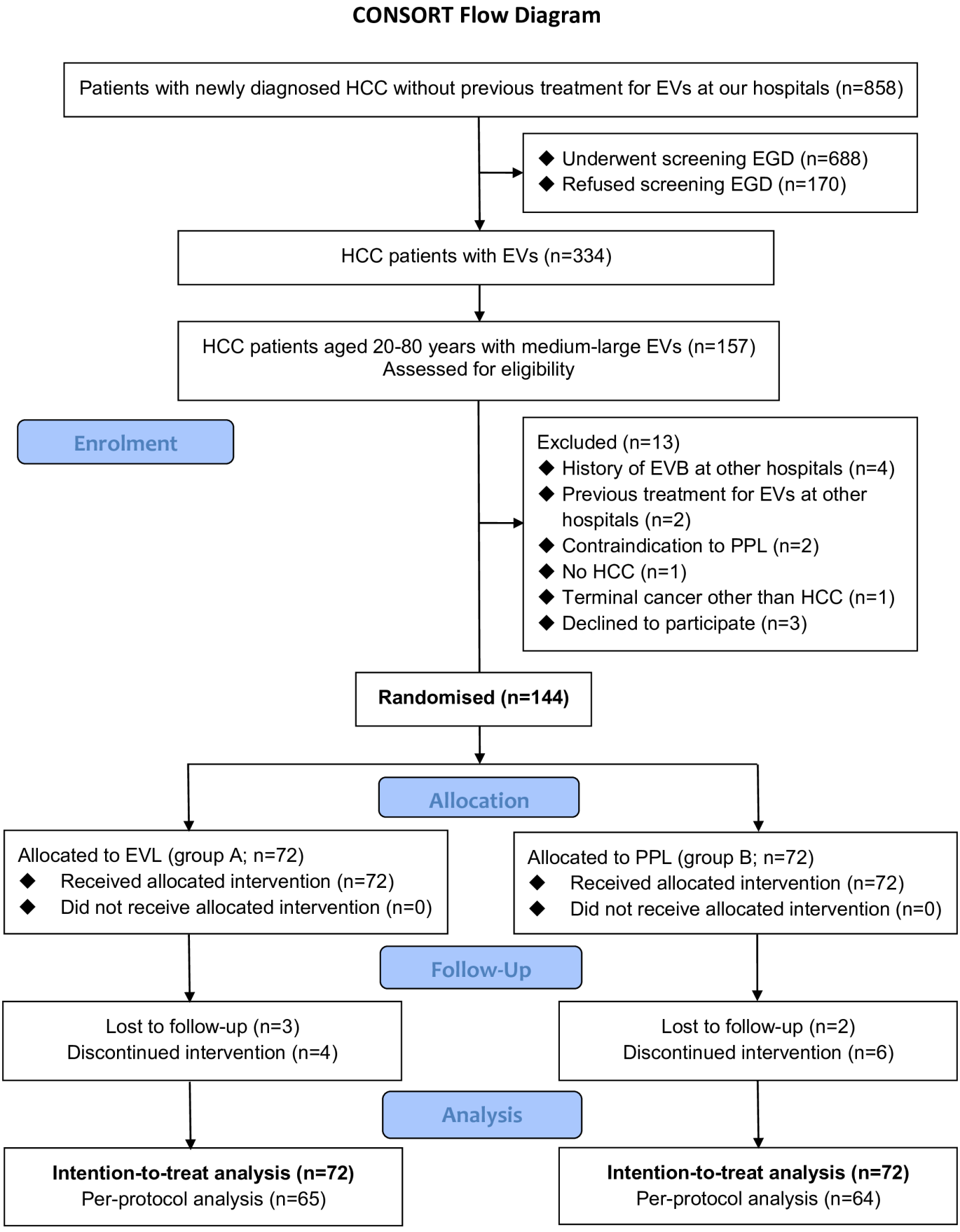

Figure 1 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study. EGD, oesophagogastroduodenoscopy; EVB, oesophageal variceal bleeding; EVL, endoscopic variceal ligation; EVs; oesophageal varices; HCC, hepatocellular carcinoma; PPL, propranolol.

Table 1 Baseline characteristics

Variables	EVL (group A) (n=72)	PPL (group B) (n=72)	P value
Patient demographics			
Age, years	64 (56–71)	61 (55–70)	0.662
Sex			0.846
Male	54 (75.0%)	55 (76.4%)	
Female	18 (25.0%)	17 (23.6%)	
Aetiology of liver disease			
HBV	40 (55.6%)	41 (56.9%)	0.867
HCV	23 (31.9%)	21 (29.2%)	0.717
Alcohol	11 (15.3%)	9 (12.5%)	0.630
Others	7 (9.7%)	11 (15.3%)	0.313
Largest variceal size			0.289
F2	45 (65.3%)	51 (70.8%)	
F3	27 (34.7%)	21 (29.2%)	
Red colour sign	53 (73.6%)	50 (69.4%)	0.580
PHG	55 (77.5%)	56 (77.8%)	0.964
Gastric varices*	15 (20.8%)	19 (26.4%)	0.433
GOV-1	6 (8.3%)	11 (15.3%)	
GOV-2	9 (12.5%)	8 (11.1%)	
Serum biochemistry tests			
Albumin, g/dL	3.3 (2.8–3.8)	3.2 (2.9–3.8)	0.970
Total bilirubin, mg/dL	1.4 (1.0–2.5)	1.4 (1.0–2.1)	0.275
ALT, U/L	49 (33–76)	50 (30–79)	0.848
AST, U/L	62 (41–97)	63 (47–114)	0.358
Creatinine, mg/dL	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.530
INR	1.16 (1.09–1.31)	1.21 (1.11–1.39)	0.109
Prolonged PT, s	0.9 (0–2.5)	1.0 (0–2.4)	0.832
Platelet, k/mm^3	98 (75–142)	102 (67–146)	0.906
Haemoglobin, g/L	121 (105–131)	115 (98–126)	0.184
Presence of ascites	40 (55.6%)	39 (54.2%)	0.867
Presence of HE	5 (6.9%)	4 (5.6%)	>0.999
Child-Pugh score	7 (6-8)	7 (6-8)	0.741
Child-Pugh class			0.830
A	30 (41.7%)	29 (40.3%)	
B	32 (44.4%)	35 (48.6%)	
C	10 (13.9%)	8 (11.1%)	
HCC factors			
Tumour size, mm	40 (21–80)	38 (20–87)	0.884
Multiple tumours	42 (58.3%)	43 (59.7%)	0.865
PVT†	29 (40.3%)	25 (34.7%)	0.491
Extrahepatic metastasis	15 (20.8%)	14 (19.4%)	0.835
AFP, ng/mL	25.9 (6.2–2895.3)	52.3 (9.5–2263.3)	0.460
HCC staging and treatment			
BCLC stage			0.960
A	21 (29.2%)	19 (26.4%)	
B	15 (20.8%)	17 (23.6%)	
C	27 (37.5%)	28 (38.9%)	
D	9 (12.5%)	8 (11.1%)	
Treatment modality			0.846
Curative	18 (25.0%)	17 (23.6%)	
Surgical resection	8 (11.1%)	4 (5.6%)	
RFA	10 (13.9%)	12 (16.7%)	
LT	0 (0%)	1 (1.4%)	
Non-curative	54 (75.0%)	55 (76.4%)	
TACE	23 (31.9%)	25 (34.7%)	
Sorafenib	12 (16.7%)	7 (9.7%)	
Lenvatinib	0 (0%)	2 (2.8%)	
ICI	0 (0%)	2 (2.8%)‡	
ICI plus lenvatinib	4 (5.6%)§	5 (6.9%)¶	
Chemotherapy	1 (1.4%)	3 (4.2%)	
Radiotherapy	1 (1.4%)	2 (2.8%)	
Best supportive care	13 (18.1%)	9 (12.5%)	

Values are n (%) or median (IQR).
*Two patients in group A and five patients in group B received gastric variceal obturation with a mixture of *N*-butyl-2-cyanoacrylate and lipiodol injections at a 1:1 ratio.
†All PVT were tumorous.
‡One patient received pembrolizumab, and one received nivolumab followed by pembrolizumab.
§All four patients received pembrolizumab plus lenvatinib.
¶Four patients received pembrolizumab plus lenvatinib, and one received nivolumab plus lenvatinib.
AFP, alpha-fetoprotein; AL(S)T, alanine (aspartate) aminotransferase; BCLC, Barcelona Clinic Liver Cancer; EVL, endoscopic variceal ligation; GOV, gastro-oesophageal varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; ICI, immune checkpoint inhibitor; INR, international normalised ratio; LT, liver transplantation; PHG, portal hypertensive gastropathy; PPL, propranolol; PT, prothrombin time; PVT, portal vein thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation.

rates of 50% and 6-week mortality rates of 26%–48%, both of which are higher than those of patients without HCC.[8–11]

Treatment with non-selective beta-blockers (NSBBs) can prevent decompensation in patients with clinically significant PHT. Endoscopic variceal ligation (EVL) is recommended for compensated patients with high-risk EVs who are contraindicated for or intolerant of NSBBs.[12] However, EVB risk factors in patients with HCC differ from those in patients with cirrhosis.[13] HCC increases the hepatic venous pressure gradient (HVPG) through arteriovenous shunting within the tumour and changes in hepatic architecture.[14–16] Furthermore, tumour thrombosis in the portal vein contributes to PHT and increases variceal bleeding.[13 15 17] Whether NSBBs are sufficient to reduce HVPG levels and prevent EVB in patients with HCC is unclear. Whether fragile patients with HCC can tolerate NSBBs or regular EVL is also questionable. This study aimed to compare the efficacy and safety of EVL and NSBBs in the primary prevention of EVB in patients with HCC with medium-to-large EVs.

MATERIALS AND METHODS

Patient selection and study design

This investigator initiated, two-centre, open-label, randomised trial enrolled participants from Taipei Veterans General Hospital and Kaohsiung Veterans General Hospital in Taiwan. All patients with newly diagnosed HCC without previous treatment for EVs at our hospitals were advised to undergo screening oesophagogastroduodenoscopy (EGD). Patients were consecutively enrolled if they were between 20 and 80 years of age and had medium (F2) and/or large (F3) EVs, according to Beppu *et al*'s classification.[18] HCC was diagnosed based on the American Association for the Study of Liver Diseases criteria.[19] Cirrhosis was diagnosed based on a combination of medical history, physical examination findings, biochemical data, imaging studies and liver biopsy.

Patients were excluded if they had (1) a history of EVB; (2) previous treatments for EVs, including EVL, endoscopic injection sclerotherapy (EIS), transjugular intrahepatic portosystemic shunt (TIPS) or surgery; (3) used NSBBs within 2 weeks before enrolment; (4) contraindications for NSBBs, including atrioventricular block, heart failure, chronic obstructive pulmonary disease, asthma, poorly controlled diabetes or severe peripheral arterial disease; (5) other terminal illness, such as terminal malignancy other than HCC, heart failure or renal failure; (6) become pregnant; or (7) refused to participate.

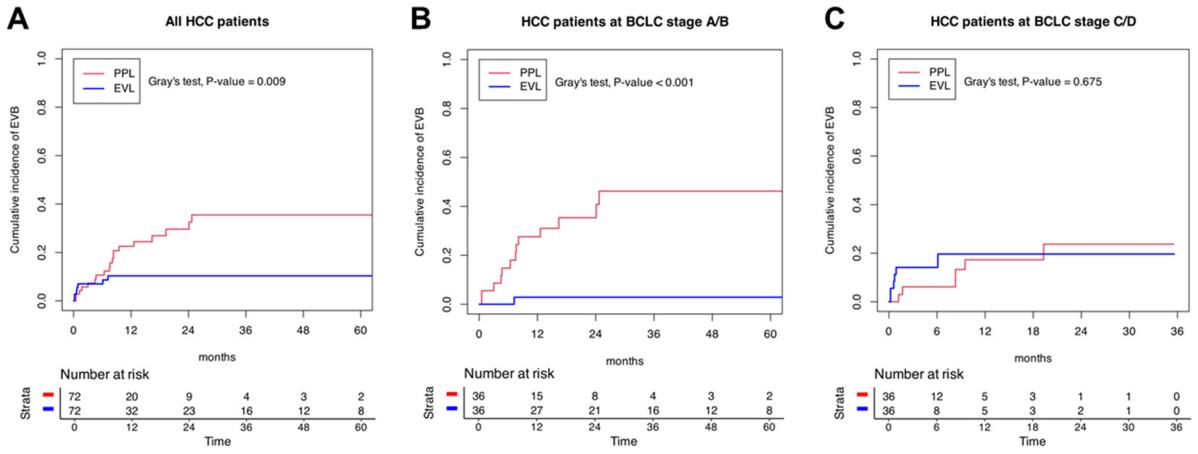

Figure 2 Intention-to-treat analysis of cumulative incidence of oesophageal variceal bleeding (EVB) in patients with hepatocellular carcinoma (HCC) receiving endoscopic variceal ligation (EVL) or propranolol (PPL). (A) All patients with HCC. (B) Patients with HCC at Barcelona Clinic Liver Cancer (BCLC) stage A/B. (C) Patients with HCC at BCLC stage C/D.

Eligible patients were centrally registered and randomly assigned to receive EVL (group A) or propranolol (PPL; group B) within 1 week of basal endoscopy. A randomisation code was computer generated using a 1:1 ratio in blocks of eight and prepared by the study centres. Investigators were blinded to the block size. The allocation sequence was concealed by a researcher with no clinical involvement in the trial using sequentially numbered, opaque, sealed and stapled envelopes. To prevent disruption of the allocation sequence, envelopes contained the participants' names and medical record numbers. Corresponding envelopes were not opened until the patient provided informed consent. None of the patients, investigators or statisticians were blinded to the treatment assignments. All participants provided written an informed consent prior to enrolment. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Endoscopic variceal ligation

EVL was performed for patients in group A by four experienced endoscopists using a GIF-XQ260 or GIF-HQ290 endoscope (Olympus Optical, Tokyo, Japan) with a Speedband Superview Super 7 multiple band ligator (Boston Scientific, Marlborough, Massachusetts, USA). EVL was repeated every 3–4 weeks until variceal eradication was achieved on endoscopy or until the patient died. Follow-up endoscopy was performed 1 month after variceal eradication, followed by every 3 months for two times, every 6 months for two times and annually thereafter. If follow-up endoscopy noted recurrent EVs, EVL was restarted every 3–4 weeks until the recurrent EVs were endoscopically eradicated again.

Propranolol

PPL was initiated at 10 mg two times per day for patients in group B. The dose was titrated every 3 days during hospitalisation or every 7 days in the outpatient clinic, aiming to achieve a 25% drop in the resting pulse rate (PR) to no lower than 55 beats/min, while maintaining the systolic blood pressure (SBP) >90 mm Hg.[20 21] The maximal daily dose was 320 mg. Treatment compliance was assessed at each follow-up visit by questioning patients or their relatives and counting the number of pills whenever possible.

Clinical assessment and follow-up

When patients in group A achieved EV eradication or patients in group B reached the target dose, follow-up visits were arranged every 2–3 months until the last visit to the hospital or death. All treatment-related adverse events (AEs) were recorded. If the patient had any signs of gastrointestinal bleeding during follow-up, standard treatments, including vasoactive drugs

Table 2 Competing risk regression analysis modelling factors associated with EVB in all patients with HCC

		Univariate regression model			Multivariate regression model		
Characteristics		SHR	95% CI	P value	SHR	95% CI	P value
Platelet count, 10^3/mm^3	>100 vs ≤100	0.767	0.355 to 1.660	0.500			NA
Prothrombin time, INR	>1.2 vs ≤1.2	0.846	0.387 to 1.850	0.680			NA
Total bilirubin, mg/dL	>2.0 vs ≤2.0	1.240	0.542 to 2.840	0.610			NA
Albumin, g/dL	>3.0 vs ≤3.0	1.100	0.494 to 2.430	0.820			NA
Ascites	Yes vs no	1.320	0.622 to 2.810	0.470			NA
PVT	Yes vs no	1.070	0.482 to 2.370	0.870			NA
AFP, ng/mL	>10 vs ≤10	2.570	0.993 to 6.660	0.052			NS
BCLC stage	Stage C/D vs A/B	1.040	0.492 to 2.200	0.920			NA
Largest variceal size	F3 vs F2	1.940	0.914 to 4.120	0.085	2.115	1.002 to 4.467	0.050
Prophylactic method for EVB	EVL vs PPL	0.338	0.139 to 0.823	0.017	0.347	0.134 to 0.893	0.028

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; EVB, oesophageal variceal bleeding; EVL, endoscopic variceal ligation; HCC, hepatocellular carcinoma; INR, international normalised ratio; NA, not applicable; NS, not significant; PPL, propranolol; PVT, portal vein thrombosis; SHR, subdistribution HR.

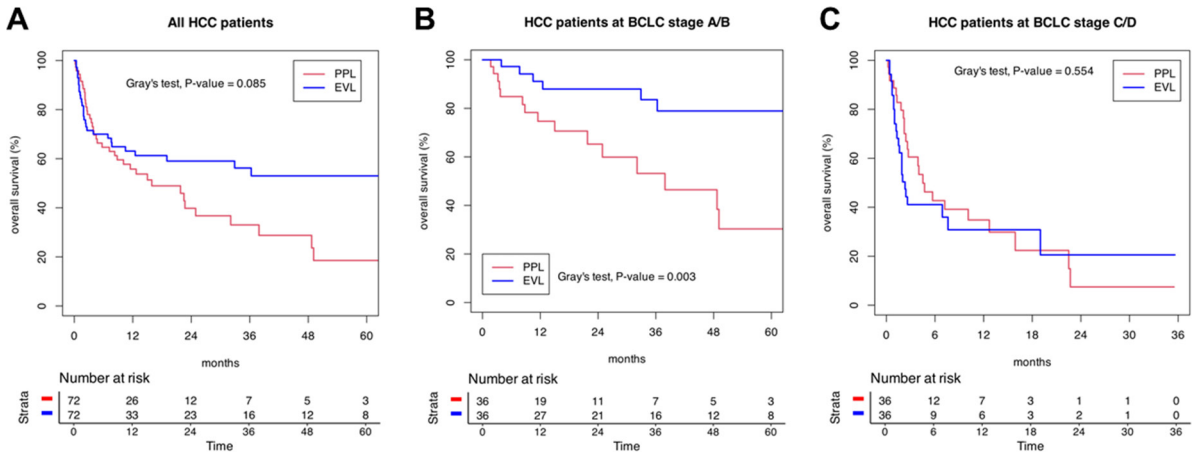

Figure 3 Intention-to-treat analysis of probability of overall survival in patients with hepatocellular carcinoma (HCC) receiving endoscopic variceal ligation (EVL) or propranolol (PPL). (A) All patients with HCC. (B) Patients with HCC at Barcelona Clinic Liver Cancer (BCLC) stage A/B. (C) Patients with HCC patients at BCLC stage C/D.

(terlipressin, somatostatin or octreotide), empiric antibiotics (third-generation cephalosporin or quinolone) and blood transfusions were administered. Emergency endoscopy was performed to identify the bleeding source. If EVB was confirmed endoscopically, EVL was first performed for haemostasis. If initial haemostasis was not achieved with EVL, salvage therapy, including EIS, TIPS or surgery, was performed individually, according to the clinical condition. HCC surveillance using serum alpha-fetoprotein (AFP) and imaging was performed every 2–3 months.

Study outcomes

The primary outcome of this study was the cumulative incidence of EVB. Secondary outcomes were the cumulative incidences of other upper gastrointestinal bleeding (UGIB), first/further non-bleeding liver decompensation, overall survival (OS) and AEs.

Definitions

EVB was defined as new-onset haematemesis, coffee ground vomitus, haematochezia or melena combined with active spurting or oozing from EVs, the presence of a white nipple on EVs, or medium-to-large EVs found without another possible bleeder, as well as haemoglobin level decreases of >20 g/L within 24 hours after admission.[8 22 23] Post-EVL ulcer bleeding was also considered EVB. Clinically significant bleeding was assessed according to the Baveno III criteria: (1) transfusion requirement of ≥2 units of blood within 24 hours of time zero, (2) SBP<100 mm Hg or a postural change of >20 mm Hg, and/or (3) PR >100/min at time zero.[24] Other UGIB was defined as new-onset haematemesis, melena or both combined with overall haemorrhage from the upper gastrointestinal tract except for EVB. Events that defined first/further nonbleeding liver decompensation were based on the Baveno VII consensus.[12] Gastric varices were classified by Sarin's classification.[25] The cirrhosis severity was assessed using the Child-Pugh classification.[26] HCC was classified by the Barcelona Clinic Liver Cancer (BCLC) staging system.[27] A portal vein thrombus was considered tumorous if it expanded the vessel or was enhanced on dynamic imaging.

Sample size calculation and statistical analysis

According to a randomised trial comparing EVL and PPL for the primary prevention of EVB in patients with cirrhosis, the probability of EVB was 43% in the PPL group and 15% in the EVL group at 18 months.[23] We conservatively assumed a 25% difference between the two groups of patients with HCC. A type I (α) and II (β) errors were set as 0.05 and 0.15, respectively. The calculated sample size was 60 patients in each group.[28] We estimated that 15% of patients would be lost to follow-up. Thus, this study required the randomisation of 144 subjects.

The primary analysis was based on the intention-to-treat (ITT) principle for all randomised patients. In addition, we performed a per-protocol (PP) analysis for patients who received the assigned treatment regularly. Continuous variables are expressed as median (IQR) and were analysed using the Mann-Whitney U test. Categorical data are expressed as frequency (percentage) and were analysed using the χ^2 test with Yates correction or Fisher's exact test, as appropriate. The cumulative incidence function (CIF) of EVB, other UGIB, non-bleeding liver decompensation and OS were estimated using non-parametric method accounting for competing events. Gray's test was employed to compare the CIF curves between groups.[29] Prognostic models were developed to identify independent factors associated with EVB and OS by applying competing risk regression, as proposed by Fine and Gray.[30] Liver transplantation and death were considered competing events for all models, except for the OS models, in which liver transplantation was considered the only competing event. Only clinically relevant variables with potential impact on outcomes in the univariate analysis ($p<0.1$) were included in the multiple regression models. For variables with first-order interactions ($p<0.05$) with the prophylactic method (EVL/PPL), subgroup analysis was performed to identify the subpopulation with optimal benefit from the prophylactic method. Two-tailed p values <0.05 were considered statistically significant. Statistical analyses were performed using R V.4.3.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Patient characteristics

Between June 2011 and April 2021, 858 patients with newly diagnosed HCC without previous treatment for EVs at our hospitals were advised to undergo EGD screening. Among the 688 patients who agreed to undergo EGD, 157 patients aged 20–80 years with medium-to-large EVs were screened for eligibility

Table 3 Competing risk regression analysis modelling factors associated with OS in all patients with HCC

Characteristics		Univariate regression model			Multivariate regression model		
		SHR	95% CI	P value	SHR	95% CI	P value
Age, years	>65 vs ≤65	0.914	0.568 to 1.470	0.710			NA
Sex	Male vs female	1.290	0.753 to 2.200	0.360			NA
HBsAg-positive	Yes vs no	1.240	0.775 to 1.980	0.370			NA
Anti-HCV-positive	Yes vs no	0.760	0.458 to 1.260	0.290			NA
AST, U/L	>40 vs ≤40	4.630	1.860 to 11.600	0.001	3.011	1.359 to 6.670	0.007
Platelet count, $10^3/mm^3$	>100 vs ≤100	1.570	0.976 to 2.520	0.063			NS
Prothrombin time, INR	>1.2 vs ≤1.2	1.200	0.745 to 1.930	0.450			NA
Total bilirubin, mg/dL	>2.0 vs ≤2.0	4.520	2.760 to 7.400	<0.001	3.263	1.795 to 5.930	<0.001
Albumin, g/dL	>3.0 vs ≤3.0	0.624	0.385 to 1.010	0.057			NS
Ascites	Yes vs no	1.680	1.050 to 2.670	0.030			NS
Tumour size, mm	>30 vs ≤30	3.730	2.250 to 6.180	<0.001			NS
Tumour number	Multiple vs single	2.980	1.760 to 5.050	<0.001			NS
PVT	Yes vs no	3.790	2.310 to 6.230	<0.001			NS
AFP, ng/mL	>10 vs ≤10	4.480	2.460 to 8.140	<0.001	2.638	1.340 to 5.190	0.005
BCLC stage	C/D vs A/B	6.840	3.920 to 12.000	<0.001	4.388	1.919 to 10.040	<0.001
Prophylactic method for EVB	EVL vs PPL	0.656	0.402 to 1.070	0.092			NS

AFP, alpha-fetoprotein; AL(S)T, alanine (aspartate) aminotransferase; BCLC, Barcelona Clinic Liver Cancer; EVB, oesophageal variceal bleeding; EVL, endoscopic variceal ligation; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; INR, international normalised ratio; NA, not applicable; NS, not significant; OS, overall survival; PPL, propranolol; PVT, portal vein thrombosis; SHR, subdistribution HR.

(figure 1). Thirteen patients were excluded according to the exclusion criteria. The remaining 144 patients were randomised to group A or B at a 1:1 ratio and included in the ITT analysis. In group A, three patients were lost to follow-up, and four discontinued interventions; in group B, two were lost to follow-up, and six discontinued interventions. Finally, 65 patients in group A and 64 in group B were included in the PP analysis.

The most common aetiology of liver disease was HBV infection (56.3%), with no significant between-group difference regarding viral suppression at baseline (p=0.678) or during follow-up (p=0.421; online supplemental table 1). Among the 144 enrolled patients, 142 (98.6%) had cirrhosis, and 2 developed HCC directly after chronic HBV infection (one patient per group). These two groups did not show significant differences in baseline patient characteristics (table 1).

Haemodynamic response and variceal eradication

Patients in group B had a lower SBP, diastolic blood pressure and PR than those in group A 1 month after randomisation (all, p<0.001; online supplemental table 2). Forty-two (58.3%) patients in group B reached a target dose of PPL, including 24 (66.6%) with BCLC stage A/B and 18 (50.0%) with BCLC stage C/D. The stable dose of PPL was 40 (20–80) mg. Forty (55.6%) patients in group A achieved variceal eradication at last follow-up, including 31 (86.1%) with BCLC stage A/B and 9 (25.0%) with BCLC stage C/D. The number of EVL sessions performed was 2 (1–4) in group A, 4 (2–5) in patients who achieved variceal eradication and 1 (1–2) in those who did not achieve eradication. The number of bands applied was 12 (7–17). The time to variceal eradiation was 3.3 (1.9–7.5) months.

Oesophageal variceal bleeding

After a follow-up of 7.4 (1.9–33.6) months in group A and 4.7 (2.2–12.9) months in group B, 7 patients in group A and 19 in group B experienced EVB. In the ITT analysis, the 0.5, 1, 2 and 5-year cumulative incidence (95% CI) of EVB was 7.0% (1.0%–13.0%), 10.3% (3.0%–17.7%), 10.3% (3.0%–17.7%) and 10.3% (3.0%–17.7%), respectively, in group A and 10.6% (3.1%–18.2%), 22.5% (12.0%–33.1%), 29.6% (17.2%%–42.0%) and 35.5% (21.8%–49.3%), respectively, in group B. Patients in group A had a lower cumulative incidence of EVB than their counterparts in the ITT analysis (Gray's test, p=0.009; (figure 2A). In multivariate analysis, EVL (subdistribution HR (SHR) 0.347, 95% CI 0.134 to 0.893, p=0.028) and largest variceal size (SHR 2.115, 95% CI 1.002 to 4.467, p=0.050) were independent prognostic factors of EVB (table 2).

We identified a first-order interaction between the prophylactic method and BCLC stage in the EVB model. Therefore, subgroup analysis stratified by BCLC stage was performed. Among patients with BCLC A/B, only 1 patient in group A and 13 in group B experienced EVB. The cumulative incidence of EVB was lower in group A than in group B (p<0.001; figure 2B). In multivariate analysis, EVL (SHR 0.064, 95% CI 0.008 to 0.513, p=0.010) was the only independent predictor of a lower risk of EVB (online supplemental table 3). In contrast, for patients with BCLC C/D, six patients each in groups A and B experienced EVB. The cumulative incidence of EVB was not different between the two groups (p=0.675; figure 2C). The number of patients who experienced EVB in the two groups stratified by BCLC stage and treatment integrity is provided in online supplemental figure 1.

Similar to the ITT analysis, the PP analysis results showed that the cumulative incidence of EVB was lower in group A than in group B in all patients with HCC (p=0.015) and in patients with BCLC A/B (p<0.001) but was similar between the two groups in patients with BCLC C/D (p=0.584; online supplemental figure 2).

No differences were observed in EVB between the two groups in patients with HCC with portal vein thrombosis (PVT) (p=0.611; online supplemental figure 3), BCLC C only (p=0.269; online supplemental figure 4) and BCLC C treated with sorafenib (p=0.840) or without sorafenib (p=0.265; online supplemental figure 5). In contrast, the cumulative incidence of EVB was lower in group A than in group B among patients with HCC without PVT (p<0.001; online supplemental figure 6).

Other UGIB

Other UGIB occurred in nine patients in group A and in five patients in group B during follow-up (online supplemental table 4). The cumulative incidence of other UGIB was not different between the two groups (Gray's test, p=0.296; online supplemental figure 7).

Non-bleeding liver decompensation

No differences were observed in the cumulative incidence of development/worsening of ascites (Gray's test, p=0.699), hepatic encephalopathy (p=0.805), spontaneous bacterial peritonitis (p=0.161) and hepatorenal syndrome (p=0.713) between the two groups (online supplemental figure 8).

Overall survival

After a follow-up of 7.7 (2.0–33.6) months in group A and 7.3 (2.4–16.3) months in group B, 30 patients in group A and 40 in group B died (online supplemental table 4). Three patients in group A and two in group B underwent liver transplantation. The OS was not significantly different between the two groups in the ITT analysis (Gray's test, median OS: not reached vs 15.9 months, p=0.085; figure 3A). In multivariate analysis, aspartate aminotransferase (AST) >40 U/L (SHR 3.011, 95% CI 1.359 to 6.670, p=0.007), total bilirubin >2.0 mg/dL (SHR 3.263, 95% CI 1.795 to 5.930, p<0.001), alpha-fetoprotein (AFP) >10 ng/mL (SHR 2.638, 95% CI 1.340 to 5.190, p=0.005) and BCLC stage C/D (SHR 4.388, 95% CI 1.919 to 10.040, p<0.001) were independent predictors of poorer OS (table 3).

We found a first-order interaction between the prophylactic method and BCLC stage in the OS model. Therefore, subgroup analysis stratified by the BCLC stage was performed. Notably, in the subgroup of patients with BCLC A/B, patients in group A had a better OS than their counterparts (median OS: not reached vs 37.9 months, p=0.003; figure 3B). EVL (SHR 0.268, 95% CI 0.104 to 0.694, p=0.007) and total bilirubin >2.0 mg/dL (SHR 2.789, 95% CI 1.039 to 7.484, p=0.042) were independent prognostic factors of OS in patients with BCLC A/B (online supplemental table 5). However, in the BCLC C/D subgroup, no between-group difference in OS was observed (median OS: 2.3 months vs 4.5 months, p=0.554; figure 3C).

The PP analysis showed that OS was better in group A than in group B, both in the entire HCC cohort (p=0.046) and in patients with BCLC A/B (p=0.004) but was similar between the two groups in patients with BCLC C/D (p=0.601; online supplemental figure 9).

No differences in OS were observed between the two groups in patients with HCC with PVT (p=0.541; online supplemental figure 3), BCLC C only (p=0.788; online supplemental figure 4),and BCLC C treated with sorafenib (p=0.416) or without sorafenib (p=0.668; online supplemental figure 10). In contrast, OS was better in group A than in group B among patients with HCC without PVT (p=0.045; online supplemental figure 6).

Adverse events

The two groups had no difference in the proportion of patients with any AE (p=0.230; table 4). However, patients in group B had a higher incidence of weakness (22.2% vs 9.7%, p=0.041), dizziness (12.5% vs 0 %, p=0.003) and exertional dyspnoea (13.9% vs 0%, p=0.001) than those in group A. Six and eight patients in group B discontinued and reduced PPL, respectively, due to AEs. Clinically significant bleeding was observed in 2 of 7 patients with EVB in group A and in 10 of 19 patients with EVB in group B. Three patients in group A experienced post-EVL ulcer bleeding; none of these episodes were fatal.

Table 4 Adverse events

Variables	EVL (group A) (n=72)	PPL (group B) (n=72)	P value
Any adverse event	24 (33.3%)	31 (43.1%)	0.230
Weakness	7 (9.7%)	16 (22.2%)	0.041
Dizziness	0 (0%)	9 (12.5%)	0.003
Exertional dyspnoea	0 (0%)	10 (13.9%)	0.001
Nausea	0 (0%)	3 (4.2%)	0.245
Vomiting	0 (0%)	2 (2.8%)	0.497
Bradycardia	0 (0%)	1 (1.4%)	>0.999
Hypotension	0 (0%)	3 (4.2%)	0.245
Anorexia	1 (1.4%)	1 (1.4%)	>0.999
Dysphagia	5 (6.9%)	0 (0%)	0.058
Chest pain	4 (5.6%)	0 (0%)	0.120
Abdominal fullness	4 (5.6%)	0 (0%)	0.120
Cough	3 (4.2%)	0 (0%)	0.245
Post-EVL ulcer bleeding	3 (4.2%)	NA	NA

Values are n (%).
EVL, endoscopic variceal ligation; NA, not applicable; PPL, propranolol.

DISCUSSION

This study showed that EVL was more effective than PPL in preventing initial EVB in patients with HCC and medium-to-large EVs. Notably, EVL not only reduced EVB but also improved OS in patients with BCLC stage A/B HCC. However, the advantages of EVL were not observed in patients with BCLC stage C/D HCC. This is the first randomised trial to demonstrate the superiority of EVL over PPL as a primary prevention strategy in patients with HCC with medium-to-large EVs.

Previous trials showed that prophylactic EIS can prevent bleeding and improve survival in selected patients with HCC and varices compared with controls.[5–7] However, EVL has now replaced EIS as the first-line endoscopic therapy for EVB owing to its lower rebleeding and complication rates.[22 31] According to the Baveno VII consensus, NSBB is recommended for decompensation prevention in patients with clinically significant PHT. EVL is recommended for compensated patients with high-risk EVs who have contraindications for or are intolerant of NSBBs.[12] However, studies exploring the role of primary prevention strategies in patients with HCC and high-risk EVs are scarce. A retrospective study reported that the primary prevention of EVB is associated with a lower mortality risk in patients with HCC.[10] Nevertheless, no randomised trials have directly compared the efficacy of EVL and NSBBs in terms of primary prevention of EVB and OS in patients with HCC; therefore, the better choice for this PHT subgroup is unclear.

In this study, we found that EVL significantly reduced the risk of initial EVB compared with PPL in patients with BCLC stage A/B HCC. As shown in online supplemental figure 1, most (86.1%) patients with BCLC A/B in the EVL group could achieve variceal eradication. Once variceal eradication was achieved, no patient developed EVB during follow-up. In contrast, only two-thirds of patients with BCLC A/B in the PPL group reached the target dose. The remaining patients failed to reach the target dose because of PPL AEs (16.6%), death before reaching the target (5.6%) or poor compliance (11.1%), thus limiting the protective effect of PPL. Notably, EVB still occurred in one-third of patients who reached the target PPL dose. In contrast to patients with cirrhosis, patients with HCC may have residual, recurrent or progressive tumours even after treatment, resulting in continual increases in portal pressure, thereby counteracting the effect of PPL. Additionally, PPL may not reduce the increased

HVPG levels caused by intratumoural arteriovenous shunting and structural changes. Furthermore, the median PPL dose was only 40 mg daily in this study, which was lower than that used in previous studies enrolling patients with cirrhosis.[23 32–34] This may be related to the fact that patients with HCC were frailer than patients with cirrhosis and required concurrent treatments for HCC, making them less tolerant to PPL.

In addition to the advantages of reducing the EVB risk, EVL also improves OS compared with PPL in patients with BCLC stage A/B HCC. In this study, only one patient with BCLC A/B in the EVL group experienced EVB that did not cause death. In contrast, in the PPL group, 13 patients developed EVB, 5 (38.5%) of whom died. In multivariate analysis, EVL was an independent predictor of better OS in the BCLC A/B subgroup. Variceal bleeding has been reported to be an independent risk factor for mortality in patients with HCC.[10] Our study demonstrated that compared with PPL, EVL significantly reduces the EVB risk, thereby improving OS in patients with BCLC A/B HCC.

However, in patients with BCLC stage C/D HCC, no significant differences in EVB and OS between the EVL and PPL groups were observed. Patients with advanced HCC are most likely to die of tumour progression and liver decompensation within a short period.[35] In this study, the OS of patients with BCLC C/D HCC are too short to demonstrate the benefits of EVL and PPL in EVB prevention. Furthermore, only a quarter of the EVL group achieved variceal eradication, and half of the PPL group reached the target dose in patients with BCLC C/D HCC. Due to the frailty of patients with advanced HCC, as well as the insufficient treatment integrity of EVL and PPL, no difference in EVB and OS can be observed between the two groups.

Recently, the advent of immunotherapy and new tyrosine kinase inhibitors has led to marked improvements in the OS of patients with advanced HCC.[36] In the IMbrave150 study, the OS was significantly longer with atezolizumab plus bevacizumab than with sorafenib (19.2 months vs 13.4 months, $p<0.001$).[37 38] The HIMALAYA trial also demonstrated the superiority of tremelimumab plus durvalumab over sorafenib for OS (16.4 months vs 13.7 months, $p=0.0035$).[39] The unavailability of current combination immunotherapy may compromise the external validity of our findings in the BCLC stage C subgroup.

Although the HCC treatments could influence the OS and even the EVB, patients in the two groups received similar treatment modalities (table 1). Given the good balance of HCC treatments between the two groups, their impact on the outcomes was similar. Notably, no patients enrolled in our study received combination immunotherapy containing bevacizumab, which may increase the bleeding risk.[37 40] Therefore, the possible effects of bevacizumab on EVB are beyond the scope of this study.

The proportion of patients with any AE was similar between the two groups. However, patients in the PPL group had higher rates of weakness, dizziness and exertional dyspnoea than their counterparts. Relatively common side effects of NSBBs may preclude treatment or require discontinuation in 15%–20% of patients with cirrhosis.[20] In our study, 19.4% (14/72) of patients with HCC discontinued or reduced PPL due to AEs, consistent with previous study results.[20]

This study had several strengths. First, this was the first randomised trial to directly compare the efficacy and safety of EVL and PPL for the primary prevention of EVB in patients with HCC and medium-to-large EVs. Second, we enrolled patients with HCC with various tumour stages and hepatic functional reserves in line with real-world clinical practice. Third, the baseline patient characteristics were comparable between the two groups, thus eliminating selection bias. Fourth, the ITT analysis results were consistent with those of the PP analysis, making our findings more reliable.

This study had some limitations. First, the HVPG measurements were lacking. Nevertheless, the feasibility of HVPG measurement in patients with HCC is limited owing to the invasiveness of the procedure and patient fragility. EVB, one of the most common PHT-related complications, was the primary endpoint. Thus, HVPG assessment was not essential for this study, according to the Baveno VII recommendations.[12] Second, carvedilol is currently the first-line treatment for primary prophylaxis in patients with clinically significant PHT.[12] However, most clinical trials and meta-analyses of carvedilol have excluded patients with HCC.[41–46] Whether carvedilol is superior to EVL or PPL for primary or secondary prophylaxis in patients with HCC remains to be clarified. In addition, at the time of the study design, limited evidence supporting the use of carvedilol existed. Third, more than half of enrolled patients had HBV-related HCC. The generalisability of our findings to areas in which HBV infection is not the major cause of HCC warrants further investigation.

In conclusion, this randomised trial showed that EVL is superior to PPL in preventing initial EVB in patients with HCC. The benefits of EVL on EVB and OS may be limited to patients with BCLC stage A/B and not to those with BCLC stage C/D. Further randomised trials with larger sample sizes are needed to draw firm conclusions on this important issue.

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