Early rebleeding and death at 6 weeks in alcoholic cirrhotic patients with acute variceal bleeding treated with emergency endoscopic injection sclerotherapy

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Abstract

Background. This study evaluated the incidence of rebleeding and death at 6 weeks after a first episode of acute variceal haemorrhage (AVH) treated by emergency endoscopic sclerotherapy in a large cohort of alcoholic cirrhotic patients.

Methods. From January 1984 to December 2006, 310 alcoholic cirrhotic patients (242 men, 68 women; mean age 51.7 years) with AVH underwent 786 endoscopic variceal injection treatments (342 emergency, 444 elective) during 919 endoscopy sessions in the first 6 weeks after the first variceal bleed. Endoscopic control of initial bleeding, variceal rebleeding and survival at 6 weeks were recorded.

Results. Endoscopic intervention controlled AVH in 304 of 310 patients (98.1%). Seventy-five patients (24.2%) rebled, 38 (12.3%) within 5 days and 37 (11.9%) within 6 weeks. No patient scored as Child-Pugh A died. Seventy-seven (24.8%) Child-Pugh B and C patients died, 29 (9.3%) within 5 days and 48 (15.4%) between 6 and 42 days. Mortality increased exponentially as the Child-Pugh score increased, reaching 80% when the score exceeded 13.

Conclusion. Despite initial control of variceal haemorrhage, 1 in 4 patients (24.2%) rebled within 6 weeks. Survival at 6 weeks was 75.2% and was influenced by the severity of liver failure, with most deaths occurring in Child-Pugh grade C patients.

Alcoholic liver disease is the leading cause of cirrhosis and portal hypertension in the Western world.[1-3] Variceal bleeding is the most serious complication of portal hypertension and substantially alters the natural history of patients with compensated alcoholic cirrhosis.[4,5] Up to 30% of initial bleeding episodes are fatal, and as many as 70% of survivors have recurrent bleeding after a first variceal haemorrhage.[6] Endoscopic therapy using either injection sclerotherapy or variceal band ligation is the emergency treatment of choice if actively bleeding oesophageal varices are present.[6-8] Although advances in treatment[9] have reduced overall mortality,[10-12] uncontrolled or recurrent bleeding from varices and the consequences of ensuing liver decompensation remain the commonest causes of death in alcoholic cirrhotic patients.[13,14] Early rebleeding has been shown to be a strong predictor of mortality and recurrent variceal bleeding substantially increases the risk of complications which further contribute to mortality,[15] emphasising that rapid and sustained control of variceal bleeding remains the principal imperative of endoscopic intervention.[16]

There is international consensus that assessment of the efficacy of treatment of bleeding oesophageal varices should be based on specific clinical outcomes.[17-19] These include the ability to achieve lasting haemostasis after the first variceal bleed, the risk of further variceal rebleeding, and death as a consequence of progressive liver decompensation.[17] In order to provide a consistent measure of standardisation and accuracy in the interpretation of data from different studies, specific and uniformly defined end-points that incorporate rebleeding and death have been formulated. The Baveno

consensus conferences[18,19] have recommended that rebleeding within 5 days after the initial treatment should be used as the first end-point to assess initial control of bleeding. As the risk of rebleeding and death remains high during the initial phase after the first bleed, the time frame recommended for the second end-point, also incorporating rebleeding and death, is 6 weeks following the first admission to hospital.[18-20]

Despite the widespread use of endoscopic therapy, few studies have specifically evaluated these endpoints in alcoholic cirrhotic patients with oesophageal varices.[21-24] Consequently, there is a paucity of accurate data on the efficacy of endoscopic control of bleeding, the frequency of early variceal rebleeding or survival in this high-risk cohort. Published results are variable and conflicting because of small sample sizes, referral bias, dissimilar study end-points, and differences in patient selection, methods and techniques of endoscopic intervention and the precise definition of rebleeding.[18,19,25] The objective of this prospective single-centre study was to evaluate the short-term efficacy at 6 weeks of flexible injection sclerotherapy in achieving control of acute variceal bleeding and preventing rebleeding and death in a large cohort of consecutively treated alcoholic cirrhotic patients with bleeding oesophageal varices.

Methods

Patient population

Consecutive adult alcoholic cirrhotic patients with endoscopically proven acute oesophageal variceal bleeding who were admitted to a specialist surgical gastroenterology unit between January 1984 and December 2006 were assessed. All patients included in the study received their first emergency and all subsequent endoscopic sclerotherapy injections in our unit. All data were recorded prospectively on a standard pro forma and entered on a computer programme maintained by a dedicated research assistant. The diagnosis of cirrhosis was established by findings on liver function tests, ultrasound and portal Doppler assessment, liver biopsy and, in selected patients, hepatic vein wedge pressure measurements. Cirrhosis was considered to be alcohol related if patients gave a history of sustained heavy alcohol consumption over several years with corroborative liver histological evidence and exclusion of other causes. The study analysis was approved by the departmental and institutional ethics and research committees.

During the 276-month study period, 632 consecutive adult patients were treated for oesophageal variceal bleeding in our unit. Of these, 206 patients had non-alcoholic causes of portal hypertension (53 cryptogenic cirrhosis, 38 hepatitis B-induced cirrhosis, 33 extrahepatic portal vein thrombosis, 23 cirrhosis secondary to chronic active hepatitis, and 59 other causes which included primary sclerosing cholangitis, primary and secondary biliary cirrhosis, splenic vein thrombosis, Budd-Chiari syndrome and haemachromatosis) and were excluded from further analysis. The remaining 426 patients had portal hypertension caused by alcohol-induced cirrhosis. Of these patients, 116 were not included in the study group because they had received endoscopic variceal band ligation, transjugular intrahepatic portosystemic stenting or liver transplantation during the initial 6 weeks after admission to hospital, or had positive hepatitis B or C viral markers as well as cirrhosis and a history of heavy alcohol consumption

(29 patients). Data in the remaining 310 patients with alcoholic cirrhosis and proven oesophageal variceal bleeding who received only sclerotherapy for bleeding form the basis of this study.

Clinical endpoints

Control of variceal bleeding was evaluated at three time points: initial control during the first presentation; rebleeding within 5 days, before the start of long-term preventive therapy; and rebleeding within 6 weeks. The primary clinical end-points of this study were: (*i*) failure to control variceal bleeding during endoscopic intervention; (*ii*) early rebleeding (<5 days) or later rebleeding (6 - 42 days) after initial endoscopic control; and (*iii*) mortality at 5 days and at 6 weeks.

Technique of sclerotherapy

The injection sclerotherapy technique used has been described previously in detail.[26-28] Both diagnostic endoscopy and injection sclerotherapy were performed using a fibreoptic endoscope (model GIF 1T20 or K10, Olympus Corp., Lake Success, NY) during the first decade of the study and video-endoscopy during the last decade. The sclerosant, 5% ethanolamine oleate, was injected using a combined intra- and paravariceal technique.[26-28] A maximum sclerosant volume of 25 ml was injected at any one sclerotherapy session for control of acute variceal bleeding. A similar volume was used when large varices (grade 4 or 5) were encountered during subsequent elective sclerotherapy. An intravariceal injection technique with smaller total volumes of sclerosant was used for elective sclerotherapy when varices were grade 3 or less in size.[26-28] The initial sclerotherapy session and the second one a week later were performed during the index admission to hospital. Subsequent sclerotherapy was undertaken at regular intervals on an outpatient basis until the varices were eradicated. Repeat injection sclerotherapy was performed whenever residual or recurrent varices were identified during surveillance endoscopy.

Rebleeding

Time zero was defined as the time of admission to hospital. Failure to control bleeding was defined as continued bleeding despite endoscopic injection and the use of balloon tamponade. Rebleeding was defined as any episode of upper gastrointestinal bleeding that occurred after the initial bleed had been successfully controlled by sclerotherapy, or if bleeding occurred subsequently between scheduled treatment sessions. All such bleeding episodes were investigated by emergency endoscopy, performed promptly after admission to hospital. Rebleeding was treated according to endoscopic findings. Additional sclerotherapy was undertaken if bleeding was due to patent residual varices. Other sources of bleeding, such as gastric and duodenal ulcers, gastric varices, erosive gastritis or portal hypertensive gastropathy, were included in the definition of rebleeding. For the purposes of the study, patient data were evaluated for 42 days from the admission date, and all bleeding events and complications related to the sclerotherapy and deaths during this period were recorded.

Statistical analysis

Data were stored on a spreadsheet registry (Microsoft Excel, Redman, WA) and Stata software (StataCorp 2003, Release 8; StataCorporation, College Station, TX) was used for the statistical analysis. Descriptive statistical methods were used

TABLE I. CHILD-PUGH GRADE, BLOOD TRANSFUSION, BALLOON TUBE AND VASOPRESSIN REQUIREMENTS TO CONTROL ACUTE VARICEAL BLEEDING

| Child-Pugh grade (N = number of patients)	A (N=44)	B (N=122)	C (N=144)	Total (N=310)	χ^2 (d.o.f)	p-value
No. of patients requiring a blood transfusion	24 (54.6%)	78 (63.9%)	109 (75.7%)	211	8.51 (2)	0.014
No. units of blood required						
Range	2 - 10	2 - 42	2 - 56	2 - 56		
Mean	4.4	7.8	10.8	9.0		
Median	4	6	6	6	21.4 (2)	<0.001
Units of blood per patient						
0	20	44	35	99		
1 - 6	22	47	57	126		
≥7	2	31	52	85	19.46 (4)	<0.001
Balloon tamponade	1 (2.3%)	17 (13.9%)	26 (18.1%)	44 (14.2%)	6.90 (2)	0.032
Vasopressin/ octreotide	0	14 (11.5%)	29 (20.1%)	43 (13.8%)	12.40 (2)	0.002
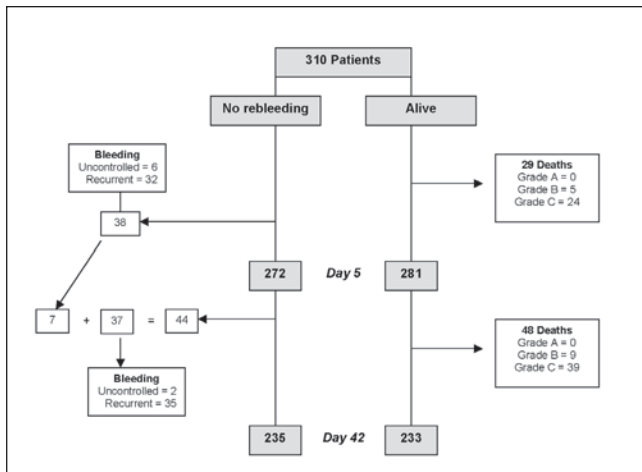
Fig. 1. Variceal rebleeding and death in 310 alcoholic cirrhotic patients assessed at day 5 and day 42.

to determine 5- and 42-day rebleeding and mortality rates. Bivariate associations between categorical variables were analysed using the χ^2 test. The Kruskal-Wallis test was used to assess blood requirements in units of blood in each of the 3 Child-Pugh grades. For all analyses, a p-value of less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance.

Results

Patient demographics

The 310 patients evaluated included 242 men and 68 women (mean age 51.7 years, range 24 - 87 years). Forty-four patients were Child-Pugh grade A, 122 were grade B and 144 were grade C when assessed on their first

admission to hospital (Table I). Two hundred and thirteen patients required a blood transfusion during the initial hospital admission. Balloon tamponade with a Sengstaken-Blakemore or Minnesota tube was used in 44 patients and vasopressin or octreotide was used in 43 (Table I). Eighteen patients received both use of a balloon tube and vasopressin. Significantly more Child-Pugh grade C patients required a major (>6 units) blood transfusion, use of a balloon tube and vasopressin to control variceal bleeding (Table I).

Day 0 - 5 rebleeding

Emergency endoscopic injection sclerotherapy, supplemented with balloon tamponade when necessary, controlled acute variceal bleeding in 304 of 310 patients (98.1%) (Fig. 1). In 6 patients (1.9%) variceal bleeding was not controlled despite using pharmacological and endoscopic therapy and balloon tamponade (Fig. 1). A further 32 patients had recurrent variceal bleeding within 5 days of initial endoscopic control and as a group required a further 39 emergency endoscopic variceal injection procedures (sclerosant volume mean 16.1 ml, median 15 ml, range 4 - 30 ml) to achieve definitive endoscopic variceal haemostasis. The 5-day endoscopic failure rate in achieving variceal haemostasis was 12.3% (38 of 310 patients).

Day 6 - 42 rebleeding

Rebleeding after the initial 5-day assessment and up to 6 weeks after the index variceal injection occurred in 44 (15.7%) of the 281 patients who survived more than 5 days (Fig. 1). Seven of the 44 patients had bled during the first 5 days and had further rebleeding episodes during this later period. These 44 patients had a total of 48 bleeding episodes and underwent a total of 83 repeat variceal injections (sclerosant volume range 2 - 30 ml, mean 13.5 ml, median 12.3
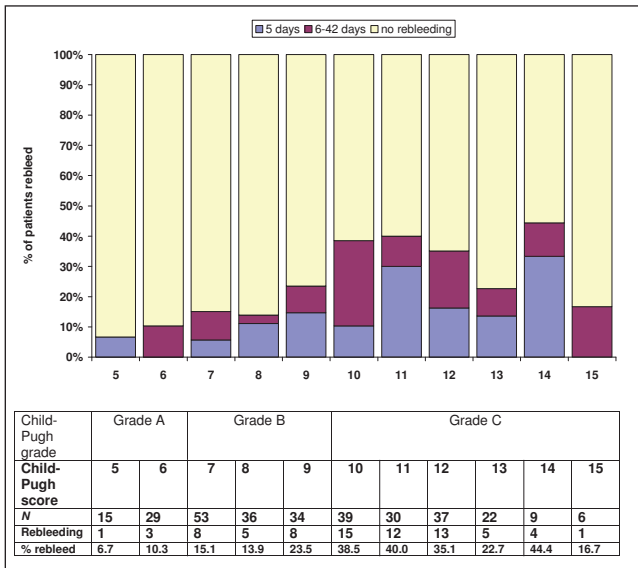
Fig. 2. Variceal rebleeding according to Child-Pugh score.

Child-Pugh grade	Grade A		Grade B			Grade C					
Child-Pugh score	5	6	7	8	9	10	11	12	13	14	15
N	15	29	53	36	34	39	30	37	22	9	6
Rebleeding	1	3	8	5	8	15	12	13	5	4	1
% rebleed	6.7	10.3	15.1	13.9	23.5	38.5	40.0	35.1	22.7	44.4	16.7

Fig. 3. Six-week mortality according to Child-Pugh score.

Child-Pugh grade	Grade A		Grade B			Grade C					
Child-Pugh score	5	6	7	8	9	10	11	12	13	14	14
N	15	29	53	36	34	39	30	37	22	9	6
Deaths	0	0	1	3	10	9	12	20	10	7	5
% deaths	0	0	1.9	8.3	29.4	23.1	40	54.1	45.5	77.8	83.3

ml) during the 6 - 42-day period. In this group 38 bleeding episodes were from varices and 10 from non-variceal sources including duodenal ulcer (N=1), portal hypertensive gastropathy (N=2), Mallory-Weiss tear (N=1) and oesophageal ulceration (N=2), with 4 sites not identified with certainty during endoscopy. Of the 44 patients who rebled, 13 (29.5%) died during the 6-week period. Overall 75 patients (24.2%) rebled during the 6-week assessment period after initial control during the index admission (Fig. 1). The incidence of rebleeding increased according to Child-Pugh score, with 25 (15.1%) of the 166 patients in grades A and B rebleeding compared with 50 (34.7%) of the 153 patients in grade C (Fig. 2). Significantly more Child-Pugh grade C patients than grade A or B patients rebled (p<0.001) (Table II).
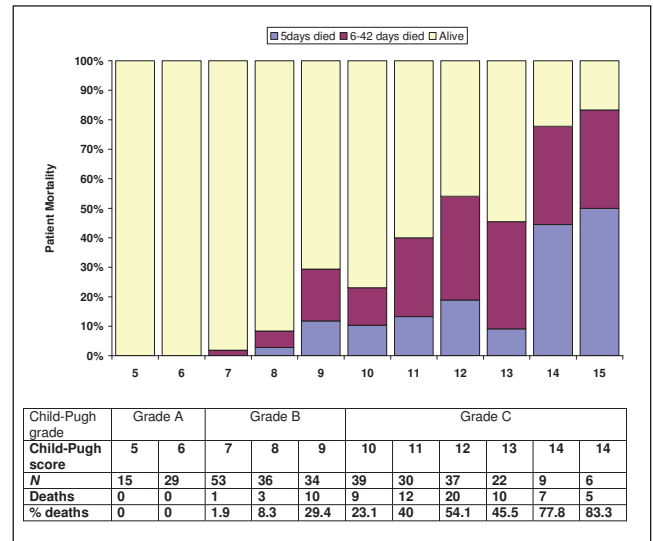
Overall mortality

Seventy-seven patients (24.8%) died during the 6-week study period (Fig. 1). Twenty-nine (9.3%) died within 5 days of admission and 48 (15.4%) between day 6 and day 42. No Child-Pugh grade A patients died, 14 grade B patients died, and 63 grade C patients died. Liver failure was the commonest cause of death (29 patients). Twelve patients died of hepatorenal failure and 11 of pneumonia and respiratory failure. Death in 25 patients was a consequence of continued or recurrent variceal bleeding. Survival at 5 days and 6 weeks in Child-Pugh grade A patients was 100% and 100% respectively, in grade B patients 96% and 92.7%, and in grade C patients 83.4% and 73% (Fig. 3). Significantly more grade C patients than grade A or B patients died (Table III). Mortality increased exponentially as the Child-Pugh score

TABLE II. REBLEEDING ACCORDING TO CHILD-PUGH GRADE

Variable	Class	Total	Rebleed <42 days	% rebleed	χ^2	p-value	Odds ratio	95% confidence interval
Child-Pugh grade	A	44	4	9%				
	B	122	21	17.2%				
	C	144	50	34.7%	17.41	<0.001	2.42	1.56 - 3.75

TABLE III. MORTALITY ACCORDING TO CHILD-PUGH GRADE

Variable	Class	Total	Died ≤42 days	% died	χ^2	p-value	Odds ratio	95% confidence interval
Child-Pugh grade	A	44	0	0				
	B	122	14	11.4%				
	C	144	63	43.7%	53.79	<0.001	6.91	3.79 - 12.58

increased, with a mortality rate of 78% for a score of 14 and 83% for a score of 15 (Fig. 3).

Sclerotherapy-related oesophageal complications

The 310 patients received 786 injection treatments (342 emergency, 444 elective) during a total of 919 endoscopy sessions in the 42-day period. A total of 338 complications were documented in 159 patients during surveillance or unscheduled endoscopy after a prior variceal injection. Minor complications of sclerotherapy were common after acute injection for active bleeding and included dysphagia, transient fever and pulmonary atelectasis. Mucosal ulceration at an injection site was found at follow-up endoscopy on 333 occasions in 155 patients. An oesophageal stricture at the injection site occurred in 5 patients after sclerotherapy. None required oesophageal dilatation and all 5 resolved spontaneously. No intramural oesophageal haematoma or oesophageal perforations occurred in any of the 310 patients.

Discussion

This study used a large single-centre dataset of alcoholic cirrhotic patients with portal hypertension and bleeding varices to assess the efficacy of endoscopic injection sclerotherapy in achieving primary haemostasis and preventing subsequent variceal rebleeding and death. The data demonstrated that endoscopic therapy was highly effective in controlling acute bleeding from oesophageal varices and that ultimate survival was influenced by both rebleeding and underlying liver reserve. Sustained control of acute bleeding is a critical requirement in variceal management because each subsequent bleed worsens marginal liver function.[29] However, despite urgent endoscopic and pharmacological therapy, variceal bleeding recurs in up to 20% of patients after the initial endoscopic intervention.[30,31] In addition, early variceal rebleeding significantly increases the risk of death within 6 weeks of the initial bleed.[30,32] Although initial endoscopic intervention controlled acute variceal bleeding in 98% of patients, 10.3% rebled within 5 days and 24.2% during the first 6 weeks. The 6-week rebleeding rate in the present study was higher than the 18.6%[33] and 19%[29] reported by other authors, probably because of our strict prospective rebleeding definition and a high-risk alcoholic cirrhotic cohort. The incidence was similar to the 23% reported by Hartigan et al.,[22] but significantly lower than the 31% mortality reported in an earlier study by Graham and Smith.[34]

It is clear from our observations and those of others[20,35,36] that the efficacy of sclerotherapy in controlling acute oesophageal variceal bleeding and mortality from bleeding are closely related to the severity of the underlying liver disease. As anticipated, mortality in our study increased exponentially as liver reserve diminished. There were no deaths in Child-Pugh grade A patients, and in this cohort with preserved liver function early mortality was not influenced by the severity of the bleeding episode. Our data demonstrated that Child-Pugh grade C patients, who have the least hepatic reserve, were more likely to have a major bleed and require pitressin or octreotide and balloon tamponade in addition to sclerotherapy to control acute bleeding. Our study shows that in this high-risk group, even when sclerotherapy successfully controlled variceal bleeding, progressive liver failure resulted in high mortality rates in the first 6 weeks after admission,

especially in patients with a Child-Pugh score >13, who had an 80% mortality.

Recent data show that mortality from variceal bleeding has decreased substantially from the 42% mortality reported in the seminal study by Graham and Smith in 1981[34] to current levels of around 20%.[30] This significant improvement in survival reflects improvement in both general management of severely ill cirrhotic patients and treatment of hepatic decompensation, which strongly influence the prognosis.[37] While it has been suggested that complications of portal hypertension, including variceal bleeding, are predictors of mortality in patients with liver cirrhosis, survival appears to be largely dependent on the severity of the underlying liver disease and it is now recognised that the degree of hepatic dysfunction is of overriding prognostic significance for patient survival.[37] Our study evaluated mortality at two time points: at 5 days, when mortality is considered a direct consequence of the bleeding episode, and at 6 weeks, when it is a function of the adequacy of liver reserve. Overall survival for the entire cohort was 90.6% at 5 days and 75.2% at 6 weeks. The survival rate at 6 weeks in our cohort of decompensated alcohol-related cirrhotic patients was similar to the 23.6%,[33] 18.4%,[36] 19.0%[29] and 17.5%[11] reported by other authors, but higher than the 15.3% mortality reported by Boix et al. in 274 patients with cirrhosis of different causes evaluated between 1997 and 2006.[38]

Although several prognostic models have been proposed to predict mortality in patients with cirrhosis, the Child-Pugh score remains the most widely used scoring system both in clinical practice and in clinical research[39] and is equal to or superior than other predictive systems in determining mortality within the first 6 weeks after a major variceal bleed.[39-43] In a systematic review of 118 studies of cirrhotic patients, the most common independent predictor of death was the overall Child-Pugh score, followed by each of the five components of the Child Pugh score.[39] The advantages of the Child-Pugh score over more complex scores such as the Model for End-Stage Disease (MELD) score is that the Child-Pugh score is simple and easy to use and can be calculated at the bedside using mental arithmetic. Two significant flaws in the Child-Pugh score, however, are subjectivity in the assessment of the degree of ascites and encephalopathy and inability to distinguish mild from severe grade C patients with sufficient discrimination.[44] The Child-Pugh grade and scores in our study showed a significant association between grade A, B and C patients and the incidence of rebleeding and death at 6 weeks.

Several important and unresolved issues relating to the specific roles of injection sclerotherapy as opposed to variceal banding in the management of patients with actively bleeding oesophageal varices remain. In most centres worldwide endoscopic variceal ligation has now replaced injection sclerotherapy in the elective treatment of oesophageal varices.[45] Injection sclerotherapy is an invasive endoscopic procedure which requires a high degree of manual dexterity, skill and experience, especially during a major acute variceal bleed.[46,47] Unlike endoscopic variceal band ligation, sclerotherapy is not standardised and there is wide variation in the injection technique, including the type and strength of sclerosant used, the method and frequency of injection, and the regularity of endoscopic surveillance.[20,45] Data from randomised controlled trials of patients with acute variceal bleeding show equivalence between endoscopic variceal liga-

tion and injection sclerotherapy in achieving initial haemostasis. Furthermore, randomised controlled trials indicate that ligation achieves more rapid eradication of varices with lower rates of recurrent bleeding and fewer complications such as strictures and perforation during elective therapy.[48] Despite these advantages, a survey by the American College of Gastroenterology International GI Bleeding Registry shows that sclerotherapy is still used as frequently as banding for endoscopic intervention during index bleeding, and more frequently than banding for control of variceal rebleeding.[49] The practical advantages of endoscopic sclerotherapy include its ability to achieve definitive control of variceal bleeding under direct vision, ease of use, convenience and low cost. A recent meta-analysis assessing emergency sclerotherapy for acute variceal bleeding in randomised trials suggests that sclerotherapy at the time of the initial endoscopy should remain the first-choice therapy.[8] An additional consideration reported in several randomised controlled trials comparing band ligation with sclerotherapy is a higher long-term variceal recurrence rate in patients undergoing band ligation.[48] If this observation is confirmed by other studies, the consequences could reduce or even abolish the long-term advantage of band ligation over sclerotherapy.[50] The results of this study using sclerotherapy serve as the reference level for comparison by future endoscopic ligation studies.

The results of our study clearly define the course and prognosis of patients with decompensated alcohol-related cirrhosis and bleeding varices. Despite substantial improvement in overall survival in recent years,[51,52] the 6-week mortality after variceal bleeding remains discouragingly high, especially in Child-Pugh grade C patients,[53] who die either from uncontrolled initial variceal bleeding or early rebleeding, or subsequently from the consequences of infection, liver and renal failure in the first weeks after a bleeding episode. As shown in this and other studies, most deaths were due not to bleeding but to the detrimental systemic consequences that lead to progressive deterioration of liver function.[36] The presence of advanced Child-Pugh score (>13) in this study identified patients at higher risk of dying. Our study confirms the observations of others[22] that, in experienced centres endoscopic injection sclerotherapy can be performed safely and effectively in alcoholic cirrhotic patients with actively bleeding oesophageal varices. However, even under optimal conditions, currently available treatment options fail to control initial variceal bleeding or prevent early rebleeding in up to 20% of patients, some of whom may require rescue intervention. Because most patients who fail first-line endoscopic and pharmacological therapy are at high risk and have marked liver decompensation complicating the variceal bleeding, transjugular intrahepatic portosystemic shunting (TIPS) has become the most widely used salvage therapy but still has an overall mortality in excess of 30%.[54] The essential future requirements for improving survival in these high-risk patients are self-evident and include effective control of acute variceal bleeding, prevention of further rebleeding and minimising deterioration of liver function. The early recognition of endoscopic failures and implementation of newer technologies for local control, including self-expanding oesophageal metal stents,[55] enhanced efficacy of long-acting drugs[56] and improved quality PTFE-coated TIPS stenting,[57] should provide better haemostasis in this high-risk cohort.

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