

PREDICTION OF OUTCOME FOLLOWING ACUTE VARICEAL HAEMORRHAGE

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I declare that this thesis has been composed by myself. Its content relates to work initiated and carried out by myself during my clinical appointments to the University Department of Surgery, Glasgow Royal Infirmary from August 1979. Contributions by other individuals are clearly indicated in the Acknowledgements.

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## ABSTRACT

Between August 1979 and September 1982, acute variceal haemorrhage has been managed in the University Department of Surgery, Glasgow Royal Infirmary by a policy of oesophageal tamponade and injection sclerotherapy. Haemorrhage was controlled in 90% of admissions with an admission mortality of 28%. Recurrent haemorrhage occurred in half the patients surviving their first admission to hospital despite entering a programme of elective sclerotherapy. The results of this management policy are reviewed and the means of selecting patients for more aggressive therapy discussed. The deficiencies of a modified Child's classification in selection of patients are highlighted and overcome by the development of a prognostic index obtained by regression analysis on data collected on patients managed over this 3 year period.

The admission prognostic index clearly defines 'high' and 'low' risk groups and 'predicts' outcome following admission in 90% of patients. The use of this index is validated in a further group of patients managed by a similar policy. Further regression analysis is used to obtain a prognostic index for alcohol cirrhotic patients alone and to determine the factors associated with one year survival. These indices are used to audit the management policy. Prothrombin, creatinine and encephalopathy are shown to have a clear association with outcome when measured at the time of variceal haemorrhage whereas other factors

such as albumin and haemoglobin emerge as having prognostic value when measured one month following the acute episode.

The possible applications of these prognostic indices are investigated in a prospective two centre study assessing the efficacy of propranolol in preventing recurrent variceal haemorrhage. It is shown that they can be used to exclude patients from entry into a study assessing the longterm benefit of propranolol when the prospects of short-term survival are limited. Their value in auditing management and their possible use in withdrawing treatment are shown. The prognostic indices are used to compare results of treatment at the two hospitals and are shown to be of value in analysing the results of the trial.

These prognostic indices provide an objective means of evaluating patient management and may allow selection of patients for consideration of other treatment options.

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Prediction of outcome following admission with variceal haemorrhage.  
Br. J. Surg. 1985, 72, 91-95.



Garden, O.J., Utley, R.J. and Carter, D.C.

The prevention of recurrent variceal haemorrhage by chronic injection sclerotherapy.

Scot. Med. J. 1985, 30, 148-151.

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Factors influencing the risk of rebleeding and one year survival following acute variceal haemorrhage.

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- i. Introduction
- ii. History of management of variceal haemorrhage
- iii. Natural history of variceal haemorrhage
- iv. Assessment and selection of patients in management of portal hypertension
- v. Aim of thesis



i. INTRODUCTION

In this review of the literature, an attempt is made to trace the evolution of the treatment of variceal haemorrhage and to record the natural history of this condition. The methods used to assess the severity of the underlying liver disease are discussed, particular emphasis being placed on the development of classifications and scoring systems and their use in selecting patients for different therapeutic options.

ii. THE HISTORY OF THE MANAGEMENT OF VARICEAL HAEMORRHAGE

Although Creuveilhier and Baumgarten described an external collateral circulation in cirrhosis in 1829, it was not until 10 years later that oesophageal varices were first identified by Powers (Kleckner, 1960). Frerichs associated the presence of oesophageal varices and splenomegaly with cirrhosis in 1879 but it was Banti four years later, who described the clinical syndrome comprising cirrhosis, splenomegaly, anaemia and haematemesis. His belief that cirrhosis was induced by a splenic toxin subsequently misled investigators over the next 50 years in directing surgical management of the condition at the spleen.

By 1876 Eck had performed the first portacaval anastomosis in dogs and had suggested that this operation might be of value as a means of controlling ascites in the cirrhotic patient. In 1903 Vidal, a French surgeon, performed the first successful



end-to-side portacaval shunt in man for this condition but McIndoe (1928) was the first in the English literature to suggest that the Eck fistula would arrest the development of varices. By the mid 1930's opinion had moved away from Banti's theory on the aetiology of cirrhosis and Larrabee (1934) and Rousselot (1936) independently identified the liver as the actual site of obstruction causing portal hypertension.

In 1938, Rousselot and Whipple performed the first shunt, albeit unsuccessfully, for variceal haemorrhage in the United States of America (Grannis, 1975) and were followed by Blakemore and Lord who performed shunts beginning in 1942. Their work quickly established the role of portal systemic shunting operations in the management of bleeding oesophageal varices and with the development of oesophageal balloon tamponade, a decade of intense enthusiasm ensued. By 1975 it was estimated that some 100,000 shunts had been performed worldwide (Bengmark, 1975). However, by the 1960's several controlled trials had cast serious doubts on the value of shunt surgery and had shown that survival was not enhanced for the prophylactically shunted patient (Jackson et al, 1968; Resnick et al, 1968; Conn et al, 1972). These studies showed that prophylactic shunts offered no benefit over medical therapy since only 25-40% of patients with alcohol cirrhosis subsequently bled and the poor survival and increased risk of developing hepatic encephalopathy appeared to outweigh the possible benefits of surgery. Although portacaval

shunt consistently reduced the risk of variceal haemorrhage, it was not shown to significantly prolong the duration of survival even in the therapeutically shunted patient (Jackson et al, 1971; Resnick et al 1974; Rueff et al, 1976). In addition the control of haemorrhage was achieved at the cost of a high incidence of disabling encephalopathy.

Paralleling the popularity of shunt surgery in the United States of America, several investigators in Europe attempted a direct surgical approach to the problem of variceal haemorrhage. In 1930, Westphal had shown that compression of the bleeding varix with an oesophageal sound was a simple method of arresting haemorrhage. Several investigators in the late 1940's (Rowantree et al, 1947) suggested that an inflatable balloon could be used to compress the coronary veins as they communicate with the varices. In 1950 Sengstaken and Blakemore described the use of a three-lumen oesophago-gastric tube which compressed the fundal and oesophageal veins. This tube and its four-lumen modification (Edlich et al, 1968) could be used as a means of temporarily controlling haemorrhage but the high risk of further haemorrhage on removal of the tube led others to consider a more permanent direct approach.

In 1939, Crafoord and Frenckner described the technique of repeatedly injecting a sclerosant via an oesophagoscope directly into the varices to control variceal haemorrhage. Interest in this technique was

slow to develop because of the enthusiasm for shunt surgery. Although it was not until 1955 that Macbeth reported its use in the United Kingdom, Johnston and Rogers (1973) were responsible for its general adoption as a means of controlling variceal haemorrhage. At the present time it appears to be the most popular method of arresting and preventing recurrent variceal haemorrhage in the United Kingdom (MacDougall et al, 1982; Sinnett et al, 1982), and interest in its use is increasing in the United States of America (Galambos, 1983). Although sclerosis of varices via the transhepatic route has been described, recent results would suggest that it has limited value in the management of these patients (Bengmark et al, 1979).

A more aggressive direct approach to the problem of variceal haemorrhage was pursued by Boerema and Crile who independently described trans-oesophageal ligation of varices in 1949 and 1950. Intermittent reports of its successful use were described by Walker in 1964 and by George and Pugh in 1973. Johnston in Belfast has the largest experience of stapled oesophageal transection but has restricted its use to the elective patient (Johnston, 1982). The role of this therapeutic option in the management of bleeding varices has yet to be defined.

Until recently, the pharmacological management of portal hypertension was able only to produce a temporary reduction in portal venous pressure sufficient to arrest variceal haemorrhage. Vasopressin was first shown to

lower portal venous pressure by Clarke in 1928, but it was Kehne in 1956 who demonstrated that it could control bleeding from oesophageal varices. Shaldon and colleagues (1960) showed that it was effective in arresting haemorrhage when given as a bolus intravenous dose in all eight patients assessed. Although its successful use has been recorded when infused through the superior mesenteric artery (Conn et al, 1975), it is more frequently given as a peripheral infusion and control of haemorrhage is reported using this method in 9-86% of patients (Sagar et al, 1979; Freeman et al, 1982). A synthetic analogue of vasopressin, triglycyl lysine vasopressin (glypressin), has a more prolonged action, may have fewer side effects and may be more effective in controlling haemorrhage (Freeman et al, 1982). Interest has recently been shown in the use of somatostatin. Thulin and colleagues (1979) reported its use in a series of five patients, all of whose episodes of variceal haemorrhage was controlled. In a controlled study, Kravetz et al (1984) showed that it was as effective as vasopressin in controlling haemorrhage.

All these pharmacological agents offer temporary control of haemorrhage but propranolol has been shown to produce a sustained reduction in portal venous pressure, liver blood flow and cardiac index (Lebrec et al, 1981). In one study of cirrhotic patients who had gastrointestinal haemorrhage and were treated with propranolol, the proportion who remained free of gastrointestinal bleeding after one year was 96%

compared to 50% in a placebo group (Lebrec et al, 1981). However, further studies in patients with varying degrees of liver failure and cirrhosis failed to demonstrate any effect on rebleeding rate or survival (Burroughs et al, 1983). Further studies are required to determine the role of this mode of therapy in the longterm prevention of variceal haemorrhage.

It is of interest to note that Eck recommended the application of the portacaval fistula in man based on experimental operations on eight dogs, seven of which died immediately following the operative procedure, the eighth escaping from the kennel at 10 weeks at which time patency of the shunt was not established. The management of portal hypertension has pursued a similar course over the last century. Intense enthusiasm has followed the description of each new therapeutic modality only for enthusiasm to wane as controlled studies have revealed their limitations.

### iii. THE NATURAL HISTORY OF VARICEAL HAEMORRHAGE

Haemorrhage from oesophageal varices is relatively uncommon accounting for between 3-5% of all cases of upper gastrointestinal haemorrhage managed in hospital (Hislop et al, 1966; Johnston et al, 1973; Forrest et al, 1974). The mortality of this condition is high, the prognosis generally being determined by the severity of the underlying hepatocellular disease (Novis et al, 1976; Sherlock, 1982). Attempts to improve survival by arresting haemorrhage and preventing recurrent

haemorrhage must take into account the natural history of the liver disease since the management policy may compromise liver function.

Stone and colleagues (1968) reviewed the outcome of 155 patients presenting over a six year period with cirrhosis. Only 12% of this population presented with gastrointestinal haemorrhage and in half of them, it was a terminal event. Seventeen percent subsequently bled from oesophageal varices and the main cause of death was liver failure (34%) and hepatoma (18%). The five year survival of the total population was 14%. Mortality was worse if ascites was one of the presenting features and in the sub-group with cryptogenic cirrhosis as the cause of portal hypertension. Saunders and colleagues (1981) have confirmed the poor prognosis in cryptogenic cirrhotic patients, the five year survival of 14% being considerably lower than 36% and 60% for alcoholic cirrhosis and chronic active hepatitis respectively. Death in this large series of 512 patients was most often due to liver failure (37%), hepatoma (20%) and gastrointestinal haemorrhage (16%). Those patients presenting with well compensated liver disease had a much better prognosis than those with ascites or encephalopathy on presentation. In alcohol cirrhotics survival was improved in both the decompensated and compensated patients if they abstained from alcohol.

Few studies have satisfactorily documented the outcome for patients who have not undergone treatment for their variceal haemorrhage. Hislop (1966) described



the course of 63 patients presenting at two general hospitals over a 22 year period. Thirty-four (54%) did not survive the initial admission although three of these underwent surgery. At five years only nine patients had survived (14%) but 16 of the 63 patients had undergone an operative procedure.

In a review of patients admitted with variceal haemorrhage to the San Francisco Hospital, Cohn and Blaisdell (1958) found that 337 (74%) of 456 patients did not survive their first admission to hospital. Recent studies have not shown such an unfavourable outcome, although Novis and colleagues (1976) demonstrated an admission mortality of 48% following presentation with acute variceal haemorrhage in patients not treated beyond oesophageal tamponade. A better impression of the natural history of acute variceal haemorrhage can be gained by looking at the outcome of patients assigned to control groups when an active form of therapy is being assessed. The early studies of therapeutic portacaval shunt surgery provide such an opportunity, albeit in a selected patient population. In both the VA Cooperative (Jackson et al, 1971) and Boston Inter-Hospital Liver Group studies (Resnick et al, 1974) the risk of recurrent variceal haemorrhage in non-treated patients was 65-70%. In the study of Resnick and colleagues (1974), 67% of these episodes of variceal haemorrhage occurred within the first year. Although these same investigators documented episodes of variceal haemorrhage beyond 18 months of follow-up, it should be

noted that 44% of these patients in the control group underwent an emergency portacaval shunt. Jackson and his colleagues (1971) found an identical incidence and timing of rebleeding in their medical control group and noted that 72% of all episodes of haemorrhage were moderate or severe. The overall mortality of control patients at five years was 52% and 54% for the Boston and VA studies respectively. In the latter study the primary cause of death was variceal haemorrhage in 41% of the patients assigned to the medical group whereas 21% died of progression of liver disease. In the Boston study (Resnick et al, 1974) death resulted from recurrent variceal haemorrhage in 67% of patients. These figures are substantiated by the experience of Rueff and colleagues (1976) whose controlled study of therapeutic portacaval shunt had a control group of 49 patients, 35 (71%) of whom experienced recurrent variceal haemorrhage. Twelve of the 35 (34%) died but seven of these patients underwent emergency shunt surgery. One and three year survival for the control group was 79% and 56% respectively and was not significantly altered for those patients who underwent emergency surgery. In interpreting these data, it has to be borne in mind that the patients studied were a selected population. In the VA hospital's study, the 79 patients entered were selected from a total of 832 presenting to these hospitals with acute variceal haemorrhage. Similarly the strict entry criteria in the study of Rueff and his colleagues (1976) resulted in the



exclusion of 211 patients such that only 89 (30%) patients were deemed suitable for this study.

Given the selectivity of the patients included in control studies of portacaval shunting, a more realistic impression of the natural history of variceal haemorrhage might be obtained by looking at studies assessing less invasive therapeutic modalities. In a more recent study assessing the efficacy of injection sclerotherapy (MacDougall et al, 1982), only nine of 141 patients (6%) admitted with variceal haemorrhage died on that admission. During a mean follow-up period of 9.5 months, the frequency of rebleeding was 75% in the control group who did not receive sclerotherapy. Moreover, the risk of rebleeding was greatest in those patients with severe liver disease. In this same study one year survival for the medically treated group was 58% and 77% of these deaths were thought to have been a direct result of variceal haemorrhage. In a further study assessing injection sclerotherapy in the longterm prevention of recurrent variceal haemorrhage, Terblanche and colleagues (1983) noted that 77% of patients sustained recurrent haemorrhage and the majority of these episodes occurred within the first six months of presentation. The one year survival of 50% was similar to that of the study of MacDougall and colleagues (1982) but only 8% of deaths in the control group were as a direct result of variceal haemorrhage. The lower mortality due to variceal haemorrhage may be accounted for by the fact that the control group received

injection sclerotherapy on each occasion that the patient presented with acute variceal haemorrhage. Although MacDougall and colleagues (1982) did not undertake injection sclerotherapy for acute variceal bleeds, 17% of their control group did undergo some form of active treatment.

In a study assessing the efficacy of propranolol in reducing the incidence of recurrent variceal haemorrhage, Lebrec and colleagues (1981) noted a 45% incidence of recurrent variceal bleeding at one year in the group of patients on placebo therapy. However, their study was undertaken in a selected group of cirrhotic patients who had no evidence of ascites, encephalopathy and jaundice. In a further similar study, Burroughs and colleagues (1983) had a similar incidence of rebleeding (50%) in their non-treated control group and in 18% of these patients this episode of bleeding was fatal. Although the authors of this latter study felt that they were dealing with a patient population manifesting more severe liver dysfunction than in the study of Lebrec and colleagues (1981), 60% of the patients entered into the study were assigned to a modified Child's grade A and 10% of their patients were graded C. All the patients entered into this particular study survived admission to hospital, although seven patients died before entry into the study, giving an admission mortality of 12%. The follow-up period was too short to allow estimation of one year survival.

From a review of these controlled studies, it can be seen that assessment of any therapeutic option must take into account the natural history of bleeding oesophageal varices but since the majority of deaths associated with variceal bleeding occur soon after the index bleed, any substantial improvement in longterm survival must improve survival for the early period (Graham et al, 1981). Most studies have purposely excluded early mortality and this has caused difficulties in interpreting and translating these results to the management of all patients presenting with acute variceal haemorrhage.

iv. ASSESSMENT AND SELECTION OF PATIENTS IN THE  
MANAGEMENT OF PORTAL HYPERTENSION

In 1954, Nachlas and others readdressed the question of survival of the variceal bleeder in an attempt to define the role of surgery. Although 60% of their patient population succumbed from their initial haemorrhage, only a third of the remainder died during the subsequent year. They noted that neither the cause of death nor the severity of haemorrhage was related to differences in the state of liver decompensation, though such differences were seen in the survivors of variceal haemorrhage. At a time when prophylactic shunts were shown not to improve survival, the use of physiological criteria to define the risk of surgery were becoming accepted. The description of a classification by Child in 1964 to record the degree of risk following

portacaval decompression occurred when interest in the therapeutic shunt was at its height. The classification used five variables of liver function to grade patients A, B or C depending upon the severity of the individual variable (Table 1.1). Using this grading system, survival rates decrease from grades A to C but in comparing these studies, there is a wide disparity in survival rates for individual grades (Table 1.2) (Foster et al, 1971; Graham, et al, 1972; Resnick et al, 1974; Orloff et al, 1980).

Child's original classification was rather inflexible in grading the severity of liver disease in that one adverse parameter, such as a low serum albumin, was sufficient to place a patient who otherwise had good liver function into grade C. The difficulties in using such a subjective system were well illustrated by Graham and Smith (1981) who found that 72% of their patient population were assigned grade C on the basis of the serum albumin alone but only 7% of the patients had encephalopathy severe enough to assign them to the same category (Table 1.3). Despite these limitations, many investigators have persisted in using this original classification as an indicator of operative mortality and long-term prognosis following shunt surgery (Shields, 1977) and as a means of selecting patients for consideration of shunt surgery (Johnston, 1981). Campbell and colleagues (1973) modified Child's grading by scoring each of the individual five parameters of liver function (Table 1.4) but it still included the

Table 1.1    Clinical and biochemical classification of patients with cirrhosis described by Child et al (1964) and used to assess risk in patients undergoing portosystemic shunting for variceal haemorrhage.

Group	A	B	C
Designation	Minimal	Moderate	Advanced
serum bilirubin (mg%)	<2.0	2.0-3.0	>3.0
serum albumin (mg%)	>3.5	3.0-3.5	<3.0
ascites	none	easily controlled	poorly controlled
neurological disorder	none	minimal	advanced; 'coma'
nutrition	excellent	good	poor; 'wasting'

Table 1.2 Survival of patients presenting with variceal haemorrhage in relation to original Child's classification and treatment.

<u>author</u>	<u>operation</u>	<u>class</u>		
		<u>A</u>	<u>B</u>	<u>C</u>
ADMISSION SURVIVAL				
Resnick	shunt	61%	21%	27%
Orloff	emergency shunt	78%	60%	41%
Foster	emergency shunt	100%	80%	15%
	elective shunt	97%	93%	56%
ONE YEAR SURVIVAL				
Graham	shunt	90%	74%	51%
Orloff	shunt	73%	45%	26%
Foster	shunt	82%	86%	-
THREE YEAR SURVIVAL				
Resnick	shunt	52%	26%	40%
Graham	shunt	72%	54%	17%
Foster	shunt	68%	72%	-
FIVE YEAR SURVIVAL				
Orloff	shunt	55%	38%	15%
Foster	shunt	33%	64%	-

Table 1.3 Classification of individual variables for  
patients presenting with variceal haemorrhage  
using original Child's classification  
(Graham et al, 1981)

criterion	no. of patients	<u>Child's class</u>		
		A	B	C
nutrition	66	31(47%)	14(21%)	21(32%)
albumin	74	4(5%)	17(23%)	53(72%)
bilirubin	77	32(42%)	16(21%)	29(38%)
ascites	76	35(46%)	27(36%)	14(18%)
encephalopathy	75	51(68%)	19(25%)	5(7%)
overall	83	3(4%)	22(26%)	58(70%)

Table 1.4 Modification of Child's original classification  
as described by Campbell et al (1973) for use  
in patients presenting with variceal  
haemorrhage

variable	<u>Points</u>		
	1	2	3
bilirubin	<2 mg%	2-3 mg%	>3 mg%
albumin	>3.5 mg%	3.0-3.5 mg%	<3.0 mg%
ascites	none	easily controlled	difficult to control
neurological disorder	none	minimal	advanced
nutrition	excellent	good	poor

risk grade A 5-8 points

B 9-11 points

C 12-15 points



subjective assessment of nutrition. In the same year, Pugh and his colleagues described a scoring system based on these same variables but included prolongation of prothrombin time and omitted the assessment of body nutrition (Table 1.5). This modified Child's classification has now been generally adopted as a means of grading liver dysfunction and appears to define short and longterm risk (Pugh et al, 1973; MacDougall et al, 1982; Sinnett et al, 1982; Burroughs et al, 1983) although there is a wide range of survival rates for individual grades.

Simert and colleagues (1978) have suggested that of the variables used in these classifications or scoring systems, bilirubin and albumin are of value in determining early and late survival respectively following elective portacaval shunting. There is debate as to whether prothrombin time can predict outcome of elective portacaval shunting (Malt et al, 1979; Orloff et al, 1980) but a prolonged prothrombin time has been shown to have a significant association with admission mortality in alcoholic hepatitis (Maddrey et al, 1978). Novis and colleagues (1976) showed that survival increased from 23% in those patients with jaundice, ascites and encephalopathy on admission to 92% in those without these manifestations.

Attempts have been made by others to use invasive measurements as a means of predicting outcome in patients undergoing surgical decompression of the portal venous system. It has been suggested that appearances

Table 1.5 Modification of Child's classification  
(Pugh et al, 1973) to assess risk in  
patients presenting with variceal  
haemorrhage

variable	<u>Points</u>		
	1	2	3
encephalopathy	nil	slight	mod-severe
ascites	nil	slight	mod-severe
bilirubin ( $\mu\text{mol/l}$ )	<34	34 - 51	>51
albumin (gm/l)	>35	28 - 35	<28
prothrombin ratio	<1.3	1.3 - 1.5	>1.5
risk grade A	5 - 6 points		
B	7 - 9 points		
C	10 - 15 points		

at splenoportography (Viamonte et al, 1970), portal venous pressure (McDermott, 1972), porto-hepatic pressure gradient (Vinel et al, 1982) and wedged hepatic blood flow (Warren et al, 1967) may be of value in patient selection and outcome determination. However, others have questioned haemodynamic selection since it has failed to improve operative mortality or longterm survival in shunted patients (Burchell et al, 1974; Smith, 1974).

Kanel and colleagues (1977) found no association between histological evidence of ongoing alcoholic hepatitis and survival in patients with cirrhosis, although some workers (Grendell et al, 1983) found the presence of panlobular fat was of value in determining outcome in patients about to undergo portasystemic shunting, others have suggested that the presence of acute hyaline necrosis is associated with a high mortality (Mikkelsen, 1974). In general terms, no invasive measurement has been shown to have an advantage over established classifications and scoring systems.

Most studies which have sought to identify good risk patients presenting with variceal haemorrhage, have been performed on patient populations undergoing portal systemic shunting. Since portal systemic shunting has been shown to have a deleterious effect upon functional hepatic reserve, it may be inappropriate to use selection criteria obtained from portal systemic shunt patients to define risk in patients managed by a more conservative policy.

The high early mortality and the more benign later course of variceal bleeders has been emphasised (Conn et al, 1972; Orloff et al, 1980; Graham et al, 1981). Smith and Graham (1982) have shown that timing, either of intervention or randomisation is the most important variable in survival analysis. They have shown that one year survival can be improved from 35% to 45% by merely excluding those patients who failed to survive the first two days of admission. Delaying therapy, therefore, selects a subgroup defined as having improved short-term and thus longterm survival. It is, of course, probable that the value of particular predictive factors is influenced in the same way that the results of treatment of variceal haemorrhage are influenced by the method of selection of patients and the timing of their entry to the treatment programme. This may partially account for the different survival rates observed between studies when patient's risk is assessed by classifications and scoring systems.

#### v. AIM OF THESIS

This thesis reviews the results of a specific management policy aimed at controlling acute variceal haemorrhage and preventing recurrent variceal bleeding. The aims of this thesis are:

- (1) to define the limitations of the management policy which employs tamponade and injection sclerotherapy as its main therapeutic procedures.

- (2) to assess the value of established classifications and scoring systems in defining risk in patients following admission with variceal haemorrhage.
- (3) to determine whether specific risk factors can be used to define short and long term survival in all patients presenting with portal hypertension and in the smaller group of patients with alcohol associated cirrhosis.
- (4) to examine the effect of the timing of assessment of liver function using clinical, biochemical and haematological measurements.

The application of possible risk factors is assessed in relation to a prospective study of beta blocker therapy (propranolol) in the prevention of recurrent variceal haemorrhage.

- i. Introduction
- ii. Patients and methods
- iii. Policy of management
  - (a) acute variceal haemorrhage
  - (b) prevention of recurrent variceal haemorrhage
- iv. Admission control of haemorrhage and survival
  - (a) results
  - (b) discussion
- v. Longterm control of haemorrhage and survival
  - (a) results
  - (b) discussion

## i. INTRODUCTION

In Glasgow Royal Infirmary, patients presenting with variceal haemorrhage have been managed by a standard policy in the University Department of Surgery since August 1979. This policy aims to achieve early localisation of the bleeding lesion with endoscopy as part of the resuscitative process. Immediate control of variceal haemorrhage is sought by oesophageal tamponade where necessary and injection sclerotherapy via a rigid Negus oesophagoscope under general anaesthesia. Stapled oesophageal transection has been reserved for recurrent haemorrhage not controlled by repeat injection sclerotherapy. Those patients surviving their initial admission to hospital were subsequently readmitted for elective sclerotherapy using the fiberoptic endoscope up until September 1982. From that time patients who survived their initial admission were considered for inclusion in a trial assessing efficacy of long acting Propranolol in the prevention of recurrent variceal haemorrhage.

The results of this management policy will be analysed in this chapter to define its limitations, to enable comparison of survival with other reported series and to determine whether the modified Child's classification can be used to identify patients who might benefit from specific or alternative therapy.

## ii. PATIENTS AND METHODS

### (a) Methods of Data Collection

Data were prospectively collected from patients with variceal haemorrhage admitted to the University Department of Surgery, Royal Infirmary, Glasgow. Patients, referred with suspected variceal haemorrhage, but who were subsequently found to have an alternative source of blood loss, were excluded from this study.

Data were collected by myself from patients and case records between August 1979 and March 1985, with the exception of the 12 month period from August 1980 to July 1981 when data were collected, under my direction, by two other members of that surgical unit. The completeness of this data collection has been verified by cross-checking against ward admission books and Unit discharge letter file.

A proforma was prepared by myself at the beginning of this prospective survey (Appendix I) and completed with the data collected on each emergency and elective patient admission.

As a member of the Department of Surgery for four of the six year study period, I was actively involved in the management and investigation of patients presenting with variceal haemorrhage and have undertaken a considerable proportion of patient therapy. During these four years, I was identified as the registrar who undertook acute and longterm management of these patients. This included passage of modified Sengstaken-Blakemore tubes, endoscopy and injection



sclerotherapy.

(b) Definitions

inclusion into study

A patient was only included in the study if haematemesis and/or melaena or the presence of melaena on rectal examination was observed, documented by the patients general practitioner or a member of the hospital medical staff. Variceal haemorrhage was confirmed by fiberoptic endoscopy under sedation (diazemuls up to 20 mg intravenously). Patients were only included in the study if they had oesophageal varices with evidence of recent bleeding (active variceal haemorrhage, clot over a varix, red or black spot overlying varix) or when oesophageal varices were present in the absence of any other defined potential cause of upper gastrointestinal haemorrhage.

liver pathology

The results of previous liver biopsies were sought from referring hospitals. All patients admitted to the University Department of Surgery underwent liver biopsy or had histology obtained at post-mortem. Only those patients with a prothrombin time prolonged by eight seconds did not undergo biopsy but this was undertaken on subsequent admissions if there was an improvement in prothrombin time. Alcohol cirrhosis was assumed to be present if portal hypertension was demonstrated by the presence of oesophageal varices and there was a history of alcohol abuse (provided by patient or relative).

#### history of liver disease

The onset of liver disease was recorded as the date of first referral to a medical practitioner with complications of liver disease (ascites, variceal haemorrhage).

#### first variceal haemorrhage

If there was a history of previous admission to hospital with upper gastrointestinal haemorrhage, this was recorded as a previous haemorrhage from oesophageal varices if this was confirmed at endoscopy as defined above.

#### further variceal haemorrhage

Further variceal haemorrhage was assumed if on admission there were signs of blood loss requiring blood transfusion with or without haematemesis and melaena, renewed evidence of hypovolaemic shock or rapidly progressive anaemia, a drop of haemoglobin of at least 2 g/dl within 48 hours of admission. Endoscopy was used to confirm recent haemorrhage from varices.

#### assessment of liver function - modified Child's classification

At the time of their initial admission to hospital, patients were assessed according to Pugh's modification of Child's classification (Pugh et al, 1973) by myself or the registrar involved in data collection. When this was not undertaken at the time of admission, patients were classified by referral to case records. In those patients surviving the first seven

days of admission, these five indices of liver function (ascites, encephalopathy, albumin, bilirubin and prothrombin ratio) were recorded and patients regraded. Survival rates were estimated from life table analysis (Kaplan and Meier, 1958).

### iii. POLICY OF MANAGEMENT

#### (a) Acute variceal haemorrhage

Patients presenting with suspected variceal bleeding were resuscitated with plasma and blood. Fresh frozen plasma or blood products were given as indicated by a prolonged prothrombin or thrombin time and a low platelet count. Vitamin K1 (10 mg intramuscular daily) and cimetidine (400 mg qid) were administered to all patients.

As part of the resuscitative procedure, the bleeding site was defined by upper gastrointestinal endoscopy. When active bleeding from oesophageal varices was demonstrated, oesophageal tamponade was instituted using the four lumen Minnesota tube or modified Sengstaken-Blakemore tube (Edlich et al, 1968). The tube was always inserted by myself or a registrar experienced in its use. The gastric balloon was inflated with 100 mls of water and 20 mls of sodium and meglumine codamide (Urimiro 340, Merck Ltd.). The oesophageal balloon was inflated with air to a pressure of 40 mmHg as indicated by an anaeroid barometer. The tube was taped under slight tension with a spatula to the cheek. The position of the tube was confirmed

radiographically immediately after placement and the patient constantly supervised by a trained nurse in the University Department of Surgery wards. Open drainage of the gastric and pharyngeal channels of the Minnesota tube was supplemented by hourly aspiration. Oesophageal tamponade was also instituted in those patients who in the course of their admission had renewed significant gastrointestinal blood loss as indicated by further haematemesis or melaena, or had changes in pulse and blood pressure suggesting further blood loss.

Lactulose (15-30 mls tid) was used to minimise or avoid encephalopathy and where encephalopathy was established, the rectum was irrigated through a rubber tube with up to 8 litres of water or until a clear return was obtained. Sedatives and analgesics were avoided. Initially neomycin was used for prophylaxis of encephalopathy. However, like others (Conn et al, 1977) no additive effect to lactulose has been found and accordingly it has not been used since August 1980.

The Minnesota tube remained in position with all balloons inflated for up to 24 hours. The oesophageal balloon was then deflated and the tube left in place for up to 12 hours. If bleeding did not recur then the tube was removed and destroyed to prevent reusage.

When the condition of the patient permitted, a Negus oesophagoscope modified by the presence of a slot on the trailing edge of the instrument (Bailey & Dawson, 1975) was passed under general anaesthesia and the oesophageal varices injected with up to 20 mls of

ethanolamine oleate through a Roberts needle. The sclerosant was injected intravariceally in 3-5 ml boluses through the slit cut in the trailing edge of the oesophagoscope, and any bleeding was controlled by rotating the oesophagoscope so that the varix was compressed. Other varices were injected in turn after rotating the instrument. Blood was aspirated by a large bore suction to retain an empty oesophageal lumen during injection sclerotherapy. Recurrent variceal haemorrhage during the admission was treated in identical fashion.

When repeat injection sclerotherapy failed to control haemorrhage, stapled oesophageal transection was performed under general anesthesia through an upper midline abdominal incision. The procedure included a devascularisation of the greater curve with ligation of the left coronary vein incontinuity. The oesophagus was mobilised and peri-oesophageal veins were ligated and divided and an attempt made to preserve both anterior and posterior vagal trunks. Through an anterior gastrostomy, dilators were introduced and the appropriate EEA stapling gun passed into the lower oesophagus. A heavy linen ligature was tied down on to the jaws of the instrument at the oesophago-gastric junction and the instrument tightened such that the full thickness of the oesophageal wall was taken into the instrument. Following firing of the gun, care was taken to withdraw the instrument and the 'doughnut' of excised oesophagus checked for the completeness of transection. Following closure of the gastrostomy, the wound was closed without

drainage of the peritoneal cavity. Splenectomy alone was undertaken when non-variceal gastrointestinal bleeding was difficult to control in the presence of thrombocytopenia (platelet count  $<30,000^3\text{mm}$ ) or when inadvertently traumatised during stapled oesophageal transection. Modified Child's grade A patients under 60 years of age with a patent portal vein, non-progressive, non-alcohol associated disease were considered for an elective Warren shunt (Henderson et al, 1984).

(b) Prevention of recurrent variceal haemorrhage

Patients who had previously had admission to hospital with acute variceal haemorrhage were readmitted initially one month following acute variceal haemorrhage and were entered into a programme of chronic injection sclerotherapy. On the day of admission for elective sclerotherapy, all patients underwent assessment which included liver function tests, serum proteins, full blood count, a coagulation screen (prothrombin, thrombin and kaolin cephalin clotting times and platelet count) and cross-matching of blood. All patients who had not previously undergone liver biopsy on a previous admission had this performed using a Trucut needle inserted in the mid-axillary line using lignocaine as 1% local anaesthetic. The severity of liver disease at the time of elective sclerotherapy was graded using Pugh's modification of Child's classification.

Following an overnight fast, patients were premedicated with atropine (0.6 mg). Using intravenous

sedation with diazemuls, endoscopy was performed with an Olympus GIF 1T endoscope. A maximum of 15 mls of ethanolamine oleate was injected submucosally in amounts of 1 ml alongside the main variceal channels using a long flexible needle (Olympus NM-3). Injection was commenced just proximal to the oesophago-gastric junction and was also carried out at a more proximal level when large varices extended high in the oesophagus. Neither a flexible sheath nor oesophageal tamponade was employed. Patients were discharged following overnight observation and further elective injections were performed initially at monthly intervals until varices had decreased sufficiently in size to allow injection at progressively longer intervals until obliteration was achieved.

Recurrent acute haemorrhage necessitating emergency readmission was treated by oesophageal tamponade and injection sclerotherapy using the Negus oesophagoscope under general anaesthesia. Stapled oesophageal transection was used only where repeat injection sclerotherapy failed to control haemorrhage.

#### iv. ADMISSION CONTROL OF HAEMORRHAGE AND SURVIVAL

##### (a) Results

Sixty-nine patients were referred for treatment of bleeding varices between August 1979 and September 1982. The mean age of patients was 51 years (range 17-83 years). There were 47 male and 22 female patients. The underlying cause of portal hypertension



is shown in Table 2.1.

One patient with massive haemorrhage at the time of endoscopy died before treatment could be instituted. Of the remaining 68 patients, 21 were admitted on a second occasion, eight were admitted with a third haemorrhage and two with a fourth haemorrhage giving a total of 100 admissions.

#### oesophageal tamponade

Bleeding settled without tamponade on 35 of these admissions. Oesophageal tamponade was successful in controlling haemorrhage on all but two of the remaining 64 admissions. The first of these two patients was admitted with liver failure and a severe coagulopathy and the second died of a cardio-respiratory arrest on attempted passage of a Minnesota tube.

Variceal haemorrhage recurred during admission on 37 occasions. Reinstitution of tamponade controlled haemorrhage in 31 of these 37 episodes. One patient died from a respiratory arrest on attempted passage of the tube and a further patient died from haemorrhage not controlled by tamponade and caused by a mucosal tear of the oesophagus at rigid oesophagoscopy. One patient, who pulled up the Minnesota tube with all balloons inflated, died from massive haemorrhage and aspiration. Post-mortem examination revealed a full thickness tear of the oesophagus with mediastinal haematoma. Two other patients also removed fully inflated tubes but only complained of transient dysphagia and did not rebleed.

Thus control of haemorrhage with oesophageal



TABLE 2.1 Cause of portal hypertension and admission mortality in 69 patients presenting on 100 occasions with acute variceal haemorrhage

	<u>no.</u> <u>patients</u>	<u>no.</u> <u>admissions</u>	<u>no.</u> <u>deaths</u>
alcohol cirrhosis	48	72	22
primary biliary cirrhosis	4	6	1
chronic active hepatitis	4	5	1
cryptogenic cirrhosis	4	5	1
idiopathic	4	5	1
portal vein thrombosis	3	4	0
post-hepatic cirrhosis	1	2	1
metastatic breast carcinoma	1	1	1
Total	69	100	28

tamponade was achieved in 92% of the 99 occasions when tamponade was employed. The mortality directly attributable to tamponade was 4%.

#### injection sclerotherapy

Injection sclerotherapy was performed on 82 of the 100 admissions with variceal haemorrhage. In the remaining 18 admissions, the patient did not have sclerotherapy; one patient (described above) exsanguinated at endoscopy; four patients died from progressive liver failure before sclerotherapy; three patients had oesophageal transection; two patients deemed suitable for shunting had elective surgery without complication on the same admission; three patients died from bleeding not controlled by tamponade; two patients received no further treatment following control of haemorrhage by tamponade; and in three patients found to be bleeding from gastric varices, haemorrhage settled without treatment in two and following treatment with the neodymium-YAG laser in one.

Injection sclerotherapy was undertaken on 90 occasions (seven patients underwent sclerotherapy on more than one occasion). Complications occurred in three instances. One patient developed pyrexia and surgical emphysema soon after the procedure although a gastrograffin swallow did not demonstrate an oesophageal leak. Initial conservative treatment appeared successful but seven days later an episode of haematemesis was followed by signs of mediastinitis.

Thoracotomy and oesophagectomy were performed but the patient died from respiratory failure and septicaemia. Histology of the resected oesophagus revealed perforation at the site of a small squamous cell carcinoma which had not been identified either at fiberoptic endoscopy or rigid oesophagoscopy. One patient developed stridor following oesophagoscopy and required thoracotomy. One patient previously described, had further haemorrhage which was not controlled by tamponade after injection sclerotherapy.

#### oesophageal transection

Oesophageal transection was performed in ten patients. The indication in nine was recurrent variceal haemorrhage despite injection sclerotherapy, and in the remaining patient transection was carried out because of the development of laryngeal stridor following rigid oesophagoscopy on a previous admission. Only one patient had further haemorrhage during the admission in which transection was performed. Five patients died (50%) after oesophageal transection, four as a result of multi-system failure, associated with terminal haemorrhage in one, and one from left ventricular failure in the immediate postoperative period.

#### other procedures

Splenectomy was performed in one patient who bled from gastric erosions after treatment of bleeding varices and whose platelet count remained consistently below 30,000 mm<sup>3</sup>. Two patients underwent uneventful

shunt surgery (one Warren shunt, one end-to-side portacaval shunt), performed as an elective procedures during the first admission with variceal haemorrhage. Both patients who had non-cirrhotic portal hypertension had been considered previously for elective portal systemic shunting.

mortality and control of haemorrhage on admission

Using this policy of management, only ten of the 69 patients presenting on 100 occasions died because of continuing blood loss; one at endoscopy before any treatment could be instituted; two from oesophageal tears (one as a result of oesophagoscopy and the other from oesophageal tamponade); three patients with severe coagulation defects continued to bleed despite oesophageal tamponade; two patients arrested whilst having a Minnesota tube inserted; one encephalopathic patient with terminal liver disease had a haematemesis which was not treated beyond tamponade; one patient with advanced liver disease continued to bleed following injection sclerotherapy and oesophageal tamponade. Control of haemorrhage was, therefore, achieved on 90% of admissions.

Fifteen patients died during their admission primarily from liver failure but with evidence of other system failure. Two patients died from left ventricular failure, and one from multi-system failure and septicaemia following oesophagectomy for a perforated oesophagus. The admission mortality was 28% (Table 2.2).

TABLE 2.2 Control of haemorrhage and admission mortality in relation to modified Child's classification (after Pugh et al, 1973) for 69 patients admitted on 100 occasions with acute variceal haemorrhage

<u>Child's class.</u>	<u>n*</u>	<u>no. admissions with haemorrhage</u>	<u>control of haemorrhage</u>	<u>admission mortality</u>
A	5	6	6 (100%)	0
B	16	23	22 (96%)	3 (13%)
C	48	71	62 (87%)	25 (35%)
Total	69	100	90	28

\*Grading on first presentation

An attempt was made to assign patients according to Child's original classification. In the absence of an assessment of 'nutritional status', patients were graded A, B or C for each of the four criteria; encephalopathy, ascites, serum albumin and serum bilirubin. Of the 100 patient admissions, only seven patients were assigned to the same grade for all four criteria. In 30 admissions, three of four criteria were assigned to the same grade (for example encephalopathy A, ascites A, serum albumin A, serum bilirubin B) and in 63 admissions two of four criteria were the same. In 49 patient admissions, patients were assigned both good risk (grade A) and bad risk (grade C) using different criteria (for example encephalopathy A, ascites B, serum albumin C, bilirubin B).

Table 2.2 shows the admission mortality for each of the grades in Pugh's modified scoring system. All patients assigned to modified Child's grade A had haemorrhage controlled and survived admission but both control of haemorrhage and survival was poorer for Child's grade C patients than modified Child's grade B patients.

#### (b) Discussion

Any successful management policy should achieve early localisation of the bleeding lesion with endoscopy as part of the resuscitative process. Failure to use endoscopy may result in inappropriate treatment and Novis et al (1976) have reported that 33% of their



patients with known varices were found to be bleeding from another site. This failure to define the source of haemorrhage on admission may account for the poor and variable results of vasopressin as a means of controlling variceal haemorrhage. When used in intravenous bolus form, control is reported in up to 50% of cases (Conn et al, 1975; Novis et al, 1976; Sagar et al, 1979), but vasopressin may be more effective when administered as a continuous infusion (Sagar et al, 1979). Recent studies suggest that somatostatin may be as effective (Kravetz et al, 1984) or better (Jenkins et al, 1985) than continuous infusion of vasopressin in controlling acute variceal haemorrhage.

In this series of 100 patient admissions, the efficacy of tamponade in the primary control of variceal haemorrhage closely matches the success rate of 85-92% reported by others (Pitcher, 1971; Novis et al, 1976). Oesophageal tamponade was successful in controlling haemorrhage on 97% of occasions following admission and only 84% of occasions when haemorrhage recurred during admission and this supports the view that the clinician has a limited ability to arrest haemorrhage in the presence of severe coagulopathies seen in liver failure. The low morbidity and mortality rates reported in this series compared to those reported in other studies (Edlich et al, 1968; Novis et al, 1976; Mitchell et al, 1980) reflect the importance of management of these patients by experienced medical and nursing staff. Despite the concern regarding possible



complications of oesophageal tamponade such as aspiration, oesophageal rupture and ulceration (Reid et al, 1960; Conn et al, 1967), the modified four lumen Sengstaken-Blakemore tube (Minnesota tube) offers an effective means of arresting variceal haemorrhage (Edlich et al, 1968; Mitchell et al, 1980).

Although tamponade is effective in controlling acute variceal haemorrhage, further bleeding will occur on removal of the tube in over 50% of patients (Novis et al, 1976; Mitchell et al, 1980). The poor results obtained with emergency portacaval shunting (Orloff et al, 1980) has led investigators to consider more conservative therapeutic options. Although injection sclerotherapy had first been described by Crafoord and Frenckner in 1935, it has been Johnston and colleagues (1973) who have been responsible for popularising this technique as a means of controlling haemorrhage following tamponade. Their results and those of Terblanche et al (1979) show control of haemorrhage in 92% of admissions with an admission mortality between 18-25%. The 90% control of haemorrhage in the present series is similar to both those studies.

Devascularisation procedures were popularised by Boerema (1970) and Crile (1950). Transoesophageal ligation of the varices has been shown to be effective in arresting variceal haemorrhage (Pugh et al, 1973) and has been facilitated in recent years by the introduction of stapling instruments (Johnston 1981). In our experience of managing acute variceal haemorrhage,



stapled oesophageal transection has been undertaken in patients in whom sclerotherapy has failed to control haemorrhage, a selection factor which may account for the high (50%) mortality rate. Nonetheless, other investigators (Johnston et al, 1981) report an operative mortality of 33% when the procedure is undertaken on an emergency basis compared to 12% in patients treated electively.

Despite control of haemorrhage in 90% of patient admissions, the overall mortality remains high at 28%. This mortality reflects the high proportion of alcoholic cirrhotics with seriously impaired liver function and is in keeping with the results of other series comprising patients, the majority of whom have this as a cause of portal hypertension (Pugh et al, 1973; Terblanche et al, 1979). Although it was Child who first made a serious attempt to match preoperative findings with subsequent mortality and morbidity by using certain criteria which would allow patients to be graded as good, fair or poor risks (Child et al, 1964), other investigators have subsequently used these criteria with much less flexibility than was originally intended. In our experience, attempts to assign patients to a particular grade have been difficult in that only seven of the 100 patients had identical grading of the four criteria measured and in 49% of admissions, patients could be assigned to either grade A (good risk) or grade C (poor risk) depending upon which of the four criteria were used. The observation that many patients may not

readily fall into any of the three categories has led to the description of various scoring systems (Campbell et al, 1973; Pugh et al, 1973). Pugh and his colleagues (1973) substituted the clinical assessment of body nutrition with a measurement of prothrombin time. This scoring system has been generally adopted by many investigators and gives a useful guide to patient risk following acute variceal haemorrhage. In the present study, admission mortality increases from grade A to C using this system. Although this modified scoring system correlates reasonably well with admission mortality, the allocation of 70% of patients to grade C does not readily allow identification of individual patients at risk despite the admission mortality of 35% in this group.

#### v. LONGTERM CONTROL OF HAEMORRHAGE AND SURVIVAL

##### (a) Results

Of the 69 patients referred for treatment of bleeding varices between August 1979 and September 1982, 20 did not survive their first admission to hospital. Two patients mentioned in the previous section died soon following admission to hospital, one at endoscopy and the other from a cardiorespiratory arrest on passage of a Minnesota tube. One patient died of a cardiac arrest secondary to a myocardial infarct within 48 hours of admission and a fourth patient died in respiratory failure and septicaemia as a result of a perforation at the site of a squamous cell carcinoma following

injection sclerotherapy. Seventeen patients died from progressive liver failure. In four this was associated with uncontrolled bleeding. Admission mortality on first referral for these 69 patients was 29%.

Of the 48 patients who survived their initial admission to hospital, two subsequently underwent portacaval decompression electively, two patients have undergone no further treatment following stapled oesophageal transection and two patients have defaulted from follow-up, although were known to be alive and well 12 months from their first referral. Four patients who survived their initial admission to hospital died prior to undergoing elective sclerotherapy. The 38 remaining patients have undergone elective injection sclerotherapy on 165 occasions. A mean of 2.6 injections was required (range 1-10) to achieve variceal obliteration. Twenty-three patients rebled on 41 occasions and all but five of these episodes occurred before varices had been obliterated by sclerotherapy. Four patients bled from gastric varices but on only one occasion was surgery required to control haemorrhage.

There have been no instances of perforation of the oesophagus with the fibroptic instrument and no patient has died as a result of injection sclerotherapy. Variceal bleeding has not occurred as a direct complication within 48 hours of injection sclerotherapy. Almost all patients experienced mild retrosternal discomfort within 24 hours following injection but only three patients subsequently presented

with minor haematemesis which were shown endoscopically to have been caused by oesophageal ulceration. Three patients developed strictures which were noted at endoscopy but in only one case was the stricture symptomatic and requiring dilatation.

Of the 49 patients who survived their initial admission to hospital, 21 have since died on follow-up. In 14 death was precipitated by admission with variceal haemorrhage: 11 of these died of severe liver failure, in two treatment was withdrawn and one patient, previously mentioned, died of left ventricular failure following a myocardial infarct. The remaining seven patients died from progressive liver failure. Table 2.3 shows the mortality following admission and at one year following acute variceal haemorrhage for all 69 patients and is related to the modified Child's classification recorded at the time of the patient's initial presentation to hospital.

Ten of the 69 patients did not survive their first seven days of admission to hospital and in the remaining 59 patients, the individual patient's score (as measured from Pugh's classification) improved in 27 patients, worsened in 15 patients and remained unchanged in the remaining 17 patients. Modified Child's grading, however, improved in only 12 patients, worsened in three patients and remained unchanged in the remaining 44 patients. Table 2.4 shows the outcome for those patients regraded A, B or C at seven days from their index variceal bleed. Overall admission mortality has

TABLE 2.3 Admission and one year mortality in 69 patients presenting with acute variceal haemorrhage assessed on admission by modified Child's classification (Pugh et al, 1973)

<u>Child's class.</u>	<u>n</u>	<u>admission mortality</u>	<u>one year mortality</u>
A	5	0	0
B	16	2 (12%)	5 (31%)
C	48	18 (37%)	31 (65%)
Total	69	20 (29%)	36 (52%)

TABLE 2.4 Admission and one year mortality in 59 patients who survived to be reassessed by modified Child's classification (Pugh et al, 1973) at one week following admission with acute variceal haemorrhage

<u>Child's class.</u>	<u>n</u>	<u>admission mortality</u>	<u>one year mortality</u>
A	6	0	0
B	21	2 (10%)	7 (33%)
C	32	8 (25%)	19 (59%)
Total	59	10 (17%)	26 (44%)

improved to 83% with the exclusion of the ten patients who did not survive to seven days. One year survival has improved to 41% for the 32 patients graded C and has decreased to 67% for the 21 patients regraded B. There were no deaths at one year for the six patients graded A.

Life table analysis of the total patient population is shown on Figure 2/1 and is related to modified Child's grading in Figure 2/2. Overall, mortality was greatest at three months with a third of patients having died at this time. At one year less than half the total number of patients were still alive.

(b) Discussion

The results of treatment of variceal haemorrhage are influenced by the method of selection of patients and the timing of their entry to the treatment programme (Smith & Graham, 1982). Given the variation in entry criteria and patient populations between centres, comparison of the results of sclerotherapy have limited validity. Within these limitations, the results in terms of initial control of haemorrhage and one year survival rates are in keeping with those of patients treated in controlled studies of elective sclerotherapy. It now seems likely that injection sclerotherapy not only reduces the number of episodes of variceal haemorrhage (Terblanche et al, 1979; MacDougall et al, 1982) but also increases the duration of survival



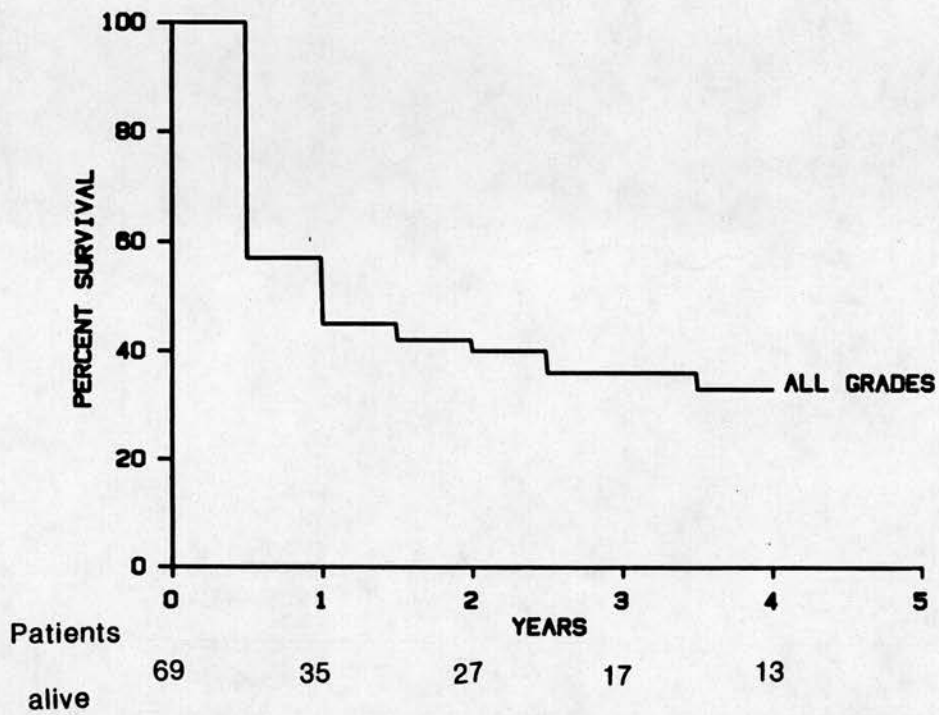


FIGURE 2/1 Life table analysis of 69 patients presenting with acute variceal haemorrhage to the University Department of Surgery between August 1979 and September 1982.



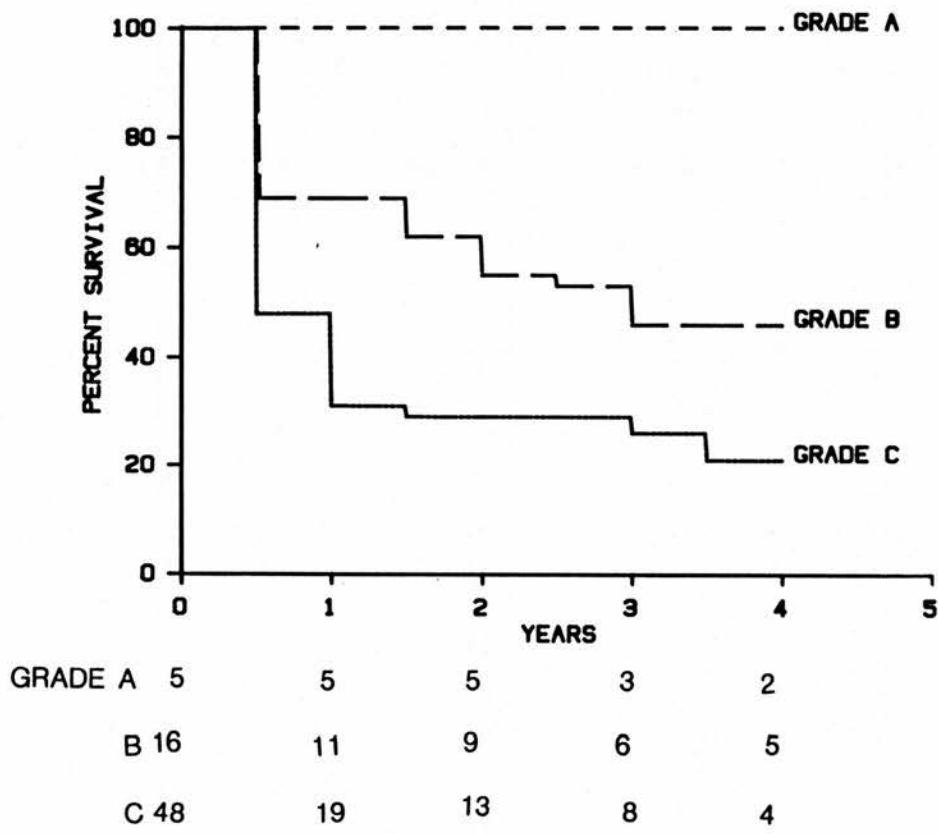


FIGURE 2/2 Life table analysis of 69 patients expressed in terms of modified Child's grading (Pugh et al, 1973) assessed at the time of initial admission with acute variceal haemorrhage. The number of patients alive at the beginning of each one year period is shown for the three grades.

(MacDougall et al, 1982). Although MacDougall and colleagues (1982) showed a significantly improved duration of survival with elective sclerotherapy, Terblanche and his colleagues (1983) found no improvement in survival over a control group which unlike the previous study, received sclerotherapy for recurrent episodes of variceal haemorrhage. The use of 'on demand' sclerotherapy might have been sufficient to mask any potential effect on survival.

A 48% incidence of recurrent haemorrhage in this series of patients is similar to that reported in other series (Table 2.5). A reduction in the interval between courses of injections may reduce the risk of early recurrent bleeding but may increase the likelihood of complications which in the present series have remained at an acceptable rate. Although some degree of retrosternal discomfort is invariable following injection, the procedure is well tolerated by patients and can be performed easily under intravenous sedation. Ulcer formation has also become clinically apparent in three patients but detection of such ulcers may be more likely if endoscopy is undertaken more frequently. In this series, haematemesis from ulceration has been minor and has settled on conservative treatment on all three occasions that it was diagnosed endoscopically. Strictures may develop as a sequel to ulcer formation (MacDougall et al, 1982; Sinnett et al 1982) but only one patient with ulceration developed a symptomatic stricture and this responded to dilatation.

TABLE 2.5 Control of variceal haemorrhage in this and other reported series of patients managed by elective injection sclerotherapy

	<u>Glasgow</u> 1985	<u>King's,</u> <u>London</u> (MacDougall 1982)	<u>Charing Cross,</u> <u>London</u> (Sinnott 1982)
no. of patients studied	38	51	35
no. rebleeding	23	22	24
no. of bleeds	42	54	29
duration of follow-up (patient months)	1078	741	-
bleeding risk factor (no. of bleeds/ patient months)	0.04	0.07	0.03

Recurrent haemorrhage may occur if varices are not obliterated with repeated injections. MacDougall and colleagues (1982) reported that in over 60% of their patients obliteration was achieved within three months with less than four courses of injections. Haemorrhage was eight times more likely if varices were not obliterated. In this series, all but six bleeds occurred prior to variceal obliteration and in four of these cases the site of haemorrhage was gastric varices. It has been suggested that only gastric varices, which are present at the time of haemorrhage from the oesophagus, will subsequently bleed (MacDougall et al, 1982) but others doubt whether gastric varices are ever the source of haemorrhage (Terblanche et al, 1979). It remains to be seen whether gastric variceal haemorrhage will present a longterm management problem in patients undergoing elective sclerotherapy.

Although it has been the policy to use rigid oesophagoscopy following admission with acute variceal haemorrhage, elective submucosal injections have been undertaken with the flexible endoscope. There is no evidence to suggest that either technique is superior. The rigid oesophagoscope provides good proximal lighting, permits ready aspiration of blood by large bore suction and allows compression of varices that have just been injected. These benefits do not appear so important when submucosal injections are carried out electively. Although injection sclerotherapy with the rigid oesophagoscope has been shown to give similar

results to fiberoptic endoscopy, there is an increased risk of perforation with the rigid oesophagoscope (Terblanche et al, 1979). It has not been found necessary to use the flexible oesophageal sheath (Williams et al, 1979) in elective sclerotherapy and since its use usually requires general anaesthesia, it has no apparent advantage over rigid oesophagoscopy in acute variceal haemorrhage. It has been suggested, however, that the use of the Williams sheath with fiberoptic sclerotherapy may lead to earlier obliteration of the varices and thereby minimise the risk of early recurrent variceal haemorrhage (Westaby et al, 1983). There is debate as to whether the sclerosant should be injected into or around the varix. Grobe and colleagues (1984) have shown that when intravariceal injection is attempted using the fiberoptic instrument, paravariceal accumulation of sclerosant occurs in 44% of cases. Similarly, 50% of attempted intravariceal injections using the rigid oesophagoscope resulted in submucosal extravasation of sclerosant (Barsoum et al, 1978). The longterm results obtained with percutaneous transhepatic portal vein catheterisation have shown that there is an unacceptable morbidity and mortality with selective obliteration of the coronary vein (Bengmark et al, 1979). These workers have suggested that its use should therefore be limited to centres familiar with the technique and should be undertaken only in patients who continue to have variceal haemorrhage not controlled by per-oesophageal sclerotherapy.

The definitive place of sclerotherapy in the longterm management of variceal haemorrhage is uncertain. Few would recommend a return to an aggressive policy of emergency portacaval shunting such as that advocated by Orloff and colleagues (1980) and elective shunting in unselected patients does not appear to improve longterm survival (Jackson et al, 1971; Rueff et al, 1976). The results of stapled oesophageal transection are encouraging but the procedure carries a high mortality in poor risk patients (Pugh et al, 1973). Propranolol has been shown to reduce portal venous pressure and early clinical experience suggests that a non-operative approach to the problem of recurrent variceal haemorrhage may be possible (Lebrec et al, 1981). However, these findings have yet to be confirmed and a recent report has shown no benefit in a group of patients with decompensated liver disease (Burroughs et al, 1983).

The early results of this management policy, which employs injection sclerotherapy as its main therapeutic option, are encouraging. It remains to be seen whether sclerotherapy or other therapeutic option can be employed to better effect in patients selected on the basis of their liver function. At the present time, grading of liver dysfunction by the modified Child's classification may not be sensitive enough to identify individual patients who might benefit from such a policy. The present results have shown that both admission and one year mortality correlate reasonably

well with individual grading of patients. Although grading altered in a quarter of the 59 patients surviving the first seven days of admission, regrading of patients at this time did not readily improve the ability of this grading system to discriminate between those patients who would survive and those patients who would not survive to one year. If selection of therapy is to be based on the individual patient's liver dysfunction, then a more sensitive method of assessing risk must be identified.

CHAPTER 3

SECTION 1 - PREDICTION OF OUTCOME FOLLOWING ADMISSION  
WITH ACUTE VARICEAL HAEMORRHAGE

- i. Introduction
- ii. Patients and methods
- iii. Results
  - (a) analysis of mortality
  - (b) potential predictive factors and admission mortality
- iv. Discussion



## i. INTRODUCTION

Child's classification (Child et al, 1964) and its modified scoring system (Pugh et al, 1973) are widely accepted as the mainstay of assessment of patients with portal hypertension. Both classifications have been used to select patients for particular treatment options (Johnston, 1981) and to assess the comparability of patient populations (MacDougall et al, 1982; Burroughs et al, 1983; Terblanche et al, 1983). Most studies, which have sought to identify good risk patients as assessed by Child's classification, have been performed on patient populations undergoing portal systemic shunting. Since this form of therapy has been shown to have a deleterious effect upon functional hepatic reserve, it may be inappropriate to use selection criteria obtained from portal systemic shunt patients to define risk in patients managed by a more conservative policy. Few investigators, however, have subjected Child's classification or its modified scoring system to critical evaluation in patients managed by a conservative policy.

The previous chapter highlighted the limitations of the modified Child's classification in defining a high risk group when the majority of patients presenting with variceal haemorrhage are assigned to grade C at the time of their initial admission. This chapter will assess the value of various risk factors in defining risk as soon as possible after admission in patients with acute variceal haemorrhage.

## ii. PATIENTS AND METHODS

The patient population studied comprised the same group whose clinical management was discussed in section iii. of Chapter 2. They included 69 patients referred for treatment of bleeding varices between August 1979 and September 1982. During this period these patients were admitted on a total of 100 occasions. These patients will be referred to subsequently as Group One.

Between September 1982 and 31 January 1984, a further 26 patients were admitted on 35 occasions with variceal haemorrhage which was managed according to the same protocol. There were five deaths in hospital in this group of patients who will be referred to as Group Two.

Patients were assessed according to Pugh's modification of Child's classification (Pugh et al, 1973). Age, sex, cause and duration of liver disease, and the period of time since first variceal haemorrhage were recorded. Patients were assessed at the time of admission for the presence of ascites and encephalopathy, grading them as present or absent. The first recorded value for serum levels of bilirubin ( $\mu\text{mol/l}$ ), alanine aminotransferase (U/l), alkaline phosphatase (U/l), urea (mmol/l), creatinine ( $\mu\text{mol/l}$ ), total protein (g/l), albumin (g/l), prothrombin ratio, kaolin cephalin clotting ratio, thrombin ratio, haemoglobin (g/dl), white cell ( $\times 10^9/\text{l}$ ) and platelet count ( $\times 10^9/\text{l}$ ) were recorded. Normal values for these variables are given in Appendix 2.

Student's t and Mann Whitney tests for independent samples of data were used to determine the significance of differences between the group of patients who died and those who were discharged in terms of mean value for each factor. Chi squared analysis was used to evaluate whether categorical variables could predict outcome. Stepwise logistic regression analysis (Appendix 3) was used to minimise the number of admission factors needed for optimal separation of patients who survived from those who died. The analysis was performed using the BMDP computer package programme PLR on an ICL 2988 computer (Dixon et al, 1977). The results are expressed as mean + standard deviation for normally distributed data and median and quartile when data were not normally distributed.

### iii. RESULTS

#### (a) Analysis of Mortality

Sixty-nine consecutive patients admitted on 100 occasions had an admission mortality of 28% (Group One). There were no deaths in the six modified Child's grade A patients, three deaths in grade B and 25 deaths in the 71 grade C patients. In Group One, admission mortality rate was 10% in the 29 patients in combined grades A and B ("good risk") and 35% in 71 grade C patients ("poor risk"). Using this system of good and poor risk categories, outcome was correctly 'predicted' in only 51% of patient admissions. In Group Two, there were no deaths in six grade A and seven grade B

patients, and five deaths in 22 grade C patients (23%).

Table 3.1 lists the deaths in both groups. Twenty-two patients in Group One died in liver failure but this was associated with a significant terminal haemorrhage in four patients. Two patients died from continued variceal haemorrhage after a positive decision had been taken to withhold further treatment; the first was a mentally retarded female with cryptogenic cirrhosis and the second an 83 year old who had experienced multiple admissions with haematemesis attributable to continued alcohol abuse. Two patients died in liver failure with uncontrolled variceal haemorrhage in Group Two.

(b) Potential Predictive Factors and Admission Mortality

Group One

Nine individual risk factors obtained from the 100 patient admissions demonstrated a significant association with admission mortality (Tables 3.2, 3.3, 3.4). Stepwise logistic regression analysis showed that only prothrombin ratio (PTR), serum creatinine (CR) and the presence of encephalopathy (ENC) (in decreasing order of significance) were independent predictors of mortality. The derived regression equation allows estimation of the predicted probability of discharge. The relationship between the probability of discharge and the three predictors is given by

$$\log (p/1-p) = 10.0 - 4.3 \text{ PTR} - 0.03 \text{ CR} - 0.85 \text{ ENC}$$

where the actual values of PTR and CR are entered and

TABLE 3.1a Characterisation of patients dying in Group One after admission with variceal haemorrhage

<u>patient</u> <u>admission no.</u>	<u>sex</u>	<u>age</u>	<u>cause of portal</u> <u>hypertension</u>	<u>Child's grade</u> <u>(Pugh's mod.)</u>	<u>p*</u>	<u>cause of death</u>
7	M	46	AC	C	0.09	liver failure, terminal bleed
8	M	61	AC	C	0.04	liver failure
9	M	39	AC	B	-	terminal bleed during endoscopy
10	M	47	AC	C	0.66	liver failure
16	M	52	AC	C	0.95**	oesophageal perforation
20	F	59	PBC	C	0.17	liver failure
23	M	56	AC	C	-	liver failure, terminal bleed
31	M	44	AC	C	0.80**	LVF after oesophageal transection
33	F	60	AC	B	-	liver failure
34	M	79	AC	B	0.95**	myocardial infarction
35	M	36	AC	C	0.02	liver failure, terminal bleed
39	M	39	AC	C	0.02	liver failure
42	M	45	AC	C	0.17	liver failure
43	F	40	AC	C	0.19	liver failure
50	M	60	AC	C	0.10	liver failure
51	M	68	Idiopathic	C	0.13	liver failure
52	M	42	AC	C	0.06	liver failure
53	M	53	AC	C	0.04	liver failure
55	F	54	CAH	C	0.90**	LVF after oesophageal transection
60	M	51	AC	C	0.02	liver failure
64	F	68	PHC	C	0.45	liver failure
72	M	26	AC	C	0.17	liver failure
77	F	38	Ca	C	0.05	liver failure
87	F	58	CC	C	0.75**	treatment withdrawn
93	M	34	AC	C	0.00	liver failure
95	M	66	AC	C	0.00	liver failure
97	F	51	AC	C	0.26	liver failure
100	M	63	AC	C	0.01	liver failure

(for Legend see Table 3.1b)

TABLE 3.1b Characterisation of patients in Group Two dying after admission with variceal haemorrhage

<u>patient admission no.</u>	<u>sex</u>	<u>age</u>	<u>cause of portal hypertension</u>	<u>Child's grade (Pugh's mod.)</u>	<u>p*</u>	<u>cause of death</u>
102	M	53	AC	C	0.26	treatment withdrawn
105	M	65	AC	C	0.21	myocardial infarction
106	M	46	AC	C	0.00	liver failure, terminal bleed
111	M	57	AC	C	0.59	liver failure, terminal bleed
129	M	57	AC	C	0.79**	myocardial infarction

AC = alcoholic cirrhosis; PBC = primary biliary cirrhosis; PHC = post hepatic cirrhosis;  
 CC = cryptogenic cirrhosis; CAH = chronic active hepatitis; Ca = carcinoma;  
 LVF = left ventricular failure

\* p = probability of discharge; see text for calculation of probability values  
 \*\*p = death occurring in low risk group

TABLE 3.2    Relationship between values of normally distributed individual variables and outcome of admission in Group One patients presenting with variceal haemorrhage

<u>variable</u>	<u>discharge</u>			<u>death</u>		
	n	mean	+ sd	n	mean	+ sd
PTR	72	1.3	0.2***	28	1.8	0.4***
KCCR	70	1.2	0.2***	26	1.6	0.4***
haemoglobin (g/dl)	72	10.5	2.1*	28	11.6	2.7*
age (years)	72	51.4	14.7	28	51.6	12.0
albumin (g/l)	72	32.4	5.5	28	30.8	6.7
protein (g/l)	72	63.3	9.7	28	62.5	7.4

PTR = prothrombin ratio;  
 KCCR = kaolin cephalin clotting ratio;  
 NS = not significant;  
 m = mean;  
 sd = standard deviation

\* p<0.05  
 \*\*\* p<0.001

TABLE 3.3 Relationship between values of individual variables not normally distributed and outcome of admission in Group One patients presenting with variceal haemorrhage

<u>variable</u>	<u>discharge</u>			<u>death</u>		
	n	median	quartile	n	median	quartile
creatinine ( $\mu\text{mol/l}$ )	69	75	60,90***	25	105	90,150***
bilirubin ( $\mu\text{mol/l}$ )	72	55	20,110**	28	165	78,324**
urea ( $\text{mmol/l}$ )	69	7.4	4.9,10.0*	25	9.5	6.0,12.9*
MFB (months)	72	4.0	0,18*	28	0	0,5*
MLD (months)	72	15	2,60	28	6	0,30
white cell count ( $\times 10^9/\text{l}$ )	71	8.1	5.5,10.7	27	12.7	6.6,18.4
platelets ( $\times 10^9/\text{l}$ )	72	105	70,150	28	118	74,190
thrombin ratio	70	1.0	1.0,1.1	26	1.0	1.0,1.2
alanine aminotransferase (U/l)	72	32	20,46	28	50	28,64
alkaline phosphatase (U/l)	72	240	170,355	28	232	157,428
number of bleeds	72	1	0,3	28	0	0,2

MFB = months since first variceal haemorrhage;  
MLD = duration of liver disease in months;

\*  $p < 0.05$   
\*\*  $p < 0.005$   
\*\*\*  $p < 0.001$



TABLE 3.4    Relationship of categorical variables and outcome in Group One patients presenting with variceal haemorrhage

	<u>no. of admissions</u>	<u>died</u>	
<b>sex</b>			
male	69	20	0.11
female	31	8	
<b>cause of portal hypertension</b>			
alcohol	72	22	0.83
other	28	6	
<b>ascites</b>			
absent	19	1	6.02*
present	81	27	
<b>encephalopathy</b>			
absent	60	9	12.57***
present	40	19	

\* p<0.05  
 \*\*\* p<0.001

ENC is coded as -1 when absent and +1 when present.

The relationship between individual values of p and death or discharge in these patients is shown in Figure 3.1 (p not calculated in six patients with unrecorded serum creatinine values). Decreasing values of p were associated with increasing risk of death; for example there were five deaths in 70 admissions (7% admission mortality) when  $p > 0.66$  ('low risk'), and there were 20 deaths in 24 admissions (83% admission mortality) when  $p < 0.66$  ('high risk'). The five deaths in the 'low risk' group are among those listed in Table 3.1. In all five cases, death was not obviously related to the degree of liver failure. The outcome following acute variceal haemorrhage was correctly 'predicted' in 90% of admissions using this p value of 0.66 as an arbitrary discriminant between 'low' and 'high' risk groups.

This model does not allow for any interaction among the three variables, PTR, CR and ENC. To determine that a useful interaction term has not been missed, further logistic regression analysis was performed limiting the search to the main terms and first order interactions only. The variables chosen for inclusion in the model were PTR, CR, ENC and CR x ENC and the equation obtained using them was

$$\log(p/1-p) = 12.3 - 0.04CR - 4.8PTR + 1.9ENC - 0.3CR \times ENC$$

This model correctly classified 94% of patients (two patients were incorrectly 'predicted' to die and four patients were incorrectly 'predicted' to be

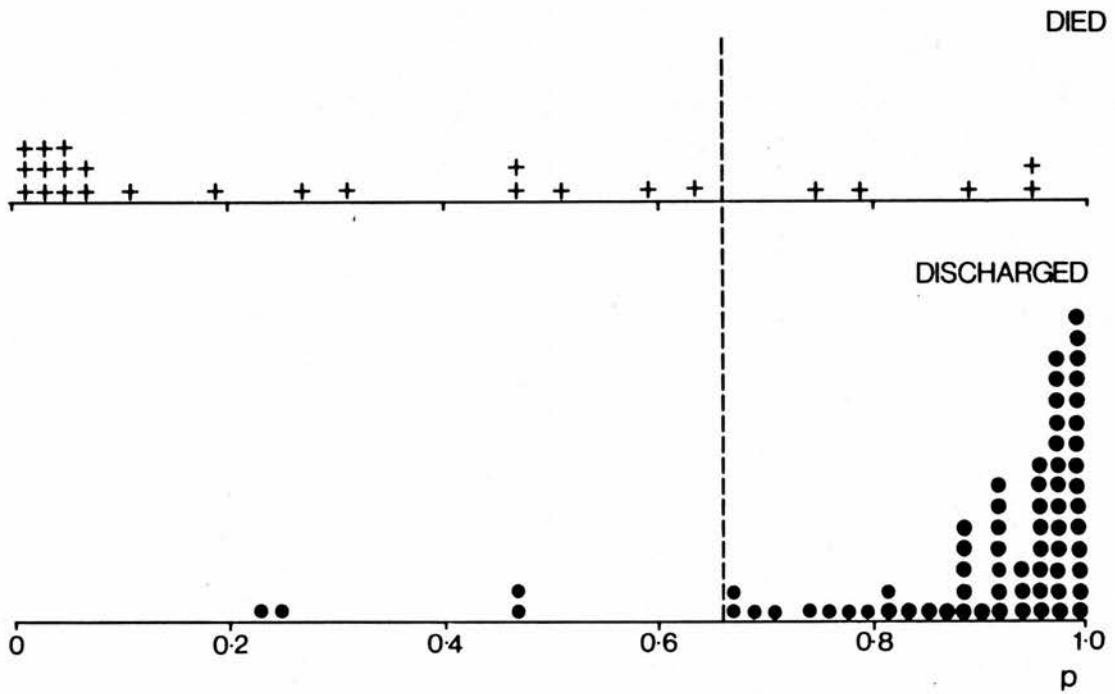


FIGURE 3/1 Probability of discharge or death for patients admitted with variceal haemorrhage in Group 1. For calculation of  $p$ , see explanation in text. An arbitrary cut-off value  $p = 0.66$  has been chosen to define 'high risk' ( $p < 0.66$ ) and 'low risk' groups ( $p > 0.66$ ).

discharged). This more complex model, by employing the interaction term (CR x ENC), is, in practice, only a slight improvement on the previous equation.

An important assumption when using logistic regression analysis (Appendix 3) on any set of data is that each continuous variable is linearly related with the log (p/1 -p). This assumption was tested for the two variables PTR and CR. Figure 3/2 demonstrates that this assumption appears to hold for CR but not for PTR which, as shown in Figure 3/3, has a quadratic shape suggesting that a squared PTR term is required. A squared PTR variable was created and added to the list of existing variables and a logistic regression analysis performed. The programme chose the variables (PTR)<sup>2</sup>, PTR, ENC and CR for inclusion in the model such that

$$\log(p/1 -p) = -9.85 -8.97(\text{PTR})^2 -0.3\text{CR} + 23.3\text{PTR} -0.73\text{ENC}$$

This does not improve prediction over the simple model in that it correctly classified 90% of patient admissions. Furthermore, there is no clinical reason for the poor prognosis associated with a low prothrombin ratio as opposed to middle range prothrombin ratio values.

#### Group Two

Using the regression equation derived from Group One patients (simple model), the individual value for each of the 35 patient admissions was determined (Fig. 3/4). There were four deaths in eight admissions when  $p < 0.66$ , although one of the four survivors died in liver

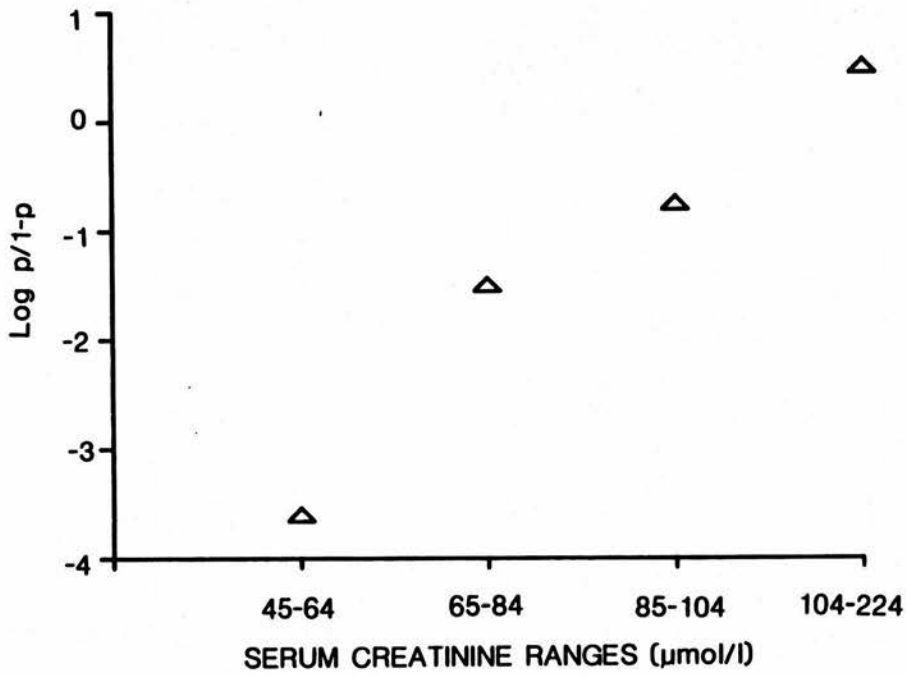


FIGURE 3/2 Relationship between  $\log (p/1-p)$  and serum creatinine (expressed as a range of values) for patients presenting with acute variceal haemorrhage.

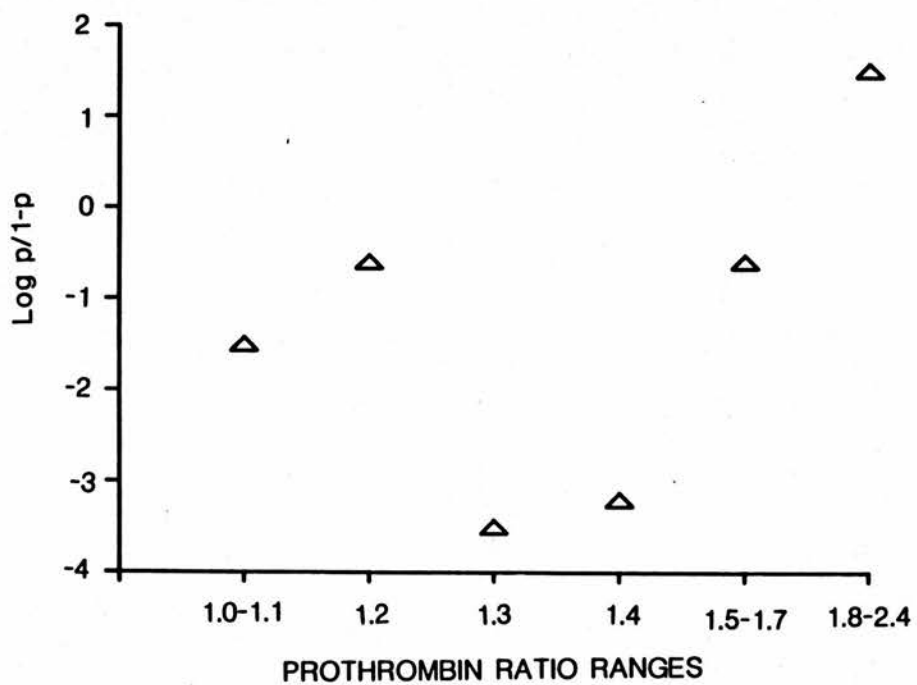


FIGURE 3/3 Relationship between  $\log (p/1-p)$  and prothrombin ratio (expressed as a range of values) for patients presenting with acute variceal haemorrhage.

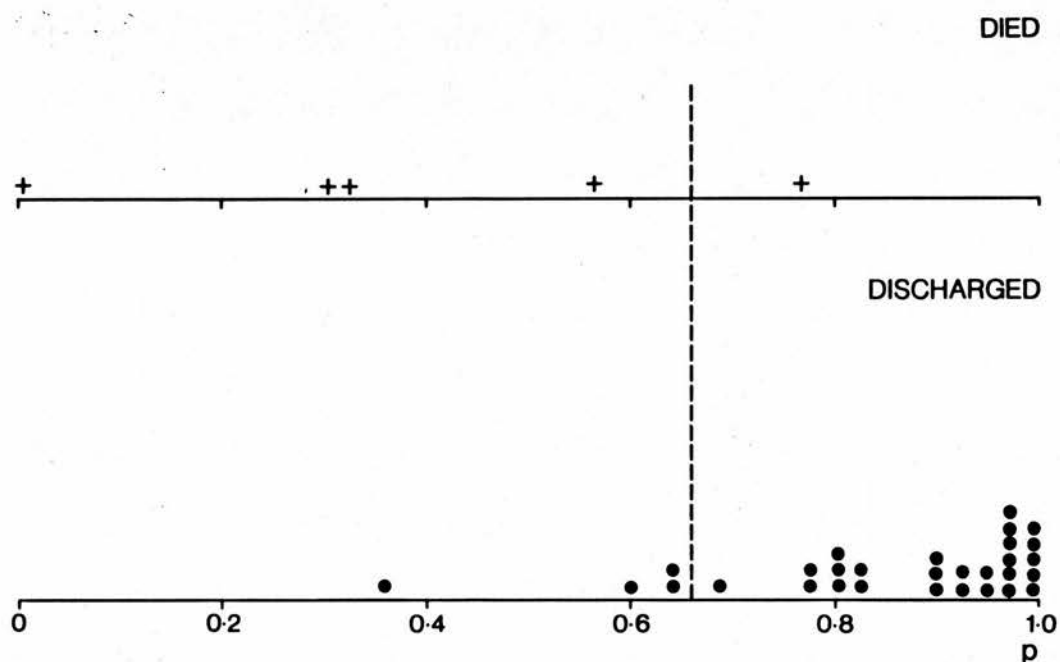


FIGURE 3/4 Probability of discharge or death for patients admitted with variceal haemorrhage in Group 2. For calculation of  $p$ , see explanation in text. An arbitrary cut-off value of  $p = 0.66$  has been chosen to define 'high risk' ( $p < 0.66$ ) and 'low risk' groups ( $p > 0.66$ ).

failure within a week of discharge from hospital. All but one of the 24 patients with a  $p > 0.66$  survived and the one death occurred in a patient who developed a cardiac arrest 24 hours following injection sclerotherapy.

Whereas the simple model wrongly classifies five patient admissions, the interaction model (CR x ENC) makes eight errors and the squared PTR (PTR)<sup>2</sup> model results in seven wrong classifications. The results of this small prospective group of patients seems to justify the use of the simple model in 'predicting' outcome.

#### iv. DISCUSSION

Mortality following acute variceal haemorrhage in the 100 patient admissions of Group One was 28% and it has been shown that nine of the 21 potential predictive factors in this group had a significant association with admission mortality. Stepwise logistic regression analysis identified prothrombin ratio, serum creatinine and the presence of encephalopathy (in decreasing order of significance) as having independent significance in 'predicting' admission mortality. The lower admission mortality of 14% in the Group Two patients cannot be explained by any alteration in management but may relate in part to the relatively smaller proportion of grade C patients. Analysis of outcome in this second series of patients using the derived regression equation suggests that the prognostic index is soundly based, although



experience with more high risk patients will be required to sustain this conclusion. The total number of admissions rather than the actual number of patients has been analysed because outcome was not always the same on each admission. Although patients readmitted with variceal haemorrhage might be expected to have an improved outcome over initial admissions, univariate analysis showed that the number of previous bleeds did not have a significant effect on outcome.

Cello and colleagues (1981) have claimed that Child's original classification which included a clinical assessment of nutrition, ascites and encephalopathy, was the most important factor in determining early mortality after portacaval shunt. In their study, however, only 34% of patients were assigned to grade C, although the admission mortality in this group was 53%. Outcome was correctly predicted in 77% of their patient admissions. In the present study, 71% of the patient population with variceal haemorrhage were consigned to Child's C grade when first seen and using the Child's predictive system, outcome is correctly predicted in only 51% of admissions. Foster and colleagues (1971) demonstrated an admission mortality of 85% in Child grade C patients following shunt surgery compared to 0% and 20% in the grade A and B patients respectively. They found this grading system useful in assessing risk following elective shunt surgery but the subjectivity of their grading was called into question by the finding that longterm survival was significantly

better in grade B than grade A patients. The usefulness of Child's grading in predicting admission mortality has been questioned by Simert and colleagues (1978) who found that bilirubin was the best predictor of early survival. Campbell and colleagues (1973) have described a scoring system to grade the severity of the five individual factors described by Child but allocation to high and low risk groups proved correct in terms of admission mortality in only 62% of their total patient population. The addition of other preoperative parameters did not improve the predictive value of this scoring system.

The present analysis highlights the predictive value of admission prothrombin ratio and is in keeping with its arbitrary inclusion in Pugh's modification of Child's original classification (Pugh et al, 1973). There is debate as to whether prothrombin time can predict outcome after elective portacaval shunting (Malt et al, 1979; Orloff et al, 1980) but a prolonged prothrombin time has been shown to have an independently significant association with admission mortality in alcoholic hepatitis (Maddrey et al, 1978). In a controlled study of portacaval shunting, Jackson and colleagues (1971) noted that an abnormal prothrombin time was associated with poorer survival in control patients although the same observation did not hold for the shunted group. It is, of course, probable that the value of particular predictive factors is influenced in the same way that the results of treatment of variceal

haemorrhage are influenced by the method of selection of patients and the timing of their entry to the treatment programme (Smith et al, 1982).

The inclusion of serum albumin and bilirubin (or jaundice) as in Child's and Pugh's classifications does not enhance prediction in the present patient population when the severity of liver disease is assessed in the period immediately following acute variceal haemorrhage. Although Simert and colleagues (1978) have suggested that bilirubin and albumin are of value in determining early and late survival respectively following elective portacaval shunting, the present analysis has shown no association between serum albumin and admission mortality and that serum bilirubin had no independent significance. Maddrey and others (1978) have shown that serum bilirubin is independently associated with admission mortality in alcoholic hepatitis. Since changes in kaolin cephalin clotting ratio closely match those of prothrombin ratio, serum creatinine has been identified as the second most important predictive factor by regression analysis. Although creatinine is of value in predicting outcome following surgery for obstructive jaundice (Blamey et al, 1983), its predictive value in portal hypertension has not previously been noted.

Attempts have been made by others to use invasive measurements as a means of predicting outcome in patients undergoing surgical decompression of the portal venous system. It has been suggested that appearances

at splenoportography (Warren et al, 1967; Viamonte et al, 1970), portal venous pressure (McDermot et al, 1972), porto-hepatic pressure gradient (Warren et al, 1967; Vinel et al, 1982), and wedged hepatic blood flow (Warren et al, 1967) may be of value in patient selection and outcome determination. Many of these studies have only assessed such measurements in patients undergoing elective surgery and others (Burchell et al, 1974; Smith, 1974) have questioned haemodynamic selection since it has failed to improve operative mortality or longterm survival in shunted patients. The value of such invasive measurements in assessing patients managed primarily by sclerotherapy has yet to be determined.

With regard to the predictive value of liver histology, Kanel and colleagues (1977) found no association between histological evidence of ongoing alcoholic hepatitis and survival in patients with cirrhosis. On the other hand, Grendell and co-workers (1983) using linear logistic regression analysis found the presence of panlobular fat taken in association with haematocrit could be used to predict outcome in 79% of patients about to undergo portaystemic shunting. This two variable combination was not improved by addition of prothrombin time. The use of histological features to predict outcome have not been used in the present patient analysis since liver biopsy may be contraindicated in the presence of a prolonged prothrombin time.

The logistic regression equation obtained from the 100 Group One admissions has clearly identified a high and low risk group of patients based on three variables which can be readily obtained within a few hours of admission to hospital. The value of these variables has been verified in a second independent group of patients and their use in assessing outcome following variceal haemorrhage appears to have considerable advantage over Child's and Pugh's classifications. Further analysis is required, however, to determine whether this prognostic index is still of value once the patient's clinical condition has stabilised and within specific patient populations since certain predictive factors may assume greater importance in patients such as those with alcoholic cirrhosis.

Nonetheless this analysis may be of value in a continuing audit of patients admitted with variceal haemorrhage and it is conceivable that it may offer a useful means of selection for entry to clinical trials. Graham and Smith (1981) have highlighted the dangers of delaying the entry of patients into clinical studies of portal hypertension. The prognostic index may provide a method which will enable identification of patients whose short-term survival is so poor that entry into long term studies is not justified. This means of selection based on liver function would not be possible in the present patient population by means of a scoring system such as the modified Child's classification. It is also arguable whether the prognostic index can be

used to identify that group of patients whose probability of survival is so low that they should be denied active treatment.



CHAPTER 3

SECTION 2 - PREDICTION OF OUTCOME IN ALCOHOL CIRRHOTIC  
PATIENTS FOLLOWING ACUTE VARICEAL HAEMORRHAGE

- i. Introduction
- ii. Patients and methods
- iii. Results
  - (a) analysis of mortality and modified Child's classification
  - (b) potential predictive factors and admission mortality
- iv. Discussion

i. INTRODUCTION

In the previous section, the cause of portal hypertension did not appear to have a significant association with outcome but this may have resulted from the small numbers of patients with non-alcohol associated cirrhosis. In order to determine whether the same variables which 'predicted' admission mortality in all patients are also applicable to the subgroup of patients with alcohol associated cirrhosis, a similar statistical analysis has been performed.

ii. PATIENTS AND METHODS

Patients admitted between 1st August 1979 and 31st September 1982 were analysed. Of the 69 patients previously described in Section 1 of this chapter, only 49 patients satisfied the criteria for diagnosis of alcohol associated cirrhosis. These patients were admitted on 72 occasions (Group One) and were managed by the same policy of tamponade, sclerotherapy and stapled oesophageal transection as described in Chapter 2. From 1st October 1982 to 31st January 1984, 20 alcohol cirrhotic patients were admitted on 22 occasions with variceal haemorrhage and were managed by a similar protocol (Group Two).

Patients were assessed using the modified Child's classification immediately following admission. The 20 potential predictive factors described in the previous section were analysed by Student's t, Mann-Whitney and Chi squared tests. Stepwise logistic regression



analysis was employed to identify those variables which had independent significance and minimise the number of admission factors needed for optimal separation of patients who survived from those who died.

### iii. RESULTS

#### (a) Analysis of Mortality and Modified Child's Grading

Overall admission mortality was 31% in the 72 Group One patient admissions. None of the three grade A patients, three of 13 grade B and 19 of 56 grade C patients died. Admission mortality was 19% in the combined grade A and B (good risk) patients and 34% in the remaining 56 grade C (poor risk) patients. Outcome was, therefore, correctly 'predicted' in 55% of admissions. In Group Two, there were no deaths in three grade A and B patients and four deaths in 19 group C patients (21%).

#### (b) Potential Predictive Factors and Admission Mortality Group One

Chi squared analysis (Table 3.5) demonstrated that of the categorical variables, only encephalopathy had a significant association with outcome. Of the continuous variables, prothrombin ratio, kaolin cephalin clotting ratio, serum creatinine, serum bilirubin, serum urea and white blood cell count were significantly greater in those patients who died than in those patients who did not survive admission to hospital (Table 3.6).

TABLE 3.5 Categorical variables and outcome in alcohol  
cirrhotic patients presenting with acute  
variceal haemorrhage

<u>variable</u>	<u>no. of admissions</u>	<u>died</u>	<u>p value</u>
encephalopathy			
absent	43	8	<0.01
present	29	14	
ascites			
absent	10	1	NS
present	62	21	
sex			
male	60	19	NS
female	12	3	

TABLE 3.6 Relationship between individual variables and outcome of admission in alcohol cirrhotic patients presenting with acute variceal haemorrhage

<u>variable</u>	<u>discharge</u>		<u>death</u>		<u>p value</u>
	value*		value*		
PTR	1.4 ± 0.2		1.9 ± 0.4		<0.001
KCCR	1.3 ± 0.2		1.7 ± 0.4		<0.001
creatinine	80	60,92	110	90,170	<0.001
bilirubin	56	30,100	175	37,287	<0.01
urea	7.0	5.0,10.5	10.5	5.9,14.5	<0.01
WBC	8.3	5.9,12.0	12.2	5.6,18.4	<0.01
albumin	32.2 ± 5.6		29.6 ± 6.7		NS
haemoglobin	10.5 ± 2.2		11.4 ± 2.5		NS
MFB	2.0	0,9	0	0,4	NS
TR	1.0	1.0,1.1	1.1	1.0,1.1	NS
ALT	32	21,45	46	29,63	NS
age	53 ± 13		50 ± 12		NS
platelets	110	80,150	113	62,188	NS
MLD	7.5	1,23	6.0	0,24	NS
protein	64.1 ± 9.0		62.6 ± 7.9		NS
alkaline phosphatase	244	190,340	209	141,335	NS

\*mean ± SD or median and quartile

NS = not significant

PTR = prothrombin ratio

KCCR = kaolin cephalin clotting ratio

WBC = white blood count

MFB = months since first variceal haemorrhage

TR = thrombin ratio

ALT = alanine aminotransferase

MLD = duration of liver disease in months

Stepwise logistic regression analysis showed that only prothrombin ratio (PTR) and serum creatinine (CR) were independent predictors of admission mortality. The derived regression equation allows estimation of the predicted probability of discharge (p). The relationship between the probability of discharge and the two predictors is given by

$$\text{Log } p/1 - p = 11.7 - 5.7 \text{ PTR} - 0.02 \text{ CR}$$

In Figure 3/5, individual values of p have been plotted for those patients who died and those patients who survived admission to hospital. Decreasing values of p were associated with increasing risk of death. When  $p > 0.4$  there were six deaths in 53 patients ('low risk' group) and all 13 patients died when  $p < 0.4$  ('high risk' group). Outcome was correctly 'predicted' in 92% of admissions.

Of the six deaths in the 'low risk' group, four were not obviously related to their liver disease. These included the patients described in the previous section who died as a result of oesophageal perforation, myocardial infarct, left ventricular failure and following withdrawal of treatment.

#### Group Two

Using the regression equation derived from Group One patients, the individual value for each of the 22 patient admissions was determined (Fig. 3/6). Both patients with a p value less than 0.4 died and all but two of the 20 patients with  $p > 0.4$  survived. One death



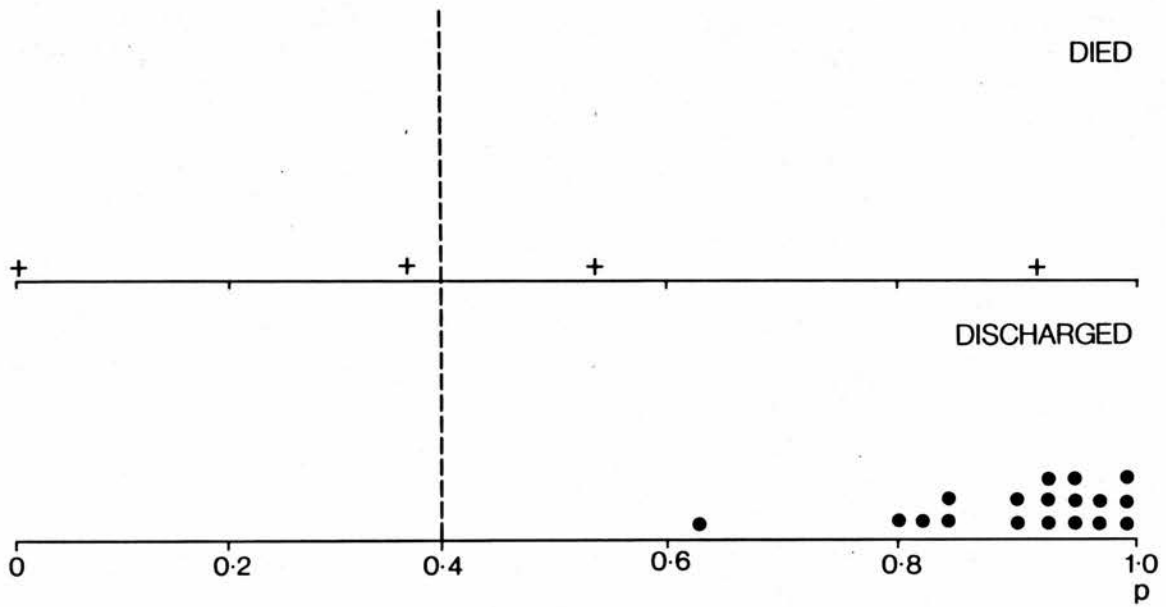


FIGURE 3/6

Probability of discharge or death for alcohol cirrhotic patients admitted with variceal haemorrhage in Group 2. For calculation of  $p$ , see explanation in text. An arbitrary cut-off value  $p = 0.4$  has been chosen to define 'high risk' ( $p < 0.4$ ) and 'low risk' groups ( $p > 0.4$ ).

was in a patient who developed a cardiac arrest 24 hours following injection sclerotherapy and the other was in a patient whose liver failure progressed during his admission and died with terminal variceal haemorrhage.

#### iv. DISCUSSION

In the smaller subgroup of patients with alcoholic cirrhosis, admission mortality of 31% was only slightly greater than the 28% admission mortality for the 100 patients presenting with acute variceal haemorrhage (Section iii). Despite a relative increase of the proportion of modified Child's grade C patients (78% versus 71%), the present analysis has, however, again clearly identified 'high' and 'low risk' groups of patients. Indeed there was a 100% mortality in the 13 patients assigned to the 'high risk' group compared to an 11% mortality in the 'low risk' group. Outcome has been correctly 'predicted' in 92% of patient admissions whereas the modified Child's classification could only do so in 55% of the patient population.

Although the same variables which had a significant association with outcome in all patients retain their significance in patients with alcohol cirrhosis, only prothrombin ratio and creatinine have independent significance. The loss of encephalopathy as a predictor of outcome in this subgroup of patients may reflect the difficulties in clinically establishing the presence of encephalopathy in patients whose confusional state may be related to alcohol excess or an acute

alcohol withdrawal state at the time of admission. Furthermore, the proportion of alcohol cirrhotic patients with encephalopathy on admission is greater than in those patients whose portal hypertension is secondary to other causes thereby reducing its discriminatory ability. Novis and colleagues (1976) recognised the presence of encephalopathy on admission was an unfavourable prognostic sign and noted an admission mortality of 77% when patients with acute variceal haemorrhage showed evidence of encephalopathy, ascites and jaundice on admission. The continued presence of encephalopathy following admission may be useful in determining outcome but its prognostic value is limited given that both prothrombin ratio and creatinine can be estimated within hours of admission to hospital and, when these factors are taken together, they can 'predict' outcome in all but 8% of the present patient population. It is, of course, possible that the subjective clinical assessment of encephalopathy is limited but the use of objective tests such as electroencephalograms and trail testing might be useful in revealing evidence of subclinical encephalopathy (Zeegen et al, 1970) or differentiating between encephalopathy and alcohol induced toxic state.

Regression analysis has determined that the presence of other acknowledged 'markers' of liver function do not have independent significance. Simert and colleagues (1978) noted that the presence of ascites and hyperbilirubinaemia before elective surgery were



useful indicators of survival at one month. In the present study, 62 of the 72 patients were judged clinically to have ascites on admission and all but one death occurred in this group. Similarly, those patients who survived admission to hospital had a lower admission serum bilirubin than those who died but the differences were not large enough to improve upon the predictive equation containing prothrombin ratio and creatinine. It is conceivable that changes in bilirubin and in the presence of ascites during the patients admission may help in determining outcome and this may account for the observations by Simert and colleagues (1978) that the continued presence of ascites and jaundice before elective surgery were unfavourable signs.

Kanel and colleagues (1977) stated that once a patient with cirrhosis has bled from oesophageal varices, the aetiology of the cirrhosis was not a major factor in determining survival after therapeutic portacaval shunt. Their study, however, comprised only 82 patients, 45 of whom had histological and clinical criteria acceptable for a diagnosis of alcohol cirrhosis. They determined that hepatic reserve as defined by Child's classification provided the best criteria for predicting survival. On the other hand, Campbell and others (1973) undertook a study of Child's criteria and survival following shunt surgery and correctly identified 59% of all short-term survivors following shunt surgery. They found that prediction of short-term survival in post-necrotic cirrhosis was 75%

but was only 50% in the alcohol cirrhotic group. In a further study assessing factors which influenced survival following therapeutic shunts, Cello and colleagues (1981) made no attempt to separate those patients with alcohol cirrhosis from those with other causes of portal hypertension. The present analysis on all patients with portal hypertension and in the subgroup of patients with alcohol cirrhosis has suggested that the factors predicting outcome may be related to the aetiology of the portal hypertension.

Grendell and colleagues (1983) have shown that certain pre-shunt hepatic histological features such as the presence of panlobular fat, either taken alone or in combination with other factors, may be useful predictors of short-term survival. Mikkelsen (1974) reported an adverse effect on survival after portacaval shunt when acute hilar necrosis was present on liver biopsy but neither Cello and colleagues (1981) nor Kanel and colleagues (1977) could demonstrate such an association. Kanel and colleagues (1977) did show that active inflammation and peacemeal necrosis in patients with chronic active liver disease was associated with a higher operative mortality following shunt surgery. The histological activity of liver disease in alcoholic cirrhosis showed no such trend. None of these studies took account of the timing of liver biopsy relative to the patients admission and further investigation is required to determine whether histological features may be useful in determining prognosis. It would be

difficult for the presence of certain histological features to improve on the prediction obtained with prothrombin ratio and creatinine, both of which can be measured immediately following admission. Orloff (1980) did not assess the effect on survival of liver histology following emergency portacaval shunt but using SGOT as an indicator of hepatocellular damage, he noted that there was a 70% survival rate if levels were lower than 100 u/l on admission whereas only 43% survived above this level. In the present study, alanine aminotransferase has not been of value in predicting outcome but in both the subgroup of alcohol cirrhotic patients and in all portal hypertensive patients, alanine aminotransferase levels have been higher in patients who did not survive admission to hospital. It is debatable whether this potential prognostic factor or indeed other factors would have predicted outcome if the present management policy had included emergency portacaval shunting as its main therapeutic option. Although Adamsons and colleagues (1977) have suggested that portal pressure measurements may help to predict when variceal haemorrhage will be controlled, the use of such measurements have not found much favour in recent years (Burchell et al 1974; Smith, 1974).

A combination of clinical, biochemical and haematological indices can be used to 'predict' outcome in patients presenting with acute variceal haemorrhage. Although only prothrombin ratio and serum creatinine on admission identify a 'high risk' group amongst the

alcoholic cirrhotic patients, the presence of encephalopathy taken with these two other factors aid prediction in all patients irrespective of the underlying aetiology of portal hypertension. Further analysis is required to establish whether these same indices of liver function are of value in determining long term survival and to establish whether the timing of such measurements alters their significance.

CHAPTER 4

SECTION 1 - PREDICTION OF ONE YEAR SURVIVAL FOLLOWING  
ACUTE VARICEAL HAEMORRHAGE

- i. Introduction
- ii. Patients and methods
- iii. Results
  - (a) Modified Child's grading and one year survival
  - (b) Potential predictive factors and one year survival
- iv. Discussion

i. INTRODUCTION

Although reduction in portal venous pressure by portacaval decompression effectively prevents recurrent variceal haemorrhage, the operation is attended by a significant postoperative mortality (Conn, 1974; Orloff et al, 1980), increased risk of encephalopathy (Malt et al, 1976; Rueff et al, 1976) and no apparent improvement in longterm survival when compared with conservative therapy (Jackson et al, 1971; Resnick et al, 1974). It has been shown that beta blockade therapy can reduce portal venous pressure in cirrhotic patients with portal hypertension (Lebrec et al, 1980). Although Lebrec and colleagues (1981) subsequently demonstrated a significant reduction in recurrent haemorrhage in treated patients, the use of adjuvant beta blockade with agents such as propranolol has not been sustained universally, with further haemorrhage being reported in up to 46% of patients receiving this drug (Burroughs et al, 1983). The move to a more conservative management policy in many centres has resulted from the encouraging results of injection sclerotherapy (Johnston et al, 1973; MacDougall et al, 1982; Terblanche et al, 1983) but the high incidence of recurrent variceal haemorrhage experienced in such treatment programmes suggests that a more aggressive policy such as stapled oesophageal transection might be more appropriate for a selected group of patients.

Selection of patients for tailored treatment options might be facilitated if high risk patients could

be identified at an early stage in management. In the previous chapter, certain indices of liver function have been demonstrated to have considerable advantage over classifications and scoring systems in predicting short term survival following admission with acute variceal haemorrhage. This chapter will concern itself with whether these same indices of liver function can be used to 'predict' long term survival for individual patients and will investigate the effect on survival prediction of delaying by one month the assessment of these patients. The therapeutic implications of assessing the severity of liver disease by such methods is discussed.

#### ii. PATIENTS AND METHODS

The patient population to be studied comprises the same group whose clinical management was discussed in Chapters 2 and 3. They include 69 patients referred for treatment of bleeding varices between August 1979 and September 1982. The one patient with idiopathic portal hypertension who subsequently underwent elective portacaval decompression has been excluded from further analysis since his management differed considerably from the remaining 68 patients.

Patient assessment was undertaken (as in Section 1, Chapter 3) immediately following initial admission to hospital with variceal haemorrhage. The 20 potential predictive factors were analysed by Student's *t*, Mann-Whitney and Chi squared tests. Stepwise logistic regression analysis was used to identify those variables

which had independent significance and minimise the number of admission factors needed for optimal separation of patients who survived from those who died.

Patients were assessed by modified Child's grading at the time of admission to hospital with variceal haemorrhage and 7 days following admission.

### iii. RESULTS

#### (a) Modified Child's grading and one year survival

Sixty-eight patients had a one year survival of 47% and a rebleeding rate of 32%. The results of management policy in relation to survival have previously been discussed in Section 4b of Chapter 2. All five grade A, 13 of the 15 (81%) grade B and 30 of 48 (62%) grade C patients survived admission to hospital (Table 4.1). Ten patients did not survive seven days in hospital and of the remaining 58 patients, modified Child's grading improved in twelve and deteriorated in three patients. All six patients regraded A, 18 of 20 (90%) grade B and 24 of 32 (75%) grade C patients survived admission to hospital (Table 4.2).

In the 68 patients graded at the time of admission, one year survival was 100% in grade A, 65% in grade B and 35% in grade C patients. In the 58 surviving patients regraded at one week following admission, one year survival was 100% in grade A, 65% in grade B and 31% in grade C (Table 4.2).



TABLE 4.1 Admission and one year mortality in 68 patients assessed by a modified Child's classification at the time of admission with variceal haemorrhage (Pugh et al, 1973)

	<u>n</u>	<u>admission</u> <u>mortality</u>	<u>one year</u> <u>mortality</u>
A	5	0	0
B	15	2 (19%)	5 (33%)
C	48	18 (38%)	31 (65%)
Total	68	20 (29%)	36 (53%)

TABLE 4.2 Admission and one year mortality in 58 surviving patients reassessed by a modified Child's classification seven days following admission with variceal haemorrhage (Pugh et al, 1973)

	<u>n</u>	<u>admission mortality</u>	<u>one year mortality</u>
A	6	0	0
B	20	2 (10%)	7 (35%)
C	32	8 (25%)	19 (59%)
Total	58	10 (17%)	26 (47%)

(b) Potential predictive factors and one year survival

Nine individual risk factors demonstrated a significant association with one year survival (Table 4.3 and 4.4). Stepwise logistic regression analysis showed that only the presence of encephalopathy (ENC), prothrombin ratio (PTR) and serum creatinine (CR) (in decreasing order of significance) were independent predictors of mortality. The derived regression equation allows estimation of the predictive probability of survival. The relationship between the probability of one year survival (p) and the three predictors is given by

$$\log p/1 - p = 7.8 - 0.76 \text{ ENC} - 2.7 \text{ PTR} - 0.05 \text{ CR}$$

where the actual values of PTR and CR are entered and ENC is coded as -1 when absent and +1 when present.

The relationship between individual values of p and death or survival at one year is shown in Figure 4/1 (p not calculated in five patients with unrecorded serum creatinine). Decreasing values of p were associated with increasing risk of death; for example, there were seven deaths in 32 patients (22% mortality) when  $p > 0.05$  ('low risk') and there were 26 deaths in 31 admissions (84% mortality) when  $p < 0.05$  ('high risk'). The outcome following acute variceal haemorrhage was correctly 'predicted' in 81% of admissions using this p value of 0.5 as an arbitrary discriminant between 'high' and 'low' risk groups.

Of the seven deaths which were 'incorrectly

TABLE 4.3 Relationship of categorical variables with survival at one year in 68 patients admitted with acute variceal haemorrhage

	<u>n</u>	<u>died</u>	
Sex			
male	46	26	NS
female	22	10	
Cause of portal hypertension			
alcohol	48	28	NS
other	20	8	
Ascites			
absent	14	3	p<0.05
present	54	33	
Encephalopathy			
absent	38	14	p<0.01
present	30	22	

NS = not significant

TABLE 4.4 Relationship between continuous variables and one year survival in 68 patients admitted with acute variceal haemorrhage

<u>factor</u>	<u>alive</u>		<u>dead</u>	
	n	value	n	value
PTR	32	1.3 ± 0.2***	36	1.6 ± 0.4***
KCCR	32	1.2 ± 0.2***	34	1.5 ± 0.4***
creatinine	31	70 60,85***	33	100 90,121***
urea	31	5.9 4.2,90**	33	9.5 7.5,12.5**
bilirubin	32	72 32,140*	36	108 42,199*
white cell count	32	9.1 ± 5.0*	35	12.4 ± 7.9*
thrombin ratio	32	1.0 1.0,1.1	34	1.1 1.0,1.1
haemoglobin	32	10.9 ± 2.3	36	11.4 ± 2.5
age	32	51 ± 15	36	52 ± 14
albumin	32	32.3 ± 4.9	36	30.4 ± 6.7
protein	32	63.4 ± 9.2	36	61.7 ± 9.5
MFB	32	0 0,12	36	0 0,0
MLD	32	15 1,72	36	1 0,25
platelets	32	100 71,156	36	109 75,171
ALT	32	34 21,44	36	35 24,64
APH	32	248 173,352	36	233 152,407

value = mean ± SD or median and quartiles where appropriate

\*\*\* p<0.001

\*\* p<0.01

\* p<0.05

PTR = prothrombin ratio;  
 KCCR = kaolin cephalin clotting ratio;  
 MFB = months since first bleed;  
 MLD = duration of liver disease in months;  
 ALT = alanine aminotransferase;  
 APH = alkaline phosphatase

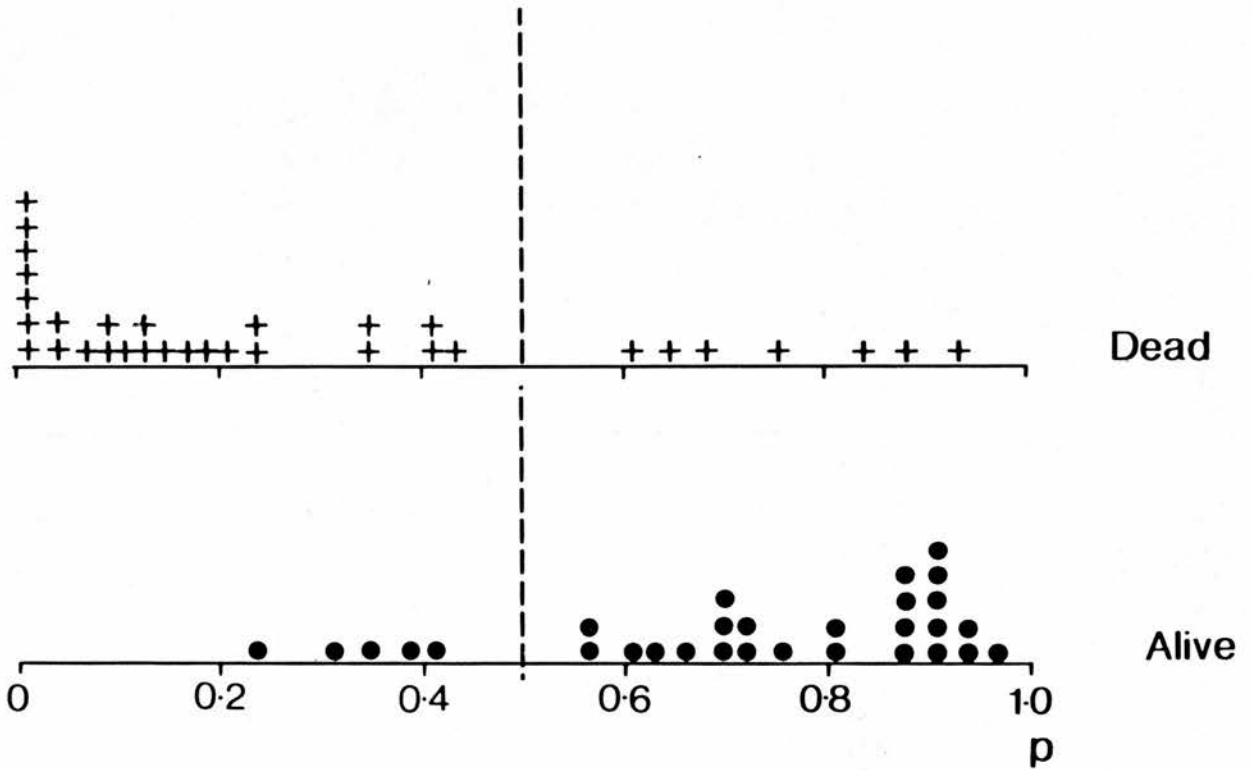


FIGURE 4/1

Probability of one year survival ( $p$ ) for patients admitted with variceal haemorrhage. For calculation of  $p$  values, see explanation in text. An arbitrary cut-off value of  $p = 0.5$  has been chosen to define 'high risk' ( $p < 0.5$ ) and 'low risk' groups ( $p > 0.5$ ).

predicted' (Table 4.5), four patients died following rebleeding and two of these deaths were associated with progressive liver failure (patients 18 and 44), two deaths were treatment related (patient numbers 11 and 40), whilst one patient (patient number 21) died of a myocardial infarct.

#### iv. DISCUSSION

This analysis demonstrates that the admission prothrombin ratio, a factor in both Child's classification and Pugh's modification, is one of the most powerful predictors of one year survival and in association with serum creatinine and the presence of encephalopathy, can 'predict' survival at one year in 81% of patients. Since the majority of deaths in this and other series (Pugh et al, 1973; Novis et al, 1976; Graham et al, 1981; Cello et al, 1981) following variceal haemorrhage occurs soon after the index bleeding episode, it might be anticipated that factors which predict admission mortality also predict death by one year. However, Malt and Malt (1979) have shown that prothrombin time, although a predictor of survival at two and five years, did not correlate with immediate survival after portacaval shunt surgery. Their finding that preoperative bilirubin and albumin were the best predictors of operative mortality and longterm survival are at variance with the present results. This difference may be related in part to a different management policy or to the heterogeneous population of

TABLE 4.5 Deaths occurring within one year in patients  
presenting with acute variceal haemorrhage  
where outcome was incorrectly 'predicted'

<u>patient no.</u>	<u>p</u>	<u>admission</u>	<u>cause of death</u>
11	0.61	1st	oesophageal perforation
21	0.65	1st	myocardial infarct
34	0.71	2nd	left ventricular failure following transection
44	0.84	2nd	recurrent bleeding, liver failure
18	0.86	3rd	recurrent bleeding, liver failure
42	0.95	2nd	recurrent bleeding, refused admission
40	0.98	2nd	oesophageal tamponade, respiratory arrest

p = probability of one year survival (see text for calculation)



elective and emergency shunt patients included in their study.

Simert and co-workers (1978) studied patients undergoing elective portacaval shunts and demonstrated that certain factors such as bilirubin and ascites were associated with survival at one month and one year. Albumin was the only other factor associated with survival at one year. Their study differed from the present analysis in that they excluded patients with very poor liver function whereas this study includes all patients admitted on an emergency basis with variceal haemorrhage; this may explain the difference between an admission mortality of 10% in their study and 31% in the present series. This would suggest that the timing of assessment of liver function with regard to the index bleed should be taken into account when assessing survival rates. Indeed, in the present series of patients it has been shown that 15 of the 58 patients who survived the first week of admission to hospital changed their modified Child's grading and in all but three, there was an improvement in grading. Smith and Graham (1982) have suggested that such an improvement in Child's classification is rare and if this system is used to select patients for shunt surgery, the resultant delay is more likely to lead to death, rebleeding and a deterioration in grading. In the present study, regrading at one week following the index bleed did not better separate those patients who survived admission from those who did not. Similarly 'prediction' of

outcome at one year was not affected by reassessing the patients modified Child's grade at 7 days.

Several workers have used both Child's classification (Resnick et al, 1974; Orloff et al, 1980) or one of its modifications (Pugh et al, 1973; Johnston et al, 1981; MacDougall et al, 1982; Terblanche et al, 1983) to assess liver function in the management of variceal haemorrhage. Campbell and colleagues (1973) modified Child's grading by scoring each of the individual five parameters of liver function. This separated high and low risk patients but correctly identified only 65% and 50% of the long and short term survivors respectively and the addition of other preoperative parameters did not improve the predictive value of the scoring system. Despite the subjectivity of some of the criteria used by Child, Cello and colleagues (1981) found that outcome was correctly classified in 70% of patients if only class C was used to identify high risk. The inclusion of preoperative haematocrit and serum globulin improved prediction of early mortality to 88%. However, longterm survival could not be determined by employing any of these seven factors, whether used alone or in combination.

In reviewing factors affecting survival following shunt surgery, Kanel and colleagues (1977) found that Child's grading of patients was superior to liver histology and other liver function tests in determining outcome. The subjectivity of their grading, however, is highlighted by the observation that grade C patients had

an extremely poor survival compared to grade B patients whose longterm survival was, in fact, better than that of grade A patients. More recently, Grendell and his colleagues (1983) have suggested that the presence of panlobular fat on histology of liver biopsy was the best indicator of one year survival in patients presenting with acute variceal haemorrhage. Although prothrombin time, presence of hyaline and haematocrit also predicted outcome, only the latter factor improved prediction beyond the presence of panlobular fat. They concluded that if a liver biopsy could be obtained, then histological features should be used to determine suitability for shunt surgery. The present study was not intended as an evaluation of the role of histological features in predicting outcome and the presence of a prolongation of prothrombin time may prevent this investigation from being undertaken. Assessment of hepatocellular damage may have a role in prediction given that serum markers of liver cell damage such as SGOT may be useful in determining outcome. Orloff and colleagues (1980) have previously suggested that this biochemical marker is useful in this context and Graham and Smith (1981) have shown that survival at one year is only 5% for patients with a value greater than 100 U/l before shunt surgery whereas survival was 36% for patients below this preoperative level. This study shows no such association with median values of 34 and 35 U/l (ALT) in those who survived and did not survive to one year. The present analysis, however,

does not rule out the possibility that this liver function test may be important in patients submitted to shunt surgery.

In the present study, the one year mortality of 65% in patients assigned to a modified Child's grade C at initial presentation is comparable to that reported in other series (Table 1.2). However, since this group of patients comprised 71% of the present patient population, the classification is not sensitive enough to define risk for individual patients. On the other hand, regression analysis allows clearer separation of high and low risk groups of patients, correctly predicting outcome in 81% of patients. Of the seven deaths which were incorrectly 'predicted', two followed treatment complications and two patients died of myocardial disease. It is arguable whether the patient who refused to take medical advice would have survived had he sought admission to hospital. The remaining two deaths must be seen as failures of the predictive system when used in patients managed by a policy employing injection sclerotherapy as its main therapeutic option. Although the system can be used as a means of auditing the present management policy, it remains to be seen whether it can be applied to groups of patients managed by other treatments.

There is conflicting evidence as to whether sclerotherapy improves longterm survival (MacDougall et al, 1982; Terblanche et al, 1983), although it appears that the risk of further haemorrhage and its severity

are reduced by this technique. This seems logical in that a reduction in the incidence of recurrent variceal haemorrhage will result in an improvement in mortality by a decrease in the number of deaths secondary to haemorrhage and associated liver failure. The study of Terblanche and colleagues (1983) showed no improvement in long term survival in the group of patients receiving elective sclerotherapy compared to the group of patients receiving sclerotherapy for acute variceal haemorrhage alone. Although there was a reduction in recurrent haemorrhage in the treated group, these results suggest that recurrent haemorrhage can be adequately treated by acute sclerotherapy and that subsequent deaths result from progressive deterioration of liver function which in itself is not affected by sclerotherapy. Of the 23 patients in the present series requiring readmission with variceal haemorrhage, ten did not survive to one year but in only four of these patients was death incorrectly 'predicted' (Table 4.5). These results would suggest that overall survival would have been improved had these four patient deaths not been precipitated by recurrent haemorrhage but long term survival is more likely to be determined by the progression of the underlying liver disease and other factors such as continued alcohol abuse.

Further studies will be required to determine which therapeutic option minimises the severity and frequency of such bleeding episodes. It has been suggested that in all future randomised clinical trials,

patients should be stratified into good and poor risk groups by Child's criteria (Graham et al, 1981; Galambos, 1983). The present analysis suggests that such scoring systems may not be sufficient to adequately separate these groups and that such stratification should be based on the predictive indices identified. Failure to do so may result in an unfair distribution of high risk patients between treatment groups. The effect of a change to a more aggressive management policy such as with stapled oesophageal transection could be observed outwith a controlled study by use of the 'predictive' system. An unfavourable effect on survival would be seen if patients who were previously assigned to the 'good risk' group did not survive to one year.

CHAPTER 4

SECTION 2 - PREDICTION OF ONE YEAR SURVIVAL USING FACTORS  
MEASURED ONE MONTH FOLLOWING ACUTE VARICEAL  
HAEMORRHAGE

- i. Introduction
- ii. Patients and methods
- iii. Results
  - (a) Outcome and modified Child's grading
  - (b) Potential predictive factors and outcome
- iv. Discussion

## i. INTRODUCTION

In previous chapters it has been suggested that the timing of the assessment of liver dysfunction may have an effect in determining which factors may predict outcome following acute variceal haemorrhage. Although some investigators have suggested that the modified Child's grading of patients is of value in this context (Pugh et al, 1973), it has been shown in previous chapters that it is of limited value in the prediction of short and longterm survival. Furthermore the modified Child's grading of patients changes within the first seven days of admission to hospital following acute variceal haemorrhage but this change in grading does not improved its ability to predict outcome.

In order to further investigate the relationship between timing of assessment of liver dysfunction and prediction of outcome, risk factors, recorded one month following the index variceal bleed, were submitted to further analysis.

## ii. PATIENTS AND METHODS

The patient population studied included 38 patients described in the previous section who survived to be assessed at one month from their initial admission with variceal haemorrhage and were entered into an elective sclerotherapy programme.

For the purposes of the present analysis, a further 15 patients referred from other hospitals one month following their index variceal bleed are



included. Of these patients, seven were referred prior to September 1982 and have not been included in previous analysis because of the anticipated effect of their late referral on subsequent survival rate (Graham and Smith, 1981). The remaining eight patients were seen after September 1982 at which time a study assessing the value of propranolol in preventing recurrent variceal haemorrhage had been commenced. These patients did not satisfy the entry criteria to the study and underwent a programme of longterm injection sclerotherapy as outlined in the previous section and in Chapter 2.

There were 35 males and 18 females with a mean age of 62 (range 17-73 years). The cause of portal hypertension in these patients was alcohol cirrhosis (34 patients), chronic active hepatitis (4 patients), cryptogenic cirrhosis (6 patients), primary biliary cirrhosis (2 patients), portal vein thrombosis (2 patients), idiopathic portal hypertension (2 patients), post-hepatitic cirrhosis (1 patient), pancreatic carcinoma (1 patient) and unknown (1 patient). Sixty-four per cent of patients therefore had alcohol associated cirrhosis.

Patient assessment was undertaken at the time of the patient's first elective admission which in all instances was between 3-5 weeks following their initial admission to the Royal Infirmary or the referring hospital with acute variceal haemorrhage. The clinical, biochemical and haematological indices of liver function measured were those recorded in Chapter 3 and Section 1

of Chapter 4. The potential predictive factors were analysed by Student's t, Mann-Whitney and Chi squared tests. Stepwise logistic regression analysis was used to identify those variables which had independent significance and to minimise the number of admission factors needed for optimal separation of those patients who survived and those who did not survive to one year.

### iii. RESULTS

#### (a) Outcome and Modified Child's Grading

Thirty four patients (64%) survived to one year and during this time 15 of these had further variceal haemorrhage which required acute sclerotherapy. Of the 19 patients who did not survive to one year, 13 patients died of liver failure (in six haemorrhage precipitated admission), one patient died of left ventricular failure following emergency stapled oesophageal transection, one patient died with a severe coagulopathy following haemorrhage from a gastric varix, in one patient treatment was withdrawn following admission, one patient died of a cerebrovascular accident and two patients died from their pancreatic and gastric carcinomas.

Outcome is shown for 53 patients as graded by Pugh's modification of Child's classification (Table 4.6) (one patient - no serum albumin recorded). Seventy-two patients were assigned to grades A and B. Only one-third of the grade C patients survived to one year. Using grades A and B as good risk and grade C as bad risk, outcome was correctly predicted in 74% of

TABLE 4.6 Modified Child's classification and one year survival in 53 patients assessed one month following admission with acute variceal haemorrhage

<u>grade</u>	<u>n</u>	<u>dead at 1 year</u>
A	16	2 (13%)
B	21	6 (29%)
C	15	10 (67%)
no grade	1	1
Total	53	19 (36%)

admissions.

(b) Potential Predictive Factors and One Year Survival

Only three individual risk factors obtained from the 53 patients demonstrated a significant association with one year survival (Tables 4.7 and 4.8). Stepwise logistic regression analysis showed that albumin (ALB), white cell count (WBC), haemoglobin (Hb.) and age (in decreasing order of significance) were independent predictors of one year survival. The derived regression equation allows estimation of the predicted probability of survival. The relationship between the probability of discharge and the four predictors is given by

$$\log (p/1 - p) = -5.2 + 0.11ALB - 0.45WBC - 0.45Hb - 0.04(age)$$

where the actual values of all the variables are entered.

The relationship between individual values of p and death or survival at one year in these patients is shown in Figure 4/2 (p not calculated in four patients with unrecorded values). Decreasing values of p were associated with increasing risk of death; for example there were seven deaths in 38 admissions (18% mortality) when  $p > 0.5$  (low risk) and there were nine deaths in 12 admissions (75% mortality) when  $p < 0.5$  (high risk). In five of the seven deaths in the low risk group, death was due to progressive liver failure. One patient died in left ventricular failure in the immediate postoperative period following stapled oesophageal

TABLE 4.7 Categorical variables and one year survival  
in patients assessed one month following  
acute variceal haemorrhage

	<u>n</u>	<u>died</u>	<u>p&lt;</u>
Sex			
male	35	14	NS
female	18	5	
Cause of portal hypertension			
alcohol	34	14	NS
other	19	5	
Ascites			
absent	36	9	0.05
present	17	10	
Encephalopathy			
absent	49	16	NS
present	4	3	

TABLE 4.8 Relationship between continuous variables  
and one year survival in patients assessed  
at one month following acute variceal  
haemorrhage

<u>factor</u>	<u>alive</u>		<u>dead</u>			
	n	value	n	value		
albumin	34	34.9 ± 5.5*	18	30.2 ± 5.8*		
PTR	34	1.3 ± 0.2*	19	1.4 ± 0.2*		
protein	33	70.9 ± 8.7	18	66.5 ± 11.4		
age	34	49.2 ± 13.4	19	54.4 ± 12.0		
bilirubin	34	27	19,44	19	30	20,69
ALT	34	31	17,54	19	34	19,56
APH	34	326	206,419	19	345	193,848
WBC	34	6.3 ± 3.1	17	7.5 ± 3.3		
haemoglobin	34	12.2 ± 2.4	19	11.9 ± 1.8		
KCCR	34	1.3 ± 0.2	17	1.3 ± 0.2		
TR	34	1.1 ± 0.7	17	1.0 ± 0.6		
platelets	34	139	107,18	19	114	83,201
urea	34	4.7	3.2,5.	16	5.1	3.8,7.1
creatinine	34	76	70,85	16	85	73,115
MLD	34	13	2,52	19	9	2,48
MFB	34	3	1,12	19	1	1,9

value = mean ± SD or median and quartile as applicable

\*p<0.05

PTR = prothrombin ratio;  
 ALT = alanine aminotransferase;  
 APH = alkaline phosphatase;  
 WBC = white cell count  
 KCCR = kaolin cephalin clotting ratio;  
 TR = thrombin ratio;  
 MLD = duration of liver disease in months;  
 MFB = months since first bleed

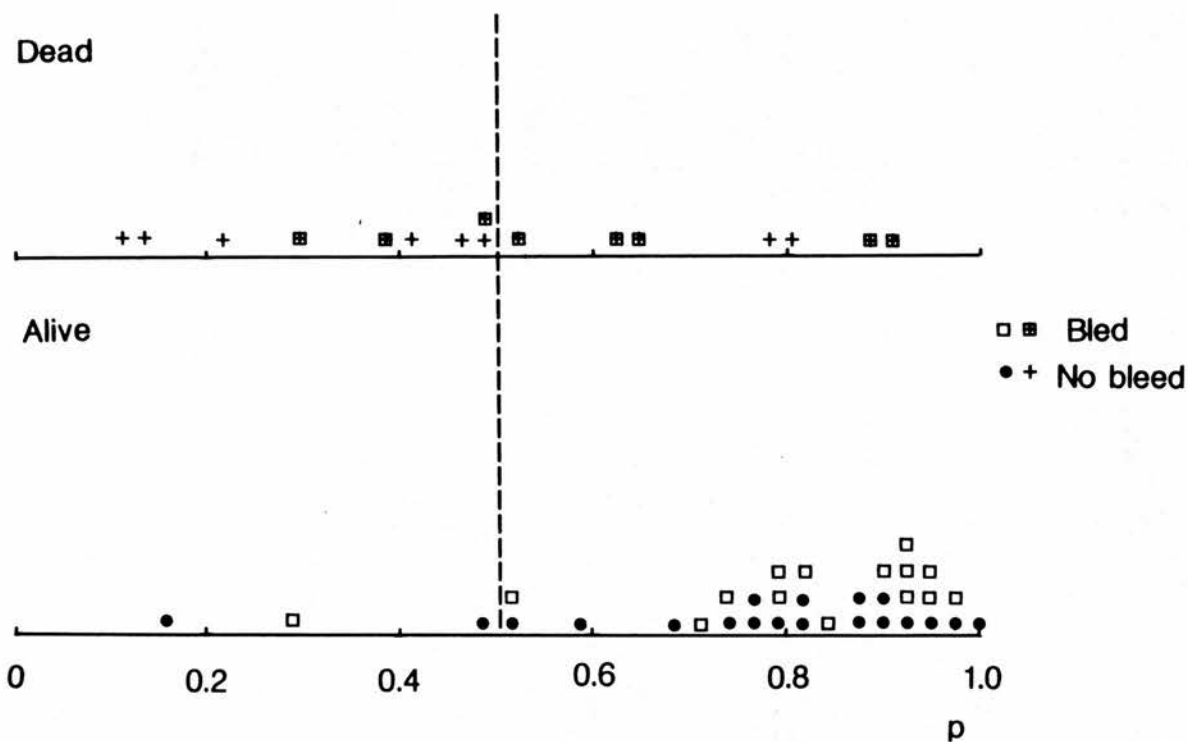


FIGURE 4/2 Probability of one year survival ( $p$ ) for patients assessed one month following acute variceal haemorrhage. For calculation of  $p$  values, see explanation in text. An arbitrary cut-off value of  $p = 0.5$  has been chosen to define 'high risk' ( $p < 0.5$ ) and 'low risk' groups ( $p > 0.5$ ).

transection for recurrent variceal haemorrhage and the seventh patient died when a positive decision was made to withdraw treatment. The outcome was correctly 'predicted' in 70% of admissions using this p value of 0.5 as an arbitrary discriminant between 'low' and 'high risk' groups.

Figure 4/2 also demonstrates the distribution of those patients experiencing further variceal haemorrhage during follow-up. The incidence of rebleeding is similar in both those patients who survived to one year (45%) and those patients who did not survive to one year (50%). Five of the seven patients who died in the 'low risk' group experienced recurrent variceal haemorrhage during the period of follow-up.

#### iv. DISCUSSION

Whereas 71% of patients were assigned to grade C at the time of acute variceal haemorrhage (section 1), 72% of the group of patients assessed one month after variceal haemorrhage were assigned to the 'good risk' grades A and B by the modified Child's classification (Pugh et al, 1973). The change in the relative numbers in these grades must be accounted for by the high admission mortality of those patients assigned to modified Child's grade C at the time of their acute variceal haemorrhage and by an improvement of liver function in those patients surviving to be readmitted one month following this index bleed. This selection of patients has resulted in only 15 patients being assigned



to a modified grade C and only five (33%) of these patients survived to one year whereas only eight (21%) of 37 patients assigned to grades A and B did not survive this period. Using the five variables of ascites, encephalopathy, albumin, bilirubin and prothrombin time, outcome at one year has been correctly 'predicted' in 74% of patient admissions. There has been, therefore, a considerable improvement in the ability of the modified Child's classification in predicting outcome when it is used to assess liver dysfunction one month following acute variceal haemorrhage as compared to its usefulness within the first week of the patient's admission to hospital with acute variceal haemorrhage.

Univariate analysis has identified only three factors, namely albumin, prothrombin ratio and the presence of ascites, which have significant association with outcome. However, stepwise logistic regression analysis has shown that albumin, white cell count, haemoglobin and the patient's age were independent predictors of one year survival. These results must be interpreted with some caution given the small numbers of patients included for analysis. Furthermore, it can be argued that the addition of 15 patients not previously included in the analysis of risk factors at the time of admission, may adversely affect the present results. Nonetheless, this group of patients have selected themselves in the same way that the remaining 38 patients have survived to be readmitted one month after

their index bleed for elective sclerotherapy.

It is of interest to note that serum albumin has emerged as a predictor of one year survival. Previous analysis has shown that this variable, when recorded immediately at the time of the patient's initial admission with variceal haemorrhage, is of no value in determining outcome. Its inclusion in both Child's original and Pugh's modified classifications is supported by the present analysis only when liver dysfunction is assessed well after the index variceal haemorrhage. Surprisingly, Malt and Malt (1979) noted that the first recorded serum albumin measured after admission for shunt surgery was the strongest predictor of longterm survival and later measurements were of limited value. In their group of elective patients, it was postulated that the infusions of albumin and blood products might effect subsequent serum albumin levels. It is possible that albumin is of no prognostic value at the time of acute variceal haemorrhage because serum albumin levels will fall when blood loss is replaced with crystalloid infusions in some patients and will rise in those patients who receive infusions of albumin and fresh frozen plasma. Its emergence as a predictor of outcome when the patient has recovered from his or her index variceal bleed, suggests that it may be a useful indicator of liver dysfunction and longterm survival. Although univariate analysis demonstrates an association between outcome and two other factors used in the modified Child's classification, multivariate

analysis has shown that both ascites and prothrombin ratio are of limited value in determining outcome when they are recorded one month following the variceal bleed.

No previous study has attempted to define the importance of timing of liver dysfunction with regard to outcome. Christensen and colleagues (1984) have looked at the prognostic value of the Child's criteria in medically treated cirrhosis in patients who had not previously experienced variceal haemorrhage. Their study demonstrated a decreased survival rate with increasing degree of abnormality of serum albumin, ascites, bilirubin and nutritional status. Survival was not significantly influenced by neurological status. However, in a further study of 488 placebo or prednisone-treated cirrhotic patients (Schlichting et al, 1983), only ascites of the 12 potential prognostic variables was of value in determining survival. In analysing the results of these studies, one difficulty which is not shared by the present series is the problem of deciding a starting point when assessment can be made during the disease process. Analysis of the present data has looked at survival with an index variceal bleed representing the starting point. This represents only one manifestation of portal hypertension and investigators looking at survival in cirrhosis have merely used referral to hospital as the starting point of these patients liver disease. In the present study, duration of antecedent liver disease has not been shown

to be associated with outcome following acute variceal haemorrhage although paradoxically the median value is greater for those patients who survive to one year.

The ability of the present prognostic index to discriminate between 'high' and 'low' risk groups of patients has been reduced due to the small number of patients studied and it has accordingly included a number of apparently unrelated variables. It is difficult to account for the potential prognostic value of the white cell count which was lower in those patients who survived to one year. It may be that the development of hypersplenism in these patients results in a reduction in portal venous pressure and that an elevated white cell count in those alcohol cirrhotic patients who die might indicate continued alcohol abuse. The similar values for haemoglobin in both those patients who survived and those who died does little to explain its emergence as a potential prognostic factor but the fact that the age of patients who survive is less than those who died is readily understandable. The loss of ascites as a determinant of survival may be accounted by the smaller number of patients with detectable ascites or by the fact that many patients will have been on diuretic therapy. Hypoalbuminaemia may be a more sensitive indicator of fluid retention in these patients. Only four of the 53 patients had clinical evidence of encephalopathy and all but one of these patients did not survive to one year. The clinical assessment of encephalopathy may not be

sensitive enough to identify patients with severely compromised liver function and the use of more objective tests such as electroencephalography and trail testing (Zeegen et al, 1970) may be of value in this context.

Using the four variables identified by regression analysis, the prognostic index has correctly 'predicted' outcome in 70% of patients. It has not been possible to prospectively assess this prognostic index against a second independent series of patients, but since the index will be most accurate in 'predicting' outcome in the group of patients from whom the data is derived, it seems likely that its prognostic value will be diminished in such a prospective series of patients. Using five variables, the modified Child's classification has correctly 'predicted' outcome in 74% of patient admissions. This figure is similar to that found by Cello and his colleagues (1981) who claimed that the original Child's classification was the most important factor in determining early mortality following elective portacaval shunt. In their series, outcome was correctly predicted in 77% of their patient admissions and it is of interest to note that the percentage of patients assigned to grade C in their study (34%) is identical to that of the patients in the present series (33%). By adopting a scoring system of the five individual factors described by Child, Campbell and colleagues (1973) were able to predict admission mortality in 62% of their total patient population. The results of these studies assessing survival following

portacaval shunting imply patient selection on the part of these investigators but confirm that a classification such as that described by Child may be the most effective method of assessing risk when liver function has improved following admission with acute variceal haemorrhage.



## i. INTRODUCTION

In Chapter 3, a prognostic index was described which appeared to offer an accurate means of identifying a 'high risk' group of patients who were unlikely to survive admission to hospital when presenting with acute variceal haemorrhage. This index, based on admission prothrombin ratio, serum creatinine and encephalopathy, was validated in a small prospective series of patients treated by an identical management policy. It was suggested that it could be used to identify those patients whose prospect of surviving was so poor that they should be denied active treatment and could provide a useful means of auditing management policy of acute variceal haemorrhage. In Chapter 4, a prognostic index for one year survival was outlined and this incorporated the same indices of liver function as predicted admission mortality. By using the one year prognostic index it appeared that most deaths occurring within one year of presentation were due to the progression of the liver disease when sclerotherapy was used to prevent recurrent variceal haemorrhage. It was suggested that the prognostic index might be used as a means of selection for entry to clinical trials.

Since September 1982 a study has been undertaken between the University Department of Surgery, Glasgow Royal Infirmary and the Gastroenterology Unit, Western Infirmary, Glasgow to determine the role of propranolol in the prevention of recurrent variceal haemorrhage. It has been suggested by Lebrec and colleagues (1980) that



beta blocker therapy and propranolol in particular may reduce the risk of gastrointestinal bleeding in patients with portal hypertension by a reduction in portal venous pressure. These same investigators (Lebrec and colleagues, 1981) showed a significant reduction in the incidence of rebleeding but a similar controlled study has been unable to confirm this observation (Burroughs et al, 1983).

The preliminary results of this ongoing study will be presented but the aim of the present analysis is

1. to examine whether the admission prognostic indices for all patients and alcohol cirrhotic patients can still be used to identify 'high risk' and 'low risk' patients presenting with acute variceal haemorrhage from September 1982 to Glasgow Royal Infirmary.

2. to determine whether assessment using the admission prognostic index identifies patients who should be denied active treatment when admitted to Glasgow Royal Infirmary.

3. to determine whether assessment of the probability of discharge or death following admission allows continuing audit of the management policy for acute variceal haemorrhage in patients presenting to Glasgow Royal Infirmary.

4. to establish whether the use of the admission prognostic index could have improved patient selection for the propranolol study by excluding those patients

unlikely to survive admission to hospital.

5. to examine the effect of a change in management policy on longterm survival by using the one year prognostic index.

6. to determine whether the one year prognostic index is applicable to the group of patients managed in the Western Infirmary and whether differences in survival rates are related to the type of patient or differences in management policy.

#### ii. PATIENTS AND METHODS

Data were collected prospectively on 60 new patients presenting on 85 occasions to the Glasgow Royal Infirmary from September 1982 to March 1985 when a study assessing the efficacy of propranolol in the longterm management of variceal haemorrhage was being undertaken. All patients have been followed up for one year to March 1986. During this same period, seven patients who had been previously admitted with variceal haemorrhage before September 1982 presented with further variceal haemorrhage on ten occasions giving a total of 67 patients presenting on 95 occasions to the Glasgow Royal Infirmary. The admission data of 30 patients who presented to the Gastroenterology Unit, Western Infirmary during the same period were reviewed.

Patients admitted to Glasgow Royal and Western Infirmarys with endoscopically proven haemorrhage from oesophageal varices were treated initially by balloon

tamponade followed by injection sclerotherapy. In the Royal Infirmary the injections were carried out using the rigid Negus oesophagoscope under general anaesthesia as previously described but at the Western Infirmary a fiberoptic endoscope and Williams tube were used under diazepam sedation. Standard measures were used to resuscitate patients and correct coagulation defects and liver failure as previously described in Chapter 2. Patients under 80 years of age with portal hypertension secondary to cirrhosis and with endoscopically proven recent haemorrhage from oesophageal varices were considered for inclusion into a study to determine the effect of propranolol on longterm survival and risk of bleeding. Patients were excluded if there was evidence on history or examination of overt ischaemic heart disease, valvular heart disease, hypertension, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, severe chronic obstructive airways disease, or chronic renal failure. Patients who had previously undergone surgical treatment of oesophageal varices or portal hypertension or who had severe encephalopathy (grade 3 or 4) or hepatorenal syndrome (serum creatinine  $>400 \mu\text{mol/l}$ ) at the point of randomisation were not considered. The trial was double blind, placebo controlled, between patient and randomised with the aim of entering a maximum of 100 patients followed for a two year period.

Within 72 hours following arrest of haemorrhage by tamponade and injection sclerotherapy, patients were

randomly allocated to receive Inderal LA (160 mg once daily) or matching placebo (1 capsule/day). Informed consent was obtained from all patients. Drug therapy was delayed until the patient was haemodynamically stable and able to understand the aims of the study.

Patients were followed in out-patient clinics with appointments at 1, 2, 4, 8, 12, 18 and 24 months and were questioned and examined for a history of gastrointestinal bleeding, compliance, evidence of hepatic encephalopathy, resting pulse rate, blood pressure and ascites. Blood was taken for routine haematology and biochemistry. Patients were instructed to report to hospital immediately if haemorrhage occurred. In this event, endoscopy was carried out to determine the source of bleeding. If severe haemorrhage was shown to be variceal in origin or if there was no other obvious non-variceal bleeding source, then the patient was recorded as a treatment failure and treated by balloon tamponade (if necessary) and further injection sclerotherapy. Severe haemorrhage was defined by one or more of the following criteria

1. fatal haemorrhage
2. shock (pulse greater than 100/minute; systolic BP <100 mmHg)
3. initial or subsequent haemoglobin <10 g/dl or fall in haemoglobin by more than 3 g/dl within 48 hours of haemorrhage

4. blood transfusion required within 48 hours of haemorrhage to maintain the circulation

5. active variceal bleeding at endoscopy

Results are expressed as means and standard deviations where appropriate and statistical analysis undertaken by Chi squared and Student's t tests. Freedom from variceal haemorrhage and survival were calculated using life table analysis.

The probability of discharge or death and one year survival were calculated at the time of the initial admission with variceal haemorrhage for each of the patients. The equation

$$\log (p/1 -p) = 10.0 -4.3 \text{ PTR} -0.03 \text{ CR} -0.85 \text{ ENC}$$

was used to predict admission survival and  $p = 0.66$  was used to separate 'high risk' and 'low risk' groups. The equation

$$\log (p/1 -p) = 11.7 -5.7 \text{ PTR} -0.02 \text{ CR}$$

was used to predict admission survival in the subgroup of alcohol cirrhotic patients using  $p = 0.4$  as the cut-off value between 'high risk' and 'low risk' groups. The equation

$$\log (p/1 -p) = 7.8 -0.76 \text{ ENC} - 2.7 \text{ PTR} -0.05 \text{ CR}$$

was used to predict one year survival in all patients using  $p = 0.5$  as an arbitrary cut-off between 'high' and 'low risk' groups.

### iii. RESULTS

#### (a) Propranolol Study

##### (1) Glasgow Royal Infirmary

Sixty-seven patients presented on 95 occasions to Glasgow Royal Infirmary between September 1982 and March 1985. The mean age of patients was 52 years (range 30-82). There were 44 male and 23 female patients. The underlying cause of portal hypertension is shown in Table 5.1. Four patients died because of continuing blood loss; two patients with severe coagulation defects continued to bleed despite oesophageal tamponade; two patients with a history of continuing alcohol abuse and recurrent variceal haemorrhage were not treated beyond tamponade. Control of haemorrhage was therefore achieved on 96% of admissions.

Table 5.2 shows the admission mortality for each of the modified Child's classification grades. The overall admission mortality was 21%.

All 67 patients admitted with variceal haemorrhage, were considered for entry to the longterm study assessing the efficacy of propranolol in preventing recurrent variceal haemorrhage. Twenty-five patients were not suitable for entry into the study. Thirteen patients died within a mean of 5 days (range 1-14 days) and were not entered to the study because they were haemodynamically unstable or were unable to consent to the study. Six patients, all of whom

TABLE 5.1 Cause of portal hypertension for 67 Glasgow Royal Infirmary patients admitted on 95 occasions and 26 Western Infirmary patients presenting with variceal haemorrhage from September 1982 to March 1985.

	<u>Glasgow Royal Infirmary</u>		<u>Western Infirmary</u>
	<u>no. patients</u>	<u>no. admissions</u>	<u>no. patients</u>
alcohol cirrhosis	51	71	16
chronic active hepatitis	8	12	1
cryptogenic cirrhosis	4	6	3
primary sclerosing cholangitis	1	3	0
Wilson's disease	1	1	1
carcinoma of pancreas	1	1	0
post-hepatitic cirrhosis	1	1	0
primary biliary cirrhosis	0	0	3
other	0	0	2
Total	67	95	26

TABLE 5.2 Control of haemorrhage and admission mortality in relation to modified Child's classification in patients presenting to Glasgow Royal Infirmary with acute variceal haemorrhage between September 1982 and March 1985

<u>modified Child's class.</u>	<u>n</u>	<u>no. admissions with haemorrhage</u>	<u>control of haemorrhage</u>	<u>admission mortality</u>
A	4	7	7 (100%)	0
B	26	37	37 (100%)	2 (5%)
C	37	51	47 (92%)	18 (35%)
Total	67	95	91 (96%)	20 (21%)



survived admission to hospital, had specific contraindications to beta blocker therapy. Four patients, admitted with variceal haemorrhage, were receiving beta blocker therapy which had been prescribed for asymptomatic oesophageal varices. These patients were successfully discharged from hospital following sclerotherapy. One patient, in whom bleeding persisted despite sclerotherapy, proceeded to stapled oesophageal transection. In one patient portal hypertension had arisen as a result of metastatic pancreatic carcinoma and she was therefore not considered for the study. She was discharged from hospital following sclerotherapy and died within three months. Forty-two patients were therefore randomised from the Royal Infirmary to the study.

### (2) Western Infirmary

During this same period, 26 patients were entered into the study from the Gastroenterology Unit, Western Infirmary. No data is available on patients excluded from the study. The mean age of patients was 56 years (range 35-75 years). The underlying cause of portal hypertension is shown in Table 5.1. According to Pugh's modification of Child's classification, there were seven grade A, 12 grade B and 7 grade C patients.

### (3) All patients

Details of the 68 patients entered into the study from both hospitals are given in Table 5.3. Follow-up was for a minimum of 12 months. Thirty-three patients

TABLE 5.3 Details of 68 patients presenting with acute variceal haemorrhage to Glasgow Royal Infirmary and Western Infirmary entered into a study assessing the efficacy of propranolol in preventing recurrent variceal haemorrhage

	<u>propranolol</u>	<u>placebo</u>
number	33	35
male/female	21 : 12	20 : 15
mean age (years) (range)	56 (30-73)	52 (29-75)
mod. Child's grade A. B. C.	5 13 15	5 18 12

were randomised to propranolol and 35 to placebo and the groups were well matched with respect to sex, age and modified Child's grading.

Twenty-six of 35 patients in the placebo group (74%) rebled whereas 18 of 33 patients in the propranolol group (55%) had further variceal haemorrhage (Table 5.4). This difference was not significant. Mortality in both groups was not significantly different with 11 patients (33%) in the propranolol group and 15 patients (43%) in the placebo group dying before two year follow-up. Three deaths in the propranolol group and ten deaths in the placebo group were thought to have been precipitated by recurrent variceal haemorrhage. Survival curves for first bleeding episode and for death have been calculated by life table analysis and are shown on Figure 5/1 and Figure 5/2 respectively.

(b) Prognostic index and admission survival

The relationship between individual values of  $p$  for all Glasgow Royal Infirmary patients and death or discharge is shown in Figure 5/3. There were five deaths in 74 admissions (7% admission mortality) when  $p$  was greater than 0.66 ('low risk') and there were 15 deaths in 21 admissions (71% mortality) when  $p$  was less than 0.66 ('high risk'). All five deaths in the 'low risk' group (Table 5.5) appear to be unrelated to the severity of the liver disease. Outcome was correctly predicted in 88% of admissions using 0.66 as the cutoff point between 'high' and 'low risk' groups.

Using the logistic regression equation obtained

TABLE 5.4 Mortality and incidence of rebleeding for 68 patients entered into the propranolol study

	<u>propranolol</u>	<u>placebo</u>	
total number	33	35	
number rebled	18 (55%)	26 (74%)	NS
number died	11 (33%)	15 (43%)	NS
bleed related deaths	3 (9%)	10 (29%)	

NS = not significant

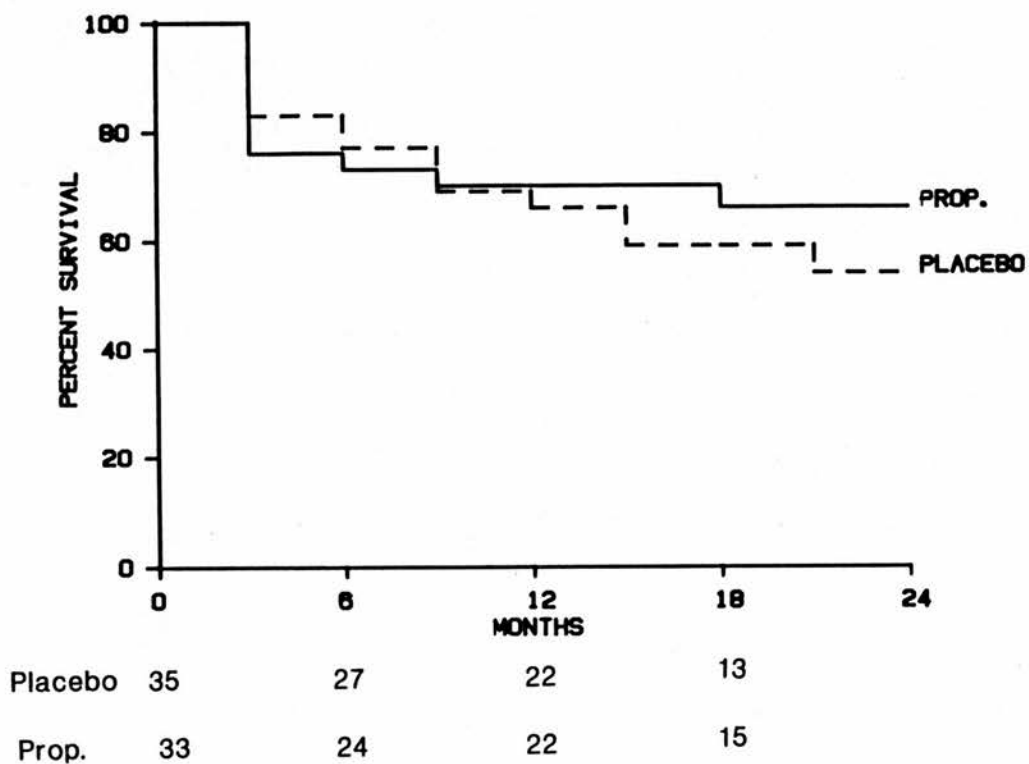


FIGURE 5/1 Duration of survival (life table analysis) of patients entered into study assessing the role of propranolol in the longterm management of variceal haemorrhage. The number of patients alive at the beginning of each six month period is shown for both placebo and propranolol (prop.) groups.

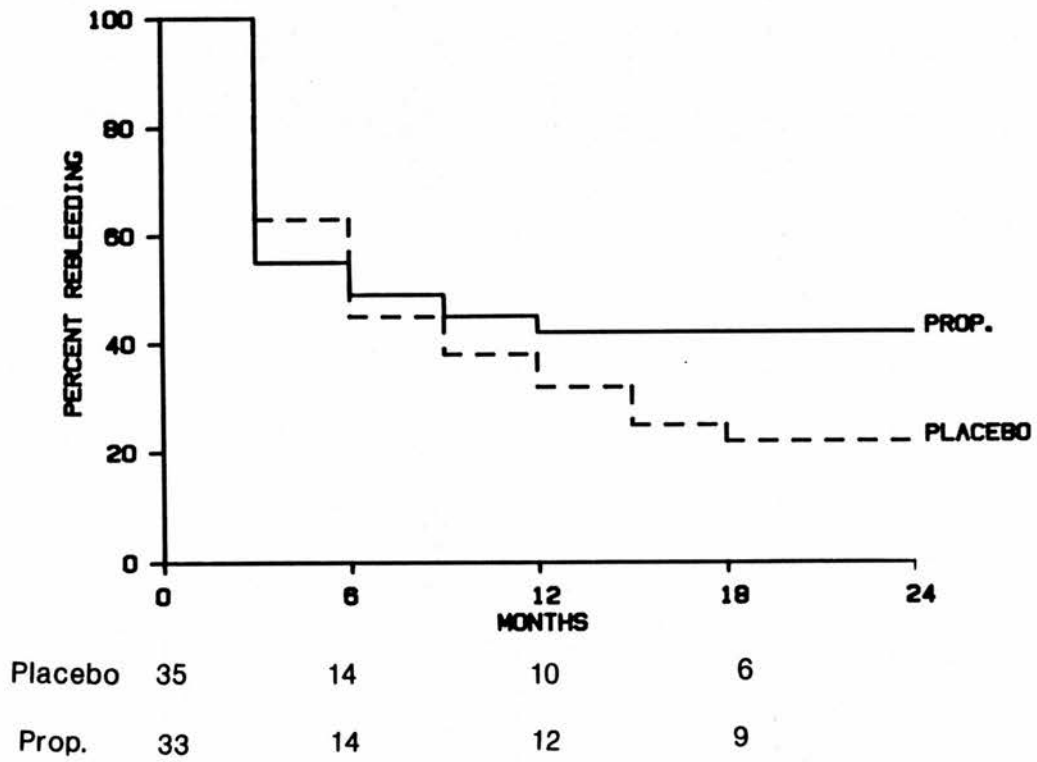


FIGURE 5/2 Risk of rebleeding (life table analysis) of patients entered into study assessing the role of propranolol in the longterm management of variceal haemorrhage. The number of patients free of variceal bleeding is shown for the beginning of each six month period for both placebo and propranolol (prop.) groups.

TABLE 5.5 'Low risk' patients admitted between September 1982 and March 1985 with acute variceal haemorrhage and in whom outcome of admission was incorrectly 'predicted'

<u>patient</u>	<u>age</u>	<u>pathology</u>	<u>bleed</u>	<u>p</u>	<u>cause of death</u>
ALL PATIENTS					
HT	71	CAH	3rd	0.69	MI
MM	42	AC	1st	0.69	perforated oesophagus
GB	54	AC	1st	0.86	CVA, bronchopneumonia
MP	66	CAH	1st	0.85	sudden death, ?MI
HS	69	AC	1st	0.98	Staph. pneumonia, LF
ALCOHOL CIRRHOTICS					
TB	37	AC	6th	0.52	treatment withdrawn
JD	35	AC	4th	0.63	treatment withdrawn
RY	82	AC	3rd	0.54	treatment withdrawn
DJ	68	AC	3rd	0.64	bronchopneumonia, LF
JJ	59	AC	3rd	0.76	uncontrolled haemorrhage
CC	63	AC	1st	0.58	liver failure
NS	57	AC	1st	0.55	MI
WM	51	AC	1st	0.63	liver failure
MM	42	AC	1st	0.81	perforated oesophagus
GB	54	AC	1st	0.82	CVA, bronchopneumonia
HS	69	AC	1st	0.99	Staph. pneumonia, LF

AC = alcohol cirrhosis;  
 CAH = chronic active hepatitis  
 MI = myocardial infarct;  
 CVA = cerebrovascular accident  
 LF = liver failure

for alcohol cirrhotic patients, the relationship between individual values of p and outcome for the Glasgow Royal Infirmary alcohol cirrhotic patients alone is shown in Figure 5/4. There were 11 deaths in 63 admissions (17% admission mortality) when p was greater than 0.4 ('low risk') and seven deaths in eight admissions (88% admission mortality) when p was less than 0.4 ('high risk'). The 11 deaths in the 'low risk' group are listed in Table 5.5. Outcome was correctly predicted in 83% of admissions.

(c) Use of prognostic index in withdrawing treatment

Of the 15 Glasgow Royal Infirmary patients whose probability of discharge was less than 0.4, only one patient survived (Figure 5/3). This patient was known to have a past history of chronic renal failure and on admission had a serum creatinine of 450  $\mu\text{mol/l}$ . He was still alive 12 months after his initial admission to hospital, there having been an increase in his creatinine to 500  $\mu\text{mol/l}$ . All 14 remaining patients died primarily because of progressive severe liver failure.

There were only seven patients amongst the subgroup of alcohol cirrhotic patients whose probability of discharge was less than 0.4 and only one of these patients (p value 0.27) survived (Figure 5/4). This was the patient referred to above.





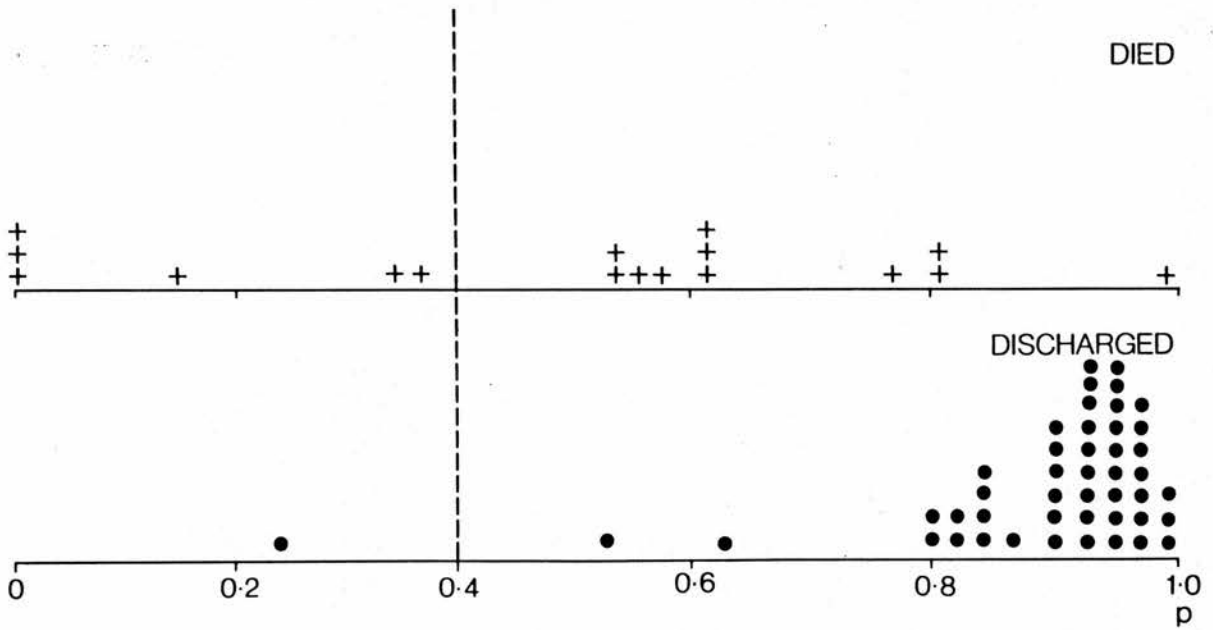


FIGURE 5/4 Prediction of outcome ( $p$ ) following admission for alcohol cirrhotic patients presenting to Glasgow Royal Infirmary between September 1982 and March 1985. For calculation of  $p$ , see text. An arbitrary cut-off value of 0.4 separates 'high risk' ( $p < 0.4$ ) and 'low risk' ( $p > 0.4$ ) groups.

(d) Prognostic index and management audit

Table 5.5 lists those 'low risk' patients from Glasgow Royal Infirmary in whom outcome of admission was incorrectly 'predicted'. One death (MM) resulted from a definite complication of therapy and in a further patient (HS) a severe staphylococcal pneumonia failed to respond to treatment following tamponade and sclerotherapy. The remaining three deaths were due to disease processes apparently unrelated to the underlying liver disease.

Of the alcohol cirrhotic patients with a p value greater than 0.4, two patients (CC, WM) who died of progressive liver failure must be regarded as failures of the predictive system. Two further patients (DJ, HS) died with progressive liver failure but this was associated with severe chest infections which did not respond to treatment. The patient who died as a result of an oesophageal perforation was amongst the group of alcohol cirrhotic patients who should have survived, and in a further patient (JJ) surgery for a bleeding gastric varix was delayed when it was not recognised that tamponade had failed to control haemorrhage. This patient subsequently died of a severe coagulopathy following emergency laparotomy for ligation of the bleeding gastric varix.

(e) Entry into propranolol study based on prognostic index

During the study period, 25 of 67 patients admitted to Glasgow Royal Infirmary were not suitable

TABLE 5.6 'Low risk' patients entered into the  
propranolol study and in whom one year  
survival was incorrectly 'predicted'

<u>patient</u>	<u>age</u>	<u>pathology</u>	<u>no. of</u> <u>bleeds</u>	<u>p</u>	<u>cause of</u> <u>death</u>
EXCLUSION					
MP	66	CAH	1	0.51	sudden death, ?MI
JM	67	Ca. pancreas	1	0.95	died of metastatic carcinoma
PLACEBO					
HT	71	CAH	3	0.52	recurrent bleed, MI
ES	35	AC	1	0.78	liver failure
WB	59	ALC	1	0.73	uncontrolled variceal haemorrhage
NG	53	ALC	1	0.88	uncontrolled variceal haemorrhage
MM	71	PBC	1	0.94	septicaemia following transection

for entry into the study. The reasons for exclusion have previously been outlined. The prognostic index correctly 'predicted' outcome in ten of the 13 patients who did not survive their initial admission to hospital; the remaining three patients died from a myocardial infarct, staphylococcal pneumonia and a cerebrovascular accident. All six patients not entered on medical grounds survived admission but two of these patients had a probability of discharge less than 0.66; one patient had an admission serum creatinine of 450  $\mu\text{mol/l}$  and the second patient whose probability of discharge was 0.62 survived. All four patients receiving prophylactic administration of propranolol at the time of admission with variceal haemorrhage were correctly 'predicted' to survive admission. In both the patient with pancreatic carcinoma and the patient requiring stapled oesophageal transection, discharge from hospital was correctly 'predicted'.

The forty-two patients from Glasgow Royal Infirmary were equally randomised to receive propranolol or placebo. The admission prognostic index correctly predicted that one patient in each group would not survive admission to hospital. In three patients in the 'high risk' group (2 placebo, 1 propranolol), the index was incorrect in 'predicting' that the patients would not survive admission but the patient randomised to receive propranolol died at home four weeks later with massive haemorrhage. In one patient who did not survive admission, outcome was incorrectly 'predicted'. This

was the patient referred to in Table 5.5 who died as a result of an oesophageal perforation (MM).

All patients in the Western Infirmary group survived admission to hospital, although two were assigned to the 'high risk' group.

(f) Effect on one year survival by a change in management policy

(1) Glasgow Royal Infirmary

Of the 25 patients excluded from the propranolol study, 16 patients did not survive to one year and in two patients outcome was incorrectly 'predicted' (Figure 5/5) when using the one year prognostic index. Patient MP (Table 5.6) was thought to have died with a myocardial infarct within 48 hours of admission to hospital. Patient JM died of her metastatic pancreatic carcinoma within 3 months of presentation. Nine patients survived to one year and in four of these, outcome was incorrectly 'predicted'.

There were 11 'high risk' and ten 'low risk' patients allocated to the placebo group (Figure 5/5). Of the seven deaths in these 21 patients, two occurred in the 'low risk' group (Table 5.6). The first of these patients (HT) has previously been discussed having died of a myocardial infarct on her third admission to hospital with recurrent variceal haemorrhage. The second patient (ES) died with progressive liver failure without experiencing further variceal haemorrhage. Six of 11 'high risk' patients in the placebo group survived

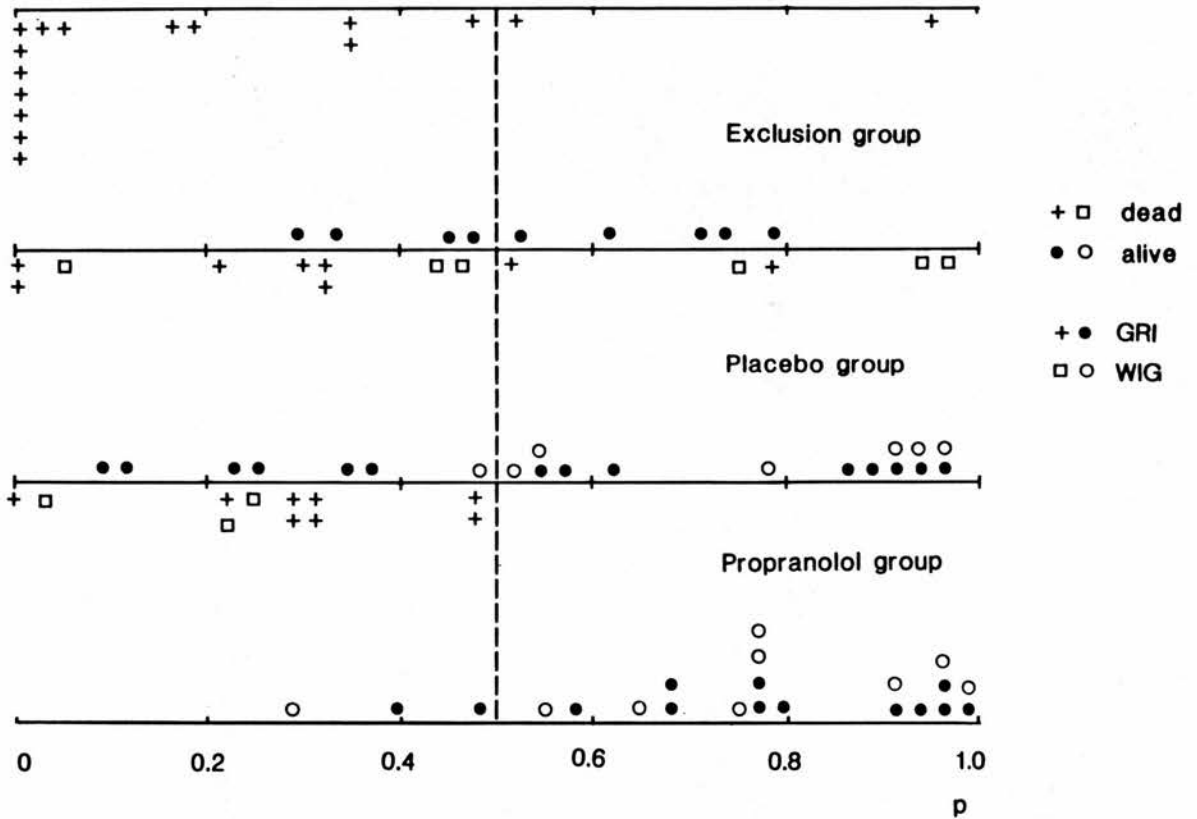


FIGURE 5/5 Prediction of one year survival in patients considered for entry to propranolol study. Values of p (prediction of one year survival) are given for patients excluded and those entered into the study from Glasgow Royal Infirmary (GRI) and Western Infirmary (WIG). For calculation of p, see text. An arbitrary cut-off value of 0.5 separates 'high risk' ( $p < 0.5$ ) and 'low risk' ( $p > 0.5$ ) groups.

to one year.

Of the 21 patients randomly allocated to the propranolol group, ten were from the 'high risk' and 11 from the 'low risk' groups (Figure 5/5). All eight deaths in these 21 patients occurred in the 'high risk' group. Two of the 'high risk' patients in the propranolol group survived to one year.

## (2) Western Infirmary

Ten of the 26 patients entered from the Western Infirmary died within one year. Seven of these deaths were in the 'high risk' group but three patients (WB, NG, MM - Table 5.6) were expected to survive. One patient with good liver function died because of failure to control variceal haemorrhage by tamponade and sclerotherapy, a further patient continued to bleed from varices despite repeated attempts at sclerotherapy and before emergency transection could be undertaken, and a third patient, who sustained a perforation of his oesophagus at attempted sclerotherapy, died with septicaemia following stapled oesophageal transection. Twelve of the 26 patients were randomised to the propranolol group and 14 to the placebo group (Figure 5/5). There was a similar distribution of relative risk patients between the two groups, there being five 'high risk' patients in the placebo and four 'high risk' patients in the propranolol group.



### (3) All patients

Of the 68 patients entered into the study, 30 were assigned to the 'high risk' group according to the prognostic index but these patients were relatively well distributed between the treatment groups (14 propranolol, 16 placebo). The number of 'high risk' patients who died was nine (56%) in the placebo and 11 (79%) in the propranolol group. The predictive system identified the five placebo patients who were assigned to the 'low risk' group and were expected to survive to one year (Table 5.6). The reasons for their deaths have been discussed above.

### iv. DISCUSSION

The preliminary results of this ongoing study of the effect of propranolol on the prevention of recurrent variceal haemorrhage are inconclusive due to the small numbers included in the study, although there does appear to be a beneficial effect with propranolol. The rebleeding rate was 55% for patients who received this drug compared to 74% in those patients who did not. Lebrec and his colleagues (1981) showed a significant reduction in the risk of recurrent gastrointestinal bleeding one year after inclusion into the study from 50% in the placebo group to 4% in the propranolol group. Only two of the 38 (5%) propranolol and four of the 36 (11%) placebo patients died within one year in their study compared to a mortality rate in the present study of 33% and 43% for the propranolol and placebo

groups. Burroughs and colleagues (1983) failed to show any reduction in rebleeding rates in an unselected group of portal hypertensive patients with varying causes of cirrhosis and differing severities of liver disease. During the follow-up period of up to 21 months, 12 of 26 patients in the propranolol group and 11 of 22 in the control group experienced rebleeding from oesophageal varices. The 74% rebleeding rate in the placebo group in the present study is considerably greater than the 50% rate seen in both the study of Lebrec and colleagues (1981) and Burroughs and colleagues (1983). This may be due to a longer period of follow-up of patients with more severe liver dysfunction. Although Burroughs and colleagues (1983) conclude that their study is of an unselected group of patients, only five of 48 (14%) patients were assigned to modified Child's grade C compared to the 40% in the present study. Furthermore there have been a large number of exclusions in this study which suggest that even if propranolol is effective in reducing the risk of further variceal haemorrhage, its use may be limited to a small number of patients.

During the 30 month period of patient recruitment for this prospective study assessing the role of propranolol in the prevention of recurrent variceal haemorrhage, 26 patients were admitted to the Western Infirmary and 67 patients presented on 95 occasions to the Glasgow Royal Infirmary. All patients admitted to the Western Infirmary survived admission but data is not

available for those patients who were excluded from entry to the propranolol study. The 21% admission mortality for the Royal Infirmary patients represents a slight improvement in the 28% rate seen over the preceding 36 month period (Table 2.2). Although this fall in mortality can be accounted for by the reduction in the number of grade C patients from 71% to 51%, the fall in admission mortality is more closely matched by the decrease in the number of 'high risk' patients as assessed by the admission prognostic index from 26% to 22%.

Although the cost of treating variceal haemorrhage by sclerotherapy is considerably less than for surgical management (Chung et al, 1983), clinicians remain concerned about the considerable strain imposed upon hospital resources by the management of acute variceal haemorrhage in patients whose longterm survival is limited (Leader, British Medical Journal, 1981). It has previously been suggested that the admission prognostic index could conceivably be used as a means of identifying patients whose prospects of surviving admission are so low that they should be denied active treatment. In Chapter 3, it was seen that none of the 13 patients with a prognostic index less than 0.2 survived admission to hospital and in the present review of 95 Royal Infirmary admissions, only one of the 15 patients with a p value less than 0.4 was still alive 12 months following admission with variceal haemorrhage. This patient, however, was known to have a degree of

chronic renal failure and his elevated admission creatinine was responsible for assigning him to an adverse risk group despite normal coagulation and the absence of encephalopathy. Although the index has not as yet been employed to determine whether therapy should be continued, it would appear that it would be useful in this context in guiding the clinician on an early decision regarding withdrawal of treatment. It is of interest to note that in the case of three alcohol cirrhotic patients (Table 5.5), the clinical decision to withdraw treatment was not supported by the prognostic index for alcohol cirrhotic patients. However, in these patients, the decision to withdraw treatment was not based on the clinical severity of liver disease but on their repeated admissions due to continued alcohol abuse.

The prognostic index has again proved useful in auditing management policy for acute variceal haemorrhage. Whereas admission mortality in the 'high risk' group was 84% before September 1982, the mortality has fallen to 71% since that time. All five deaths in the 'low risk' group appeared unrelated to the severity of the underlying liver disease. A similar audit of management policy employing the prognostic index derived for alcohol cirrhotic patients has shown that all but two of the 11 ('low risk') patient deaths in this group were again unrelated to progression of liver failure. The emergence of respiratory complications as a common cause of mortality in these patients gives cause for

concern given that both tamponade and sclerotherapy may compromise respiratory function during attempts to control haemorrhage. Oesophageal tamponade has been implicated in the past as a source of respiratory complications (Reid et al, 1960; Conn et al, 1967) and it has been suggested by others that medical means of controlling haemorrhage will not predispose to this complication (Kravetz et al, 1984; Jenkins et al, 1985). Further studies are required to determine whether agents such as somatostatin are more effective in the short term control of variceal haemorrhage.

When undertaking a study to assess the effect of a particular treatment option such as propranolol on longterm survival and risk of recurrent variceal haemorrhage, it would be useful to exclude patients whose prospect of survival in the short term is poor and is unlikely to be affected by that particular treatment option. The criteria drawn up to exclude patients from entry into the present study of propranolol and recurrent variceal haemorrhage did not include the use of a prognostic index. Nonetheless, ten of 13 patients not entered into the study, whose mean duration of survival was 5 days, could have been excluded from consideration for the study at the time of their admission to hospital by using the admission prognostic index. Similarly, two patients who were entered into the study but did not survive admission could have been identified by such an index and could have been excluded from the study since short term survival was unlikely to

have been affected by propranolol. Only two of the other 12 excluded patients had a prognostic index that assigned them to a 'high risk' group, although both survived admission to hospital. All the patients admitted to the study from the Western Infirmary were in the 'good risk' group and all survived admission to hospital. It has previously been suggested that all randomised clinical trials on variceal haemorrhage should use Child's criteria to stratify 'good' and 'poor risk' groups (Graham et al, 1981; Galambos 1983) but it has been shown in the previous chapter that these scoring systems may not be accurate enough to allow such stratification. This should be based on the prognostic factors, prothrombin ratio, encephalopathy and creatinine since the prognostic index has been shown to 'predict' outcome in 81% of admissions.

The 45% one year survival for all patients admitted from September 1982 was slightly less than the 47% survival when patients were managed by a policy employing injection sclerotherapy for the longterm prevention of recurrent variceal haemorrhage. This may reflect an improvement in longterm management of these patients, although these figures must be interpreted with caution given that several variables are involved; namely the presence of placebo and treatment groups and the inclusion of patients from a different hospital. Seventy-nine percent of 'high risk' patients in the propranolol group died whereas only 58% of 'high risk' patients died in the placebo group. These results

suggest that propranolol may have an adverse effect on liver function and hence survival. This observation is difficult to interpret but it is well established that surgical decompression of the portal venous system will have an adverse effect on longterm survival even in patients who have never bled from oesophageal varices (Jackson et al, 1968; Conn et al, 1972). The overall improvement in survival in the placebo group, however, suggests a beneficial effect with this drug which is presumably secondary to the reduction in the rate of recurrent variceal haemorrhage and this is supported by the fact that in the placebo group, all five 'low risk' deaths were associated with recurrent haemorrhage. The modified Child's grading suggests that there is a slight preponderance of 'good risk' patients (combined grade A and B) randomised to the propranolol limb of the study (55%), although the prognostic index indicates that there was a greater number of 'high risk' patients in the placebo group. This latter trend is more in keeping with the high overall mortality in the placebo group. Although there is no significant difference between the two groups in terms of overall mortality, the prognostic index has clearly shown that five deaths in the placebo group occurred in 'low risk' patients who would have been expected to survive. It is difficult to be certain whether measurement of the prognostic index would have been more accurate if it had been recorded at a time when patients had recovered from the insult of their initial variceal haemorrhage. A delay in randomisation



would have resulted in probable exclusion of two patients who did not survive admission to hospital.

The present study suggests that propranolol may have a role in the management of variceal haemorrhage but further patients will have to be accrued before this study identifies those patients likely to benefit from such therapy. The admission prognostic index has been shown to be of value in identifying patients who are suitable for entry into the study and the prognostic index for one year survival has been used to compare the patients assigned to the treatment groups. It has shown that all deaths in 'low risk' patients have occurred in the placebo group, a trend which is hidden by the overall results. Furthermore, the value of prognostic indices has been validated in patients managed by a similar policy in another hospital. The continued use of such prognostic indices for monitoring patient management and selection for entry into clinical studies seems justified. The admission prognostic index may be useful in helping the clinician to make an early decision regarding withdrawal of active support to patients with severe liver dysfunction.



CHAPTER 6

SUMMARY AND DISCUSSION

Although the management of patients presenting with acute variceal haemorrhage is both time-consuming and expensive (Chung et al, 1983), few would subscribe to the view that these patients should be treated to limited transfusion and sedation (Leading Article, 1981). Although the one year survival for all patients presenting with variceal haemorrhage to the University Department of Surgery, Glasgow Royal Infirmary is 48%, the longterm outlook for these patients may be better than for many patients undergoing apparent curative surgery for neoplasia. The large number of alcohol cirrhotic patients in the present series accounts for the excess of modified Child's grade C patients whose one year survival is only 35%. Foster and colleagues (1970) have shown a two year survival of 85% for alcohol cirrhotic patients who underwent shunt surgery and abstained from alcohol compared to a two year survival of 61% for patients similarly treated but who continued to abuse alcohol. It could be argued that the clinician will gain valuable experience from the management of the alcohol cirrhotic patient and will therefore be better equipped to deal with other patients presenting with variceal haemorrhage through no fault of their own but hospital resources could be better directed if poor risk patients could be identified at an early stage in management.

Survival following variceal haemorrhage will be dependent on the severity of the underlying liver disease. However, given that variceal haemorrhage

carries an unfavourable outlook and is one of the more common modes of death in cirrhotic patients, control of haemorrhage must be achieved without compromising liver function. The early prophylactic trials of portacaval shunting for patients with portal hypertension clearly showed that this therapeutic option may reduce longterm survival through an adverse effect on liver function (Jackson et al, 1968; Resnick et al, 1968; Conn et al, 1972). Conversely, in a study of prophylactic endoscopic sclerotherapy, Witzel and his colleagues (1985) have shown a reduction in overall mortality which was achieved by minimising the frequency of episodes of variceal haemorrhage.

The policy employed in Glasgow Royal Infirmary has been successful in gaining immediate control of variceal haemorrhage. Oesophageal tamponade has arrested haemorrhage in 90% of patients who continue to bleed on admission and the associated low morbidity and mortality in the present series is a reflection of the care that is taken in managing these patients. Conn and Simpson (1967) have shown its limitations when used by non-experienced personnel but their continued criticisms of its use in their hands seems unjustified due to their failure to correct deficiencies in their management policy (Chojkier and Conn, 1980). Hunt and colleagues (1982) have more recently shown that it can be used successfully to arrest variceal haemorrhage. Its potential for causing respiratory complications has been recognised in the present series but the evidence

supporting alternative means of controlling haemorrhage is conflicting. Vasopressin has not been used in the Royal Infirmary because of its variable results and potential hazards. The emergence of somatostatin has aroused great interest since early controlled studies show it to be as (Kravetz et al, 1985) or more effective (Jenkins et al, 1985) than vasopressin and without its potential hazardous cardiac complications. Furthermore, recent animal studies, which have suggested that it may stimulate the reticulo-endothelial system (Baxter et al, 1985) and so provide the prospect of potential additional benefit in the patient with liver failure.

Macbeth (1955) introduced the technique of injection sclerotherapy to the United Kingdom and described its use in 30 patients but emphasised the importance of chronic injections to try and prevent recurrent bleeding. In September 1979, when the present review commenced, injection sclerotherapy had been shown to be an effective means of controlling haemorrhage during admission with acute variceal haemorrhage (Johnston et al, 1973; Terblanche et al, 1979). The 90% control of haemorrhage is similar to that reported by these investigators, although the hospital mortality of 28% is slightly higher. This mortality cannot be accounted by complications of sclerotherapy but by the severity of the underlying liver disease. It now seems likely that injection sclerotherapy not only reduces the number of episodes of variceal haemorrhage (MacDougall et al, 1982; Terblanche et al, 1983) but also increases

survival duration (MacDougall et al, 1982). The 48% incidence of recurrent haemorrhage in the present series of patients undergoing elective sclerotherapy is similar to that reported in other centres (MacDougall et al, 1982; Sinnett et al, 1982). Although more frequent injection of varices in the initial management of patients results in more rapid obliteration of varices, it does not appear to significantly reduce the risk of further variceal haemorrhage (Westaby et al, 1984). Stapled oesophageal transection has been advocated as a means of achieving early variceal obliteration (Johnston, 1982) but as an emergency procedure this technique carries a high mortality. Longterm sclerotherapy has yet to be adequately tested against more aggressive treatment options, although increasing rebleeding rates are envisaged with longer follow-up of stapled oesophageal transection (Spence and Johnston, 1985).

Despite this shift from shunt surgery by clinicians in Europe and the United Kingdom in particular, portacaval decompression is still commonly used in the management of the portal hypertensive patient in the United States of America. Few American surgeons would favour the approach of Orloff and colleagues (1980) with regard to emergency portacaval shunting but the results of Warren and co-workers (1967) have encouraged many surgeons to pursue a policy of selective shunting. Although encephalopathy appears less commonly than with a non-selective shunt (Millikan

et al, 1985), the latter type of surgical procedure has yet to be fully evaluated against medical treatment alone or sclerotherapy. Recent reports regarding longterm results in the alcohol cirrhotic patient and subsequent modifications to the operative procedure suggest that selective shunting may not stand the test of time (Henderson et al, 1984).

In planning the longterm management of portal hypertension, the clinician will generally attempt to select the treatment option for the individual patient. Conn, on reflecting the poor survival rates following portasystemic shunting, stated 'that we must learn either to select better who should be shunted or to shunt better those we select' (Conn 1974). Although Child (1964) developed his criteria of liver function to help in this selection process, their use in the University Department of Surgery has been limited in the reviewed patient population, 70% of whom are alcohol cirrhotic patients. Assessment of potential predictive factors at the time of admission with acute variceal haemorrhage has shown that prothrombin time, serum creatinine and encephalopathy can be used to 'predict' outcome in up to 92% of patient admissions. The prognostic index obtained by regression analysis has been validated in subsequent patient admissions and it has been shown to be a useful means of auditing the present management policy for acute variceal haemorrhage by identifying those patients who died of complications not related to the severity of the underlying liver

disease. It has identified patients whose prospect of survival is so poor that it is debatable whether resuscitation should have been continued.

Further analysis has shown that caution must be exercised in translating the value of the prognostic index to different patient populations. Only prothrombin time and creatinine were of value in determining outcome in alcohol cirrhotic patients presenting with variceal haemorrhage, although it was gratifying to see that the separation of patients into 'high' and 'low' risk groups by the prognostic index obtained in these patients was applicable to patients managed in the Western Infirmary.

Although Graham and colleagues (1981) stated that Child's criteria do not improve during the course of the patient's admission to hospital, this study has shown that patient's grading can improve not just at one month but within a week following admission with acute variceal haemorrhage. Reassessment of risk with the modified Child's classification at one month following admission with acute variceal haemorrhage improves its ability to 'predict' longer term survival such that it is as effective as the prognostic index obtained from variables recorded at that time. Furthermore the variables identified by the new prognostic index differed from those recorded at the time of admission with acute variceal haemorrhage. Graham and colleagues (1981) have stressed the importance of timing of entry into studies and its effect on longterm survival but

this study has shown that the timing of the assessment of liver function is equally important in trying to draw comparisons between different patient populations and the results of controlled and uncontrolled studies.

The use of a 'predictive' system appears to be soundly based when applied to patients managed by injection sclerotherapy. Using the same 'predictive' system in the prospective study assessing the value of propranolol in the prevention of recurrent variceal haemorrhage, audit did not identify patients whose survival was adversely affected by administration of propranolol but it did identify several patients in the placebo group who died as a result of further variceal haemorrhage. Although the preliminary results of this study show no significant beneficial effect with beta blockade, the 'predictive' system can be used to look specifically at 'low' risk patients, there being 19 patients in each propranolol and placebo group. There were no deaths in the propranolol group but five patients (26%) died in the placebo group.

The 'predictive' system appears to have been of most value in the prospective study of propranolol in identifying patients whose longterm survival was limited. The early demise of these patients during the study may hide any real effect of propranolol on longterm survival and exclusion of these patients using the 'predictive' system would have avoided these difficulties. Furthermore, by virtue of its clearer definition of 'high' and 'low' risk groups, it allows



better comparison of the propranolol and placebo groups than the modified Child's classification.

In the future it is debatable whether this same system could be used to identify patients who would benefit from a more aggressive surgical approach to the management of variceal haemorrhage. It is probable that the dividing line between 'high' and 'low' risk groups with these existing predictive systems would move to increase the size of the 'high' risk group because of the greater stress imposed by surgery on the patient's liver function. Consideration would have to be given to the timing of the assessment of liver function in relation to the variceal bleed and operative intervention. Such assessment of risk and suitability for surgical intervention might be best undertaken at the time of variceal haemorrhage when the liver is most stressed rather than when the patient has recovered.

Future studies in the management of variceal haemorrhage may require investigation of the relationship between liver function and portal venous pressure measurements. The factors determining survival from the underlying liver disease may differ considerably from those determining the risk of further variceal haemorrhage, even although recurrent haemorrhage appears to be more common in patients with more severe liver dysfunction. It is conceivable that patients at risk of recurrent haemorrhage might be identified more readily by assessment of portal pressure or variceal size. In the past, portal venous pressure

measurements have not correlated well with risk of variceal haemorrhage (Lebrec et al, 1980) but this may again be accounted for by the timing of the measurement relative to the variceal bleed. There does, however, appear to be a relationship between variceal size and risk of further haemorrhage (Lebrec et al, 1980; Rose et al, 1983; Witzel et al, 1985) and such subjective measurements or assessment of intravariceal pressure by direct (Staritz et al, 1985) or indirect (Gertch et al, 1982) means may be used to identify those patients who are at risk of early recurrent variceal haemorrhage.

At the present time, prognostic indices provide an objective means of evaluating patient management and may allow selection of patients for consideration of other treatment options. It is conceivable, however, that a combination of such assessment of liver function and measurement of variceal pressure will be used in determining future therapy for variceal haemorrhage.

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APPENDIX 1

Proforma used to document admission of patients to  
University Department of Surgery, Royal Infirmary,  
Glasgow for management of oesophageal varices.

PRO FORMA

NAME \_\_\_\_\_

CODE \_\_\_\_\_

D.O.B. 

--	--	--

HOSP. NO. \_\_\_\_\_ M / F

ADMISSION DATE 

--	--	--

DISCHARGE DATE 

--	--	--

REFERRAL SOURCE: \_\_\_\_\_

EMERGENCY/ELECTIVE

First bleed 


Last bleed

Liver disease

No. of bleeds \_\_\_\_\_

Transfusions \_\_\_\_\_

Liver Histology 

--	--	--

+

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

PREVIOUS TREATMENT

Pitressin			
Tamponade			
Sclerotherapy			
Transection			
Other			
Propranolol			

Control Y/N

\_\_\_\_\_

ASSESSMENT

BLEEDING      Y    N

ALCOHOL      Y    N

HEPATOMEGALY \_\_\_\_\_ FB

SPLENOMEGALY \_\_\_\_\_ FB

ASCITES            1    2    3

ENCEPHALOPATHY 1    2    3

INVESTIGATIONS

SMA


\_\_\_\_\_

AMA

\_\_\_\_\_

ANF

\_\_\_\_\_

AUS. A

\_\_\_\_\_

LIVER SCAN

--	--	--

\_\_\_\_\_

\_\_\_\_\_

SPLENOPORTOGRAM

--	--	--	--

\_\_\_\_\_

\_\_\_\_\_

ENDOSCOPY

--	--	--

ENDOSCOPIST \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

MANAGEMENT

Transfusion

Date					
Blood					
Plasma					
Platelets					
Cryo.					



PITRESSIN 

--	--	--

\_\_\_\_\_

TAMPONADE 

--	--	--

CONTROL Y / N HOURS \_\_\_\_\_

TAMPONADE 

--	--	--

CONTROL Y / N HOURS \_\_\_\_\_

TAMPONADE 

--	--	--

CONTROL Y / N HOURS \_\_\_\_\_

INJECTION 

--	--	--

  
ETHANOLAMINE

NEGUS/ WILLIAMS/ FLEXIBLE  
VOL \_\_\_\_\_ NO. \_\_\_\_\_

INJECTION 

--	--	--

  
ETHANOLAMINE

NEGUS/ WILLIAMS/ FLEXIBLE  
VOL \_\_\_\_\_ NO. \_\_\_\_\_

INJECTION 

--	--	--

  
ETHANOLAMINE

NEGUS/ WILLIAMS/ FLEXIBLE  
VOL \_\_\_\_\_ NO. \_\_\_\_\_

TRANSECTION 

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\_\_\_\_\_

OTHER 

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\_\_\_\_\_

\_\_\_\_\_

COMPLICATIONS \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

COMMENT \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



FOLLOW-UP - VARICES

NAME .....

CODE .....

HOSP. NO. .....

LAST ADMISSION

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ADMISSION

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DISCHARGE

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ASSESSMENT

HEPATOMEGALY \_\_\_\_\_ FB.

SPLENOMEGALY \_\_\_\_\_ FB

ASCITES 1 2 3

ENCEPHALOPATHY 1 2 3

INVESTIGATIONS

Hb.	
WBC	
PT	
KCCT	
TT	
PLATELETS	

Bilirubin	
ALT	
Alk Phos	
Albumin	
Protein	
Urea	
Creatinine	

CHILDS    A    B    C

ENDOSCOPY

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Endoscopist: \_\_\_\_\_

NEGUS/WILLIAMS/FLEXIBLE

Ethanolamine volume \_\_\_\_\_

VARICES    MIN    MOD    LARGE

injection \_\_\_\_\_

CLINIC \_\_\_\_\_

READMISSION \_\_\_\_\_

COMMENT \_\_\_\_\_  
\_\_\_\_\_

APPENDIX 2

Range of normal haematology and biochemistry values.

Normal serum values

bilirubin	3 - 22 $\mu\text{mol/l}$
alanine aminotransferase	3 - 55 U/l
alkaline phosphatase	80 - 280 U/l
urea	2.5 - 8.0 mmol/l
creatinine	40 - 130 $\mu\text{mol/l}$
total protein	62 - 82 g/l
albumin	35 - 55 g/l

Normal haematology values

haemoglobin	male:	13.0 - 18.0 g/dl
	female:	11.5 - 16.5 g/dl
white cell count		4 - 11 x $10^9/l$
platelet count		150 - 400 x $10^9/l$
coagulation screen is expressed as a ratio:		$\frac{\text{patient value (secs)}}{\text{control value (secs)}}$
prothrombin time	control:	12 - 14 seconds
kaolin cephalin clotting time	control:	36 - 50 seconds
thrombin time	control:	6 - 9 seconds

APPENDIX 3

Summary of methodology used for stepwise logistic regression analysis.

Stepwise logistic regression is a method widely used for the analysis of dichotomous responses when both continuous and categorical predictor variables are involved. In the context of the present study, risk of death following admission with variceal haemorrhage may be defined as the probability that an individual with given characteristics will die during that admission. This probability is the proportion of individuals who would die within that fixed period, among all those in the population being sampled who would present with the given characteristics.

$X = (X_1, X_2 \dots X_m)$  is the set of variables observed at the time of admission and  $x = (x_1, x_2 \dots x_m)$  denotes the particular values observed for each patient admission. Any presumed relationship between the probability of death following admission and the characteristics of the presenting patient may be denoted by  $P_x = f(\theta, x)$ . Here  $P_x$  is the probability in question (labelled by the independent variable values  $x$ );  $f$  is some function; and  $\theta$  is a sequence of population parameters (some numerical quantities which are assumed to have the same value for all individuals in the population of interest). By an estimation of the risk of death ( $P_x$ ) is meant some particular choice of function ( $f$ ) and values for its associated parameters ( $\theta$ ). In practice, such estimations are obtained by assuming a convenient form for  $f$  and then estimating  $\theta$  for the population of interest from data or a sample of presenting individuals from that population. The data

requires the values of the independent variables (X) and the outcome variable (Y), with Y = 1 if the individual dies within the defined period (e.g. admission) and Y = 0 if he survives.

The simplest model relating  $P_x$  to  $x$  is the direct linear one:

$$P_x = \mu + \sum_{i=1}^m \beta_i x_i$$

where  $\mu, \beta_1 \dots \beta_m$  comprises the population parameters. This model may be fitted to the data by multiple linear regression analysis of Y against X. Equation 1 is a linear regression model for the expected value of Y, as the expected value of Y (given  $X = x$ ) is  $P_x$ . The validity of equation 1 is questionable because the right hand side can have values outside the range 0-1 in which probabilities are defined. A further objection concerns the distribution of Y (in multiple linear regression, Y is assumed to be normally distributed with variants depending upon X; neither condition is satisfied when Y is dichotomous).

A linear function of the variables such as the right hand side of equation 1 is relatively easy to compute and therefore of considerable value when considering applying estimation scales in practical settings. In alternative models,  $P_x$  can be defined by equating a linear function of the variables with some transformation of  $P_x$  which can take on any possible value. Although several such transformations have previously been considered, the logistic is the most



generally acceptable. The logistic transform or logit of  $P_x$  is defined by:

$$\lambda_x = \log \left[ \frac{p_x}{(1-p)} \right]$$

where  $\log$  denotes the natural logarithm. If  $P_x$  is the probability of death, the quantity in brackets is the odds and therefore the logit can also be called log odds. The resulting linear logistic model for  $P_x$ :

$$\lambda_x = \mu + \sum_{i=1}^m \beta_i x_i$$

can be fitted to the data by maximum likelihood estimation. Estimated values of  $\lambda_x$  can be converted back to estimated values for  $P_x$  by use of the relationship

$$p_x = 1 / (1 + e^{-\lambda_x})$$

or the estimated  $\lambda_x$  can itself be thought of as an indicator of risk. Maximum likelihood estimation has an advantage over linear regression analysis in that minimum assumptions on  $Y$  are invoked (the  $Y$  variables are assumed to be independent between subjects and, for each  $x$ , to have a common distribution; no distributional assumptions on  $X$  are made by either method).

Maximum likelihood estimation requires a repetitious search for the best parameter values and therefore is far more costly in terms of time than linear regression analysis, an important consideration when numbers of variables and many data cases are to be

studied. This has led to the use of linear discriminant function discriminating between two populations (in the present context the subpopulations of those who would survive or not survive admission) to approximate the linear logistic function. The linear discriminant function is also a linear function of the independent variables, relatively inexpensive to compute and can be interpreted as a valid estimate of  $\lambda_x$  under certain conditions. The conditions on X are restrictive and are violated if any of the variables are of the convenient 'yes - no' (dichotomous) type. When these conditions are not met, the reliability of standard statistical tests in discriminate analysis is also questionable. This type of analysis cannot therefore be reliably performed on the continuous and categorical variables measured in the present study.

Linear logistic regression employs the general methodology of maximum likelihood for estimation of the parameters. An expression can be written for the probability of the observed Y values occurring, given the X values and any assumed values for the parameters. The maximum likelihood estimates for the parameter values are simply those values which maximise the probability expression. The 'likelihood' associated with a given fitted equation is the maximum value. Larger likelihood values suggest better 'prediction' of the observed responses by the equation. Means of assessing the performance of the fitted model is in terms of the percentage of 'correct classifications' of

the sample observations. The model yields an estimated predicted probability ( $p$ ) of discharge for each patient and a cut-off point ( $c$ ) can be chosen so that  $p < c$  are predicted to die (i.e. at 'high risk') and patients with  $p > c$  predicted to be discharged (i.e. at 'low risk'). In this study, the value of  $c$  was chosen to provide the maximum difference in the proportions of patients classified as high risk between the outcome groups (patients surviving admission; patients not surviving admission). This 'percent correct classification', when derived from the data on which the equation was fitted, will generally overestimate the performance of the equation on a fresh sample of data. Hence the need to verify the predictive system on a second independent series of patients.