Bleeding Oesophageal Varices: Referral Bias and Survival

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In the UK, follow-up studies on subjects with varices and gastrointestinal bleeding are generally from national or regional referral centres. These studies are frequently said to be biased by the inclusion of ‘good risk’ patients referred from surrounding hospitals[1]. Such patients are believed to have a better prognosis by virtue of the fact that they have survived the initial bleed for sufficiently long to be stabilised and transferred. This, in a condition with a high early mortality, will result in a privileged group of patients with an improved survival when compared to a group of subjects admitted direct to a hospital from its local catchment area. Thus, if this degree of bias is significant, results and conclusions drawn from such studies will be of limited value in deciding management policies and assessing results in smaller units. This study assesses to what extent selection bias exists in a regional referral centre. It therefore concentrates on those subjects referred direct to one unit from the immediate catchment area of the hospital and those subjects referred from other hospitals in the vicinity to that unit.

Patients, Definitions and Methods

All subjects diagnosed as having oesophageal varices in one endoscopy unit between 1973 and 1982 and suffering their first admission to this hospital with gastrointestinal haemorrhage were eligible; 143 such patients were identified. Patients were subdivided according to source of referral: direct (direct admission to the gastroenterology unit); internal (referral to endoscopy unit from another physician without necessarily transfer of care); in-patient external (transfer from another hospital within a radius of up to 70 miles); and out-patient external (original referral for further assessment by another hospital as an out-patient).

The diagnosis made during the admission or on subsequent follow-up and based on a combination of clinical, biochemical and pathological criteria was accepted in classifying patients. The source of bleeding was determined endoscopically. It was considered as undefined if there was more than one potential site with no clear evidence as to which site had bled. The diagnosis of variceal bleeding was confirmed if there was active bleeding from a varix, adherent clot over a varix, or no other potential site[2].

Functional hepatic reserve was assessed by giving the patient a modified Child’s grade on admission[3].

Patients with extrahepatic obstruction were assigned a Child’s grade using the same criteria. Data were available to calculate a Child’s grade on admission in 111 of the 117 admissions in the direct and external groups (95 per cent).

Death was attributed to one of the following causes: hepatic failure, haemorrhage, hepato-renal failure, infection, and other (or indeterminate)[4].

In the statistical analysis, subgroup survival was compared using life-table analysis and the log-rank test[5]. Fisher’s test and ridit analysis[6] were used to compare differences between subgroups.

Results

Twenty-six of the 143 subjects were internal referrals. The remainder consisted of 37 direct referrals and 80 external referrals (63 in-patient external and 17 out-patient external). The clinical details of the whole group and the direct and external subgroups are given in Table 1. The direct and external subgroups were similar in

Table 1. Clinical characteristics of varices subjects. (P values for direct vs. external group.)

|                         | All subjects | Direct | External |
|-------------------------|--------------|--------|----------|
| Number                  | 143          | 37     | 80       |
| Male:Female             | 1.13:1       | 1.46:1 | 1.11:1   | N.S. |
| Mean age (years)        | 52.3         | 52.4   | 48.5     | P = 0.05 |
| % over 60               | 35           | 33     | 35       | N.S. |
| % Previous bleed        | 40           | 30     | 50       | P < 0.05 |
| % Alcoholic cirrhosis   | 29           | 32     | 27       | N.S. |
| % Extrahepatic block    | 12           | 19     | 12       | N.S. |
| % Child’s A             | 29           | 31     | 30       | N.S. |
| % Child’s B             | 35           | 37     | 36       | N.S. |
| % Child’s C             | 36           | 31     | 34       | N.S. |
| % Ascites present       | 38           | 32     | 38       | N.S. |
| % Encephalopathic       | 29           | 30     | 27       | N.S. |

many respects. There was the same distribution of functional hepatic reserve as judged by the Child’s grade and the same proportion with ascites and with encephalopathy in each subgroup. The proportion with alcoholic cirrhosis and with extrahepatic block was again similar between subgroups. The mean age of the external group was four years less (P = 0.05) but the proportion over 60 was not significantly increased. The proportion with a previous
Table 2. Clinical course of varices subjects. (P values for direct vs. external group.)

| All | Direct | External |
|-----|--------|----------|
| Number | 143 | 37 | 80 |
| Mean units transfused for those requiring blood | 13.7 | 11.5 | 15.3 | P<0.002 |
| Mean units transfused for whole group | 10.3 | 7.3 | 12.4 | P<0.001 |
| % Variceal source | 31 | 22 | 36 | N.S. |
| % Tamponade | 19 | 5 | 25 | P<0.05 |
| % Surgical referral | 29 | 35 | 34 | N.S. |

Gastrointestinal bleed was greater in the external group but high in both groups (P<0.05).

Table 2 gives details of the patients’ hospital courses. Compared with the direct group the external group had higher transfusion requirements (blood and packed cells) both on the basis of units transfused/subject and units transfused/subject requiring transfusion. The source of bleeding was variceal in 67 per cent of the direct group and in 82 per cent of the external group, an insignificant difference. Cases in which the source of bleeding had been classified as undefined were not included as being variceal.

Of 32 deaths in the external and direct groups 17 (53 per cent) were due to haemorrhage, 9 (28 per cent) died of hepatic failure and 5 (16 per cent) from hepato-renal failure. One death was from an unrelated cause.

Survival to discharge was 70 per cent in the direct and 74 per cent in the external group (no significant difference). Survival in those bleeding from varices was 72 per cent in both groups. Survival was strongly dependent on Child’s grade (A = 94 per cent, B = 80 per cent, C = 46 per cent). Fig. 1 compares survival in the direct and external groups using life-table analysis and shows it to be the same in both groups (P>0.1, chi square = 0.037). Survival in those over 60 compared with those under 60 was less good (P<0.01, chi square = 7.57).

Of the external referrals 62.5 per cent were from hospitals within a 15 mile radius and 79 per cent were from within 30 miles. All but one patient came from within 70 miles.

In the externally referred group 56 per cent were transferred on the day of admission or the following day and 77 per cent were transferred within one week. Comparing subjects transferred at two or more days and those transferred earlier, there was no difference in survival (P>0.1, chi square = 0.6); 2.5 per cent of subjects died within one day and 7 per cent within one week.

Over the ten-year study some changes were noted in patient referral patterns. Comparing the first five-year period (1973-77) with the second (1978-82), referrals increased — 62 per cent were in the second period — the proportion of external referrals rose from 43 per cent to 62 per cent (P<0.05), the proportion of alcoholics rose from 24 per cent to 31 per cent (P>0.1), as judged by Child’s grade, the patients had on average less severe disease (Child’s A rose from 14 per cent to 37.5 per cent (P<0.005), Child’s B fell from 44 per cent to 29.5 per

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**Fig. 1.** Life table analysis of external (——) and direct (-----) groups from hospital admission. Percentage standard error (% SE) is for the combined groups. Population under observation in each group with time is as indicated. Note discontinuity in axis. P>0.1, chi square = 0.037.

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cent \((P = 0.06)\), and Child's C fell from 42 per cent to 33 per cent \((P > 0.1)\). This change in distribution of Child's grade applied to both local and referred groups.

**Discussion**

This study investigates the degree of ‘bias’ resulting from the inclusion of externally referred patients in a study assessing prognosis of subjects with oesophageal varices and gastrointestinal bleeding. Such bias might exist either because of selection of patients by their ability to survive an initial bleeding episode for sufficiently long to be stabilised and transferred or because of selection on clinical grounds. For instance, there could be a tendency not to refer a particular group of subjects, e.g. the Child's C subject or the alcoholic. The similarity of the clinical features of the two groups suggests that this is not the case (Table 1). Two differences were present. First, more subjects in the external group had experienced a previous gastrointestinal bleed. This is to be expected, as if a local subject experienced a gastrointestinal bleed he would be more likely to be admitted to this hospital and meet the criteria for inclusion in the study at that point. There was no difference in survival to discharge in subjects with and without previous gastrointestinal bleeding when adjusted for Child's grade. Second, the mean age of the external group was four years less. However, the proportion over 60, for whom survival is less good, was similar.

While the clinical features were remarkably similar, the course of the patients differed in some respects — notably in a greater transfusion requirement (blood and packed cells) in the external group (Table 2). There was also a greater use of vasopressin but not of balloon tamponade. These differences were not reflected in the clinical outcome.

The similarity in survival both in the short term (72 per cent) and the long term (Fig. 1, \(P > 0.1\), chi square = 0.037) is in line with the similar clinical features of the two groups. It demonstrates that no significant bias in terms of overall survival exists due to the inclusion of externally referred cases along with the directly referred cases.

The reasons for this are apparent when the geographical distribution and timing of transfer are considered. Seventy-nine per cent of the subjects were referred from within 30 miles, a proportion which is probably very similar to many regional referral units. Therefore the period of stabilisation required to allow transfer is brief; 56 per cent were transferred on the day of admission or the following day and 77 per cent within one week. Early deaths were uncommon — only 7 per cent of subjects died within one week (25 per cent of deaths). In contrast, Graham and Smith[2] drew attention to the high early mortality of variceal bleeding, 76 per cent of deaths occurring within one week of the index bleed; 70 per cent of their subjects were Child's C and 91 per cent were alcoholics, figures representative of many series from the USA. They emphasised that survival in studies on such patients will closely depend on what is defined as the zero time for admission to the study. However, while it is desirable to include subjects from the time they sustain a haemorrhage, as in this study, delays of one or two days would appear to alter survival curves far less in the case of a population of subjects from the UK than from the USA.

It is also evident that the demonstration of a significant reduction in mortality by some technique (e.g. variceal sclerosis) in a population with a hospital discharge survival of 33 per cent[7] does not imply that a similar, or indeed any, reduction in mortality will occur in a population with a discharge survival of 72 per cent. Techniques have to be assessed in populations reasonably similar to those in which they are to be applied. In assessing whether the results of a study can be applied to another population the criteria used should be similar to those used in judging whether the control and test groups in the study were clinically similar, i.e. distribution of Child's grade and other features.

Series from regional referral centres can provide useful information to assist patient management in District General Hospitals, as the patient populations will be more alike than patient populations in studies from abroad and possibly than those from national referral centres.

**Summary**

The survival of subjects with varices and gastrointestinal bleeding transferred to a referral centre from outside hospitals was compared with the survival of those admitted directly. The clinical features of the two groups were very similar and survival was 72 per cent. This suggests that the bias introduced by including such external referrals in series from regional centres studying survival in these patients is small and that they provide information relevant to patient management in smaller units. Of the referrals 79 per cent were from within 30 miles, transfer occurred rapidly and early mortality was low (7 per cent by one week). These factors help to minimise bias.

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