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Sonographic prediction of variceal bleeding in patients with liver fibrosis due to *Schistosoma mansoni*

J. Richter[1], A. R. Correia Dacal[2], J. G. Vergetti Siqueira[3], G. Poggensee[1], U. Mannsmann[4], A. Deelder[5] and H. Feldmeier[6]

1 *Institute of Tropical Medicine, Berlin, Germany*
2 *Department of Parasitology, School of Medical Sciences, Maceió, Alagoas, Brazil*
3 *National Health Foundation, Alagoas, Maceió, Brazil*
4 *Department of Medical Statistics, Free University, Berlin, Germany*
5 *Laboratory of Parasitology, University of Leiden, The Netherlands*
6 *Faculty of Medicine, Free University Berlin, Berlin, Germany*

Summary Several studies have shown that the characteristic hepatic abnormalities induced by *Schistosoma mansoni* detectable by ultrasound correlate with the degree of oesophageal varices. So far the value of ultrasound for *predicting* variceal haemorrhage has not been assessed. Fifty Brazilian patients with schistosomal periportal fibrosis from Alagoas State, 18 of whom had already bled from oesophageal varices, were enrolled in a combined cross-sectional and longitudinal study and investigated clinically, by endoscopy and by ultrasound. Twenty-seven of the patients were monitored until another bleeding episode, death or for a minimum of 28 months. Eight of these patients could be followed up for a further three years. A sonographic score, which accounts for the degree of echogenic periportal thickening and of portal vein dilatation, was calculated for all patients. A highly significant correlation ($P < 0.0001$) existed between the sonographic score and the occurrence of previous variceal haemorrhage, paralleled by a similar correlation between the sonographic score and the degree of oesophageal varices ($P < 0.001$). In the 27 patients monitored longitudinally, the sonographic score indicated the risk of future variceal bleeding ($P < 0.0001$). The sonographic score reliably predicts the risk of variceal bleeding in individual patients with periportal fibrosis. Hence, the application of endoscopy, if available at all in endemic areas, may be restricted to the patients at risk of future variceal bleeding, as determined by ultrasound. Since portable devices can be carried even to remote areas, the application of the proposed score in community surveys could provide a new means for the identification of high-risk patients in *S. mansoni*-infected populations.

keywords *S. mansoni*, hepatic abnormalities, oesophageal varices, ultrasound

correspondence Joachim Richter, Institut für Tropenmedizin, Spandauer Damm 130, 14050 Berlin, Germany

Introduction

Infection with *S. mansoni* affects more than 70 million people living in 53 countries in Africa, the Arabic peninsula to South America, and the Caribbean Islands. Schistosomiasis is considered the most frequent cause of hepatic fibrosis worldwide (Warren 1984). Periportal fibrosis, a pathognomonic morphological alteration of the liver in patients with schistosomiasis, eventually leads to portal hypertension and collateral circulation, with variceal haemorrhage being the most frequent and dangerous complication of the disease (Lambertucci 1993). In a typical endemic area in Brazil, annual mortality from hepatosplenic schistosomiasis amounts to 44.8 per 100000 infected people (Prata 1987). In the major hospitals of Maceió > 7% of all hospital deaths in adults are attributable to variceal bleeding secondary to hepatosplenic schistosomiasis (Prof. J.G. Vergetti de Siqueira 1990–95, unpublished observation). The true mortality caused by this disease is probably largely underestimated by hospital statistics because the majority of patients live in remote areas, whithout access to appropriate medical care. Although mass chemotherapy campaigns during the last two decades in Brazil had resulted in a considerable reduction of the prevalence of schistosomiasis, in recent years infection rates and morbidity seem to be on the increase again, with prevalence exceeding 70% in some

areas (Prata 1987; Kloetzel *et al*. 1990). As a consequence a resurgence of severe morbidity is expected in the near future.

So far, the only method suitable for the prediction of variceal haemorrhage in patients with periportal fibrosis has been endoscopy (Saad *et al*. 1991). In endemic regions, though, endoscopy is frequently not available or limited to well-equipped hospitals of urban centres. Moreover, endoscopy as a semi-invasive method is not easily accepted by the patients and it is relatively laborious and time-consuming.

The value of ultrasound for the diagnosis and staging of periportal fibrosis in patients with schistosomiasis is now well established (Cerri *et al*. 1984; Homeida *et al*. 1988; Abdel-Wahab *et al*. 1989; Hatz *et al*. 1992). However, only a few studies have been undertaken in order to relate sonographic findings to clinical complications of hepatosplenic schistosomiasis, such as variceal haemorrhage (Davidson *et al*. 1991; Abdel-Wahab *et al*. 1993; Domingues *et al*. 1993). Moreover, to the best of our knowledge the prognostic value of ultrasound for the prediction of future variceal bleeding has never been studied. Therefore a combined cross-sectional and longitudinal clinical study was undertaken in patients with various degrees of periportal fibrosis, some of whom had already bled or were at risk to bleed from oesophageal varices.

Patients and methods

Study area and study design

The study was conducted in the state of Alagoas in north-east Brazil between November 1988 and March 1994. Its design was approved by the local ethics committee. In Alagoas economic and social life depend mainly on perennial sugar-cane cultivation. Many of the day-labourers migrate from place to place in order to find work at harvest. Infection with *S. mansoni* usually begins in childhood and reinfection is frequent during the first decades of life (Prata 1987).

Patients were enrolled after having obtained individual informed consent, and in minors also their parents' consent. The investigation was designed as an open prospective study of a cohort initially comprising 50 patients. Forty-two of them attended one of the major hospitals of Maceió, three the rural hospital of União dos Palmares. Five cases were detected by active case finding in areas of high prevalence of intestinal schistosomiasis. For logistic reasons only those patients were enrolled in the longitudinal part of the study who lived in areas permanently accessible by car, i.e. also during the rainy season, and who were not planning to move to other places during the envisaged follow-up period. Twenty-seven patients were monitored until another variceal bleeding occurred, or if no bleeding occurred, for a period of 28 months. Eight of the patients were followed-up further for 65 months in all.

Patients with visceral leishmaniasis, Chagas' disease, chronic hepatitis and chronic alcohol abuse were excluded by clinical and serological means (Schattschneider *et al*. 1992). Patients with liver cirrhosis were excluded by clinical and sonographical means, and in five cases by liver biopsy. Also patients who had undergone decompression surgery for portal hypertension were excluded from the study because operations, such as porto-caval or porto-renal shunts and splenectomy with gastro-oesophageal devascularization may considerably influence the diameter of the portal vein (Richter, unpublished observation 1987; Ali *et al*. 1992). Malaria is not endemic in north-east Brazil (WHO 1992).

After the initial episode of bleeding had been successfully coped with by emergency sclerotherapy and medical treatment, patients were investigated clinically, sonographically and parasitologically. Then all patients were treated with praziquantel at the standard dose of 40 mg/kg body weight. Patients stayed in the hospital between 5 and 37 days (median 23 days), and then left for their home. To detect reinfection, and to assess the clinical status, each patient was visited at his or her home 3, 6, 28, 53, and 65 months after recruitment, and multiple stool and blood samples were again taken. At the same time sonography was performed using a portable ultrasound scanner. If patients had suffered from variceal bleeding in the meantime, their records were retrieved from the respective hospitals where endoscopy was repeated.

Parasitological and serological examination

Fecal excretion of schistosome ova was quantitatively assessed by the Kato-Katz technique (Katz *et al*. 1990). Five slides were prepared from each of three samples obtained on different days. Thus, a total of 600 mg stool was examined. Stool examinations were repeated in the same way during follow-up investigations. To exclude false negative stool results due to day-to-day variation of egg excretion, efficacy of chemotherapy and possible reinfection were also controlled by quantification of circulating schistosome antigens in serum (Deelder *et al*. 1989; De Jonge *et al*. 1990).

Clinical examination, endoscopy and sonography

Medical history was interrogated with special emphasis to episodes of haematemesis, melaena, and ascites. A bleeding episode was defined as a previous variceal haemorrhage if it occurred within 5 days before or at hospital admission. A haemorrhage was defined as a bleeding recurrency if it occurred at least 15 days after the first bleeding at hospital admission had stopped. All patients were thoroughly examined according to a standardized protocol. Routine laboratory investigations included haematocrite, platelet count, differential blood cell count, thromboplastine time (TPT) and determination of alanin-amino-transferase (ALT). Endoscopy

was performed in 22/50 patients. Oesophageal varices were graded into 4 degrees of severity according to a scale commonly applied in Brazil: 0 = no varices, 1 = tiny varices limited to the aboral third of the ooesophagus, 2 = medium-sized varices extending to the mid third, 3 = medium-sized varices protruding into the oesophageal lumen which reached the oral third of the oesophagus, 4 = gross varices occluding the lumen of the oesophagus and extending to the oral third.

A complete abdominal US examination was performed with use of a portable scanner (Imager 2380, Siemens, Erlangen, Germany) with a 3.5 MHz linear real time transducer, fulfilling the WHO criteria for use in developing countries (WHO 1985). All examinations were performed and interpreted by the principle investigator (J.R.). The sonographist was blinded towards the laboratory and endoscopic results. Imaging variations due to power output, contrast regulation and time-gain curve were minimized as described previously (Richter *et al*. 1992a, b). Morphological alterations characteristic for periportal fibrosis were graded into three degrees of severity according to a classification described previously which was modified as follows (Richter *et al*. 1992a): *Grade 1* echogenic periportal thickening (PT) denoted typical thickening of the walls of the peripheral branches of the portal vein, appearing as hyperechoic ring echoes or parallel streaks with or without a central anechoic lumen. Hyperechoic thickening of the walls of the main portal vein branches or at portal vein bifurcation exceeding 4 mm but not 10 mm in diameter were also detected. In *grade 2 PT*, the hyperechoic patches > 10 mm expanded from the portal branches into the liver parenchyma. *Grade 3 PT* included the characteristics of grade 1 and 2 with the additional characteristic of the hyperechoic bands having reached the liver capsula. Frequently these bands caused a scarred retraction deforming the organ in a pseudonodular manner.

The portal vein was measured as its internal anterio-posterior diameter at the liver hilus during suspended inspiration but avoiding Valsalva's manoeuvre (Bolondi *et al*. 1982). Portal vein diameter was then adjusted to the body height of the individual, thereby correcting the influence of individual biometric variations (Richter *et al*. 1992b). After all measurements had been taken, an *S. mansoni* sonographic (SMS) score was computed combining the degree of periportal thickening and the dilatation of the portal vein according to the formula presented in Table 1. Hence, the SMS score could vary from 0 to 4 points.

Statistics

Since data distribution was not symmetrical and variances differed considerably, non parametric statistics were used. The Wilcoxon matched-pairs signed-rank test and Mann–Whitney test were applied where appropriate. In order to test linear association for ordered categorial data the Mantel-Haenszel test for linear association was used. Significance of difference between relative frequencies were assessed by Mantel-Haenszel or by Fisher's exact test. Frequency of bleeding episodes per time interval was modelled by a Poisson distribution. The 95% confidence intervals of the Poisson parameter were calculated. Significance of differences was calculated by a log-linear model with a binomial error and the 'log' link function.

Results

Findings at admission

No significant differences existed between the cross-sectional and longitudinal study groups in terms of demographic characteristics, laboratory findings and frequency of variceal haemorrhage prior to admission (Table 2).

Variceal bleeding did not occur in patients younger than 18 years and the proportion of patients who bled at hospital admission was significantly lower among the patients younger than 20 years compared with the older patients. Variceal bleeding occurred in a similar proportion among women and men (35.0% *vs*. 36.7%).

As expected from the dynamics of the disease, faecal egg excretion decreased with age. Neither faecal egg excretion nor schistosome antigen concentration were correlated with the occurrence of variceal haemorrhage, nor with sonographic nor with endoscopical findings.

Endoscopy revealed oesophageal varices as the only bleeding source in the 13 bleeding patients examined. Also in the nine patients, who had been examined for prognostic reasons only, oesophageal varices of a lesser extent were detected.

Table 1 The *S. mansoni* sonographic (SMS) score. The SMS score of a single patient is the sum of the score of the echodense of periportal thickening grade plus the score of the degree of portal vein dilatation

	Scores
Periportal thickening grade.	
Grade 0 or 1	0
Grade 2	1
Grade 3	2
Portal vein quotient	
(7.5 mm/m)	0
> 7.5–< 10 mm/m	1
(10 mm/m)	2
SMS score	0–4

*Portal vein quotient = diameter of the portal vein in mm divided by the body height in m (Richter *et al*. 1992b).

Table 2 Demographic characteristics, clinical and laboratory findings of study patients

	Cross-sectional patient group $n = 50$	Longitudinal patient subgroup $n = 27$
Male/female	30/20*	14/13
Age, median (range)	40 (10–77)*	44 (10–77)
Faecal egg count, median (range)		
≤ 20 years	372 (8–1000)	240 (3–720)
21–40 years	32 (8–64)	27 (1–57)
> 40 years	24 (3–147)	22 (7–98)
Circulating anodic antigen	32^{-1} (8–256)	32^{-1} (16–128)
Circulating cathodic antigen	64^{-1} (64–128)	64^{-1} (64–128)
Complaints *n* (%)		
Weakness	33 (66)	16 (59)
Abdominal discomfort	16 (32)	5 (19)
Haematemesis	18 (36)	8 (30)
Clinical findings *n* (%)		
Palpable spleen	44 (88)	23 (85)
Hepatomegaly	24 (48)	13 (48)
Subcutaneous collaterals	13 (26)	6 (22)
Ascites	10 (20)	7 (26)
Umbilical hernia	6 (12)	5 (19)
Laboratory findings *n* (%)		
Anemia§	50 (100)	27 (100)
Eosinophilia†	50 (100)	27 (100)
Clotting deficiency¶	8 (16)	4 (15)
ALAT > 25 U/l	5 (10)	4 (15)

Medians and ranges of reciprocal titres are given: serum concentrations of circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) were increased in all patients; §haematocrit < 0.41; † > 0.5×10^6 cells/l; ¶thromboplastin time < 70%.

The occurrence of variceal bleeding strongly correlated with the SMS score ($P < 0.0001$). The proportion of patients with variceal bleeding augmented in an almost linear pattern with increasing SMS score points (Figure 1). The endoscopic grade of oesophageal varices correlated to the frequency of variceal bleeding, although the significance was less strong (Figure 2) ($P < 0.04$). The SMS score correlated positively to the endoscopic variceal grade ($P < 0.001$). The relationship between prior variceal haemorrhage, endoscopically determined variceal grade and the SMS score is illustrated in Figure 2 ($P < 0.05$).

Findings during follow-up

The 27 patients were followed-up for a median of 27 months (range 4–65) (Figure 3). No patient was found to be re-infected within 28 months, whereas one of the eight patients monitored further was positive for schistome eggs after 48 months and re-treated with praziquantel (AGL) (Figure 3). Nine patients (33.3%) died during the observation period, in four of these death was caused by variceal bleeding (median survival time 12 months (range 4–50). In four patients the general physical condition had steadily deteriorated, eventually leading to progressive anaemia, ascites and hepatic failure, but bleeding did not occur. A 74 year-old lady died shortly after a cerebrovascular stroke. No relationship existed between the SMS score at baseline and the occurrence of death, regardless of whether death due to variceal bleeding was considered separately or not.

Since only eight patients could be monitored for longer

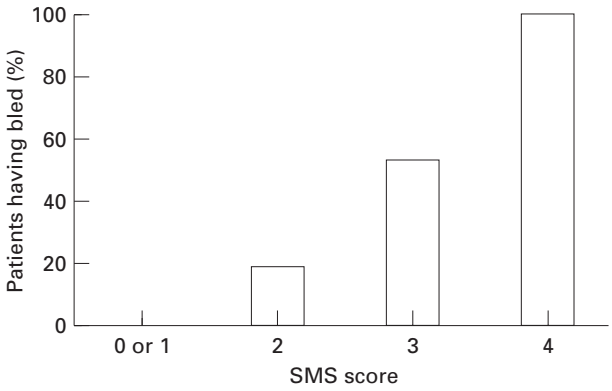

Figure 1 SMS score and proportion of patients who bled from oesophageal varices prior to hospital admission (no. of patients = 50).

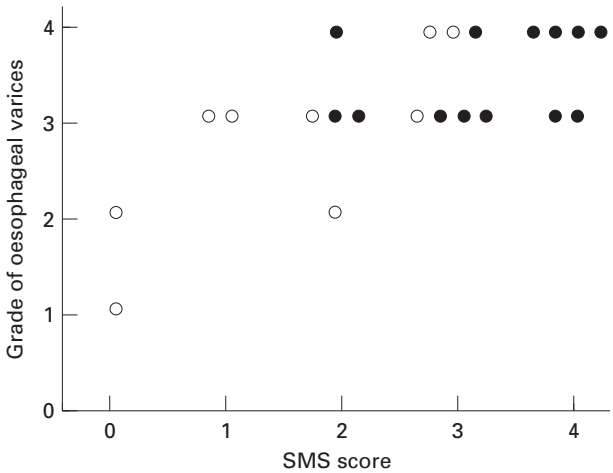

Figure 2 Relationship between SMS score, variceal grade and patients with (●) and without (○) variceal haemorrhage prior to hospital admission (no. of patients = 22).

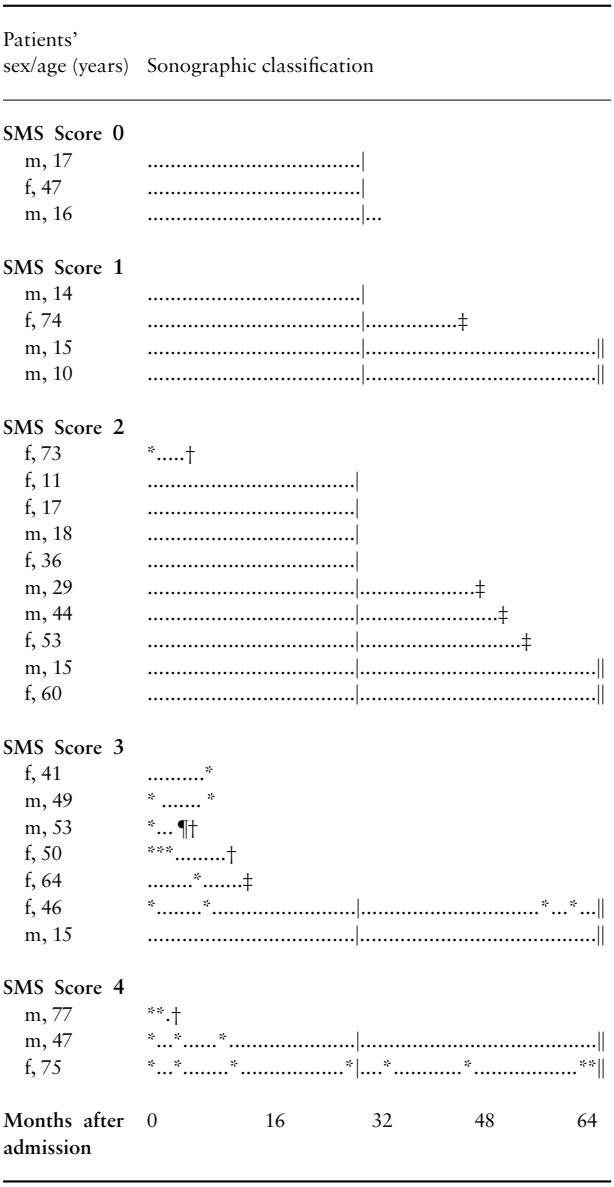

Figure 3 Natural history of patients with hepatosplenic schistosomiasis (no. of patients = 27). * variceal bleeding at admission and/or during follow-up; † Death due to variceal bleeding; ‡ death due to other causes; ...|... and of first monitoring period (month 28); ...‖ monitoring terminated at month 65.

than 28 months, the analysis of a relationship between the various disease markers, endoscopic findings, sonographic score upon admission and the occurrence of future variceal haemorrhage was restricted to 28 months in patients who did not bleed or until a first bleeding episode or recurrent bleeding in patients without or with previous variceal haemorrhage, respectively.

None of the other clinical parameters besides endoscopy and ultrasound, such as egg count, circulating antigens, liver enzymes, or clinical hepatosplenomegaly correlated to the occurrence of variceal bleeding during follow-up.

In two of the patients the first bleeding episode occurred during follow-up three and four months after admission, respectively. At admission these two patients had a sonographic score of 3 points. Each of the seven patients who had already bled prior to admission suffered from bleeding recurrences in spite of antiparasitic treatment and repeated sclerotherapy.

The highest risk of future variceal haemorrhage was associated with an SMS score of 3 or 4 as compared to patients with an SMS score ≤ 2. (odds ratio 144.0; CI 8.00–2591; $P < 0.0001$). In contrast, only one bleeding episode in one among the patients with an SMS score = 2 occurred (Figure 3). No patient with a score below 2 suffered variceal bleeding ($P < 0.0001$).

Thus, not surprisingly, the duration of bleeding-free intervals was inversely correlated to the sonographic score (Figure 4). The median time interval elapsing between admission and the first bleeding episode or recurrency was 103 days (range 16–217). During a total of 981 patient-months of follow-up the number of bleeding episodes per 10 months per patient increased from 0 in patients with an SMS score < 2 (95% CI: 0–0.0126) to 0.026 for patients with a score = 2 (95% CI: 0.0007–0.147), 0.647 (95% CI: 0323–1.1577) for patients with an SMS score = 3, and 0.821 (95% CI: 0.41–1.47) for patients with an SMS score of 4. The duration of bleeding-free intervals was significantly longer among the patients with a score ≤ 2 compared to the ones with a score of 3 and more ($P < 0.0007$).

Discussion

Variceal haemorrhage is the most frequent lethal complication of hepatosplenic schistosomiasis. The results of this study confirm the notion that neither clinical nor parasitological parameters, as, e.g. egg count, circulating schistosome antigens, liver enzymes, or hepatosplenomegaly are suitable prognostic indicators for the risk of variceal bleeding (Richter *et al*. 1992a,b). Thus, prognostic indicators for the identification of patients at risk of variceal bleeding are urgently needed. The endoscopically determined variceal grade is the only parameter so far applied, although this has never been validated prospectively in schistosomiasis (Saad *et al*. 1991, El-Sheikh Mohamed AR *et al*. 1994; Eltoum *et al*. 1994). The pivotal importance of research on the value of sonography in this respect has recently been recognized by an expert committee convened by the World Health Organization in Niamey.

The cross-sectional studies undertaken so far where

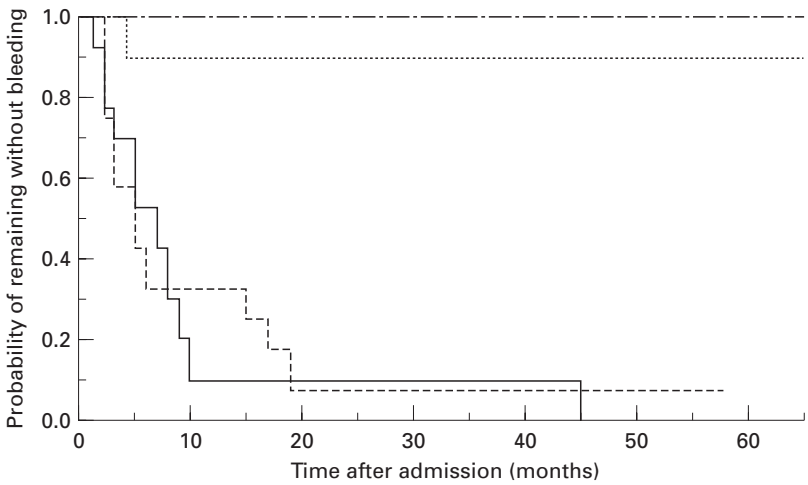

Figure 4 Relationship between the SMS score at baseline and duration of bleeding free intervals (no. of patients = 27) SMS score 4 (——); 3 (- - - - -); 2 ((·····); 1 or 0 (– · – · –).

endoscopic and sonographic findings and variceal bleeding were compared had conflicting results: whereas in earlier studies a relationship between the sonographic grade of periportal fibrosis, the occurrence of variceal haemorrhage prior to examination and/or the grade of oesophageal varices had not been found (Homeida *et al*. 1988; Davidson *et al*. 1991), more recent investigations showed that the sonographic grade of periportal fibrosis is related to prior variceal haemorrhage (Richter *et al*. 1992a; Domingues *et al*. 1993; Abdel-Wahab *et al*. 1993; Eltoum *et al*. 1994; Gerspacher-Lara *et al*. 1997).

In view of earlier studies indicating a positive relationship between the sonographically determined diameter of the portal vein adjusted to body height, the grade of oesophageal varices and the frequency of prior variceal haemorrhage as well as a positive correlation between the sonographic portal vein diameter and portal pressure (Abdel-Latif *et al*. 1981; Richter *et al*. 1992b), it was not surprising that the sonographic score significantly correlated both with the endoscopic variceal grade and with previous variceal bleeding.

The results of this study show for the first time that a sonographic score not only reflects variceal bleeding having occurred prior to ultrasound examination but also allows to predict future variceal bleeding. The following limitations in the validity of our results of the study have to be considered:

Firstly, one might assume that the cross-sectional study group and the longitudinal subgroup are heterogeneous and thus not comparable. This is unlikely, since the demographic and clinical characteristics of both groups were similar.

Secondly, the number of patients monitored is low and the time of follow-up rather short, thereby making it difficult to draw definitive conclusions. Indeed, the limited number of patients did not allow to obtain statistically significant results for each single score. Nonetheless, when the subgroups of patients with an SMS score up to 2 were combined and compared with the ones with a score of 3 and more, the increased risk of future variceal bleeding in the latter proved highly significant.

Thirdly, the sonographist, although blinded towards parasitological, laboratory and endoscopic data, was aware of the medical history and the results of the clinical examination, and therefore could have been influenced by this information when taking the ultrasound measurements. Since future clinical events which are not influencable by the examiner, such as the occurrence of variceal bleeding during the follow-up period were also correlated with the score, such an observer bias is unlikely.

Fourthly, the endoscopic classification of the variceal grade did not take into account some-well documented bleeding risk parameters, such as red markings (North Italian Endoscopy Club 1988). This, however, cannot have influenced the relation between ultrasonographic findings and the occurrence of variceal haemorrhage. Anyhow, in all cases examined endoscopically the bleeding originated from oesophageal varices and not from other sources.

Fifthly, the validity of the sonographic score might be limited by interobserver variance. When our study was initiated, the 'Cairo' classification (Jenkins & Hatz 1992) had still not been established, and the 'Managil'-classification (Doehring Schwerdtfeger *et al*. 1989) was used and obviously follow-up investigations were performed with the same methodology. For the latter classification, Doehring-Schwerdtfeger *et al*. (1992) have shown that whereas interobserver variance may influence the grading of incipient fibrosis, this is unlikely to happen in the more advanced stages, where variceal bleeding occurs. At a recent meeting in Niamey it has been recognized that the reproducibility of the grading of fibrosis whichever classification had been applied so far, may be limited by several subjective and objective

factors (Homeida *et al*. 1988; Doehring-Schwerdtfeger *et al*. 1989; Richter *et al*. 1992a, Abdel Wahab *et al*. 1992; Jenkins & Hatz 1992). This applies particularly to the 'Cairo' methodology and a similar methodology used by Abdel-Wahab *et al*. (1993) which are based on the measurement of the external diameter of portal branches because it is not clearly defined where to measure. Furthermore, since the wall thickness is not taken into account, the confounding effect of the normal anatomic variation of the diameter of portal branches at different measuring sites cannot be excluded.

Portal vein measurement using the methodology applied in our study, in contrast to other organometric parameters, as, e.g. liver size, is well reproducible between different examiners as well as by the same examiner over time (J. Richter 1995, unpublished observation). The adjustment of the portal vein diameter to body height is crucial.

Spleen measurements were deliberately not included in our score in order to avoid confounding influences by malaria, which is endemic in many areas where *S. mansoni* infections occur.

The high rebleeding rate in our prospective study illustrates that sclerotherapy alone, although its beneficial effect has been proved in Brazil (Cordeiro 1990), is still unsatisfactory in preventing variceal bleeding. Sonography could provide an important means to assess alternative or additional therapeutical approaches, such as lowering portal pressure by beta-antagonists (Kiire 1989; El Tourabi *et al*. 1994).

In conclusion, the results of this study demonstrate that sonography can be used for the prediction of variceal haemorrhage in patients with periportal fibrosis due to *S. mansoni* infection. To confirm our findings, further studies on larger numbers of patients in different endemic settings are warranted. Since the 'Managil' classification is considered 'historical', other comparable approaches in this respect, such as the image patterns recently proposed by our study group might replace the Managil grading in the score. Further studies are justified by the great advantages ultrasound has to offer: being noninvasive and harmless it is well accepted by the patients. Relatively economic portable ultrasound devices allow its application even in remote areas, where the majority of patients with schistosomiasis live (Prata 1987, Lambertucci 1993). There patients at high risk of variceal haemorrhage may be identified by ultrasonography and eventually be referred to major hospitals for treatment. In hospital practice ultrasound may help to restrict the application of endoscopy to those patients where transoesophageal injection sclerotherapy is indicated.

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