Study of the association between hemorrhage and the position of hemorrhagic stigmata in patients with esophageal varices

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Abstract. The aim of the present study was to investigate the predilection position of hemorrhagic stigmata (HS) in patients with esophageal variceal hemorrhage and provide guidance on endoscopic therapy for esophageal varices. The clinical characteristics, particularly the endoscopic manifestations of HS, in the patients who presented with gastroesophageal variceal hemorrhage and cirrhosis between January 2003 and December 2013 at our hospital were summarized and patients were grouped according to the distance of the lesion site to incisors at 35-40 and ~30 cm. The association between the location of HS and active hemorrhage was assessed. The location of hemorrhage and HS at 35-40 cm from the incisors was more common in esophageal varices patients, followed by the location at ~30 cm from the incisors (P<0.0001). The incidence of HS in esophageal varices patients in the 35-40 cm group was significantly higher than that in the ~30 cm group except for HS at 9:00 position (P<0.0001). The highest incidence of HS in the ~30 cm group was at the 3:00 position, followed by the 12:00, 6:00 and 9:00 position. Among them, there were significant differences between the 3:00 and 6:00 position, the 3:00 and 9:00 position, and the 9:00 and 12:00 position (P<0.05). The order in the 35-40 cm group was similar to that in the ~30 cm group and the incidence of HS at the 9:00 position was lowest (P<0.05). A certain association between the point of location of HS and hemorrhage was identified. HS located at 35-40 cm from the lesion site to incisors was identified to be most likely to bleed, followed by that located at ~30 cm. In addition, the incidence of HS at 9:00 position was found to be lower than that in the other positions. Therefore, HS located at ~30 cm and 35-40 cm from the lesion site to incisors should be paid attention to and the 3:00, 12:00 and 6:00 rather than the 9:00 position should be prioritized during endoscopic treatment, particularly in emergency situations.

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Introduction

Gastroesophageal varices are one of the end-stage clinical manifestations of cirrhosis. Esophageal variceal hemorrhage (EVH) is one of the life-threatening complications (1). Therefore, the diagnosis and treatment of varicose veins is of high importance. As a gold standard, endoscopy has an important role in the diagnosis and treatment of varicose veins. Current guidelines universally agree that endoscopic treatment is the sole method that is able to improve the long-term prognosis of patients affected (2-5). Besides the determination of the degree of varicose veins via endoscopy, this technique is applicable for the treatment of bleeding cases. After identification of the bleeding site by endoscopy, subsequent variceal ligation, sclerotherapy and tissue adhesive injection are feasible during the same procedure. Unfortunately, the detection rate of the bleeding site is relatively low. In the case of the bleeding site remaining undetected, identification of the predilection site is important. Treatment on the site that is most likely to bleed may significantly improve the hemostatic rate and reduce the rate of rehaemorrhagia. In the present study, the predilection site of the hemorrhage was investigated in order to provide guidance for endoscopic treatment in emergency cases. Therefore, the association between the position of hemorrhagic stigmata (HS) and hemorrhage in 832 emergency cases with gastroesophageal varices were retrospectively studied.

Patients and methods

Patients. Patients who had been admitted to the Department of Gastroenterology and Hepatology of PLA General Hospital (Beijing, China) between January 2003 and December 2013 due to gastrointestinal bleeding (GIB) with cirrhosis were retrospectively reviewed. Cirrhosis was diagnosed by assessing medical history as well as results of biochemical examination, ultrasound, computed tomography scan and, if available, other imageological examinations. The primary diseases of

the cases included hepatitis B virus (HBV) cirrhosis, HCV cirrhosis, alcoholic cirrhosis, autoimmune cirrhosis and Budd-Chiari syndrome with cirrhosis. A total of 10,305 cases, including 823 emergency cases, had been diagnosed and simultaneously treated by endoscopy. In all cases, endoscopy had been performed within 24 h after hematemesis or melena. The endoscopies had been performed by clinicians who were experienced in endoscopic treatment of gastroesophageal varices.

Clinical data. The patients diagnosed with liver cirrhosis complicated with acute esophageal and gastric varices. Liver cirrhosis was confirmed by history, biochemical examination, ultrasound, computed tomography (CT) or other imaging examinations. The etiology included hepatitis B cirrhosis, hepatitis C cirrhosis, alcoholic cirrhosis, autoimmune cirrhosis and Budd-Chiari syndrome. Patients with a history of sclerotherapy, band ligation or shunt operation, hepatic encephalopathy or hepatorenal syndrome, advanced hepatocellular carcinoma, cerebral vascular accidents or other debilitating diseases were excluded. Information on 190 cases of HS was retained and the location of HS was analyzed. The standard description of the location of HS was based on its distance from the incisors. The description of the definite point was based on its clock position under endoscopy. The number of varicose veins in most patients was three or four, but the points were concentrated at locations such as the 3:00, 6:00, 9:00 and 12:00 position. An analysis of the characteristics of the cases of HS at certain specific locations was performed. The bleeding points at 3:00, 6:00, 9:00 and 12:00 positions were described according to the common descriptive clinical method.

Statistical analysis. Statistical analysis was performed regarding the position and clock position of bleeding. The results were compared by the chi square test. All statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient data. Within the study cohort, the location of HS was determined in 372 cases during emergency endoscopy. Among them, 250 cases received a specific position diagnosis and 190 received a specific point diagnosis. According to the distribution of scattered points, the predilection site of hemorrhage was divided into two groups: The ~30 cm group (n=58) and the 35-40 cm group (n=132). Among the 190 cases, there were 132 males and 58 females (mean age, 55.66 years; 39 males and 19 females in ~30 cm group; 93 males and 39 females in 35-40 cm group).

Distribution of HS. HS was located at 27-41 cm from the incisors (Fig. 1A). The predilection sites of HS were ~30 cm and 35-40 cm from the incisors. The incidence of HS in the 35-40 cm group was significantly higher than that in the ~30 cm group (Fig. 1B). HS at 3:00 position accounted for the majority of the cases, followed by that at 12:00, 6:00 and 9:00 positions in a descending order (Fig. 1C).

Table I. Comparison of the incidence of hemorrhagic stigmata at different clock positions between the ~30 cm group and the 35-40 cm group.

	Group		
Clock position	~30 cm group (n)	35-40 cm group (n)	P-value
3:00	23	47	<0.0001
6:00	11	34	<0.0001
9:00	7	10	0.4795
12:00	17	41	<0.0001
Total	58	132	<0.0001

Comparison of HS between the ~30 and 35-40 cm groups. The incidence of HS in the 35-40 cm group was significantly higher than that in the 30 cm group at each clock position except for the 9:00 position ($P<0.0001$; Table I). In the ~30 group, the incidence of HS at the 3:00 position was significantly higher than that at other clock positions except for the 12:00 position ($P<0.05$). Moreover, there was significant difference in the incidence of HS between the 9:00 and 12:00 position ($P<0.05$; Fig. 2A). In the 35-40 cm group, the incidence of HS at the 9:00 position was significantly lower than that in the other three orientations ($P<0.05$; Fig. 2B).

Discussion

Gastroesophageal varices are a major complication of portal hypertension. The degree of varicose veins is associated with a portal venous pressure gradient. Therefore, esophageal varices are more severe in the lower esophagus, where the possibility of active hemorrhage is high. However, it is difficult to identify the bleeding site on endoscopic examination. At Department of Gastroenterology and Hepatology of PLA General Hospital, the detection ratio of endoscopic examination was determined to be 45.2%. The judgment of potential bleeding sites is important. According to our clinical experience, the positions of ~30 cm and >35 cm from incisors were the predilection sites of HS. In the present study, according to distance of HS from the incisors, a scatter plot was generated and the central tendency of HS to occur was at ~30 and 35-40 cm from the incisors. Moreover, there were more cases in the 35-40 cm group than in the ~30 group, which was consistent with our hypothesis. There were a palisade zone and a perforating zone within 5 cm of the distal esophagus, which mainly contributed to the higher incidence of HS in the 35-40 cm group.

There were vessels in longitudinal deformation, which were mainly located in the oesophagogastric junction 3-4 cm from the distal esophagus, went through the epithelial lamina and disappeared in the submucosal layer (6,7). The blood flow in the palisade zone is bi-directional, which drains into the gastric zone or perforating zone depending on the pressure at the gastroesophageal junction. The perforating zone extends from 3-5 cm of the distal esophagus to the gastroesophageal junction, which drains the blood from epithelial capillaries to perioesophageal veins, which are also known as non-proper

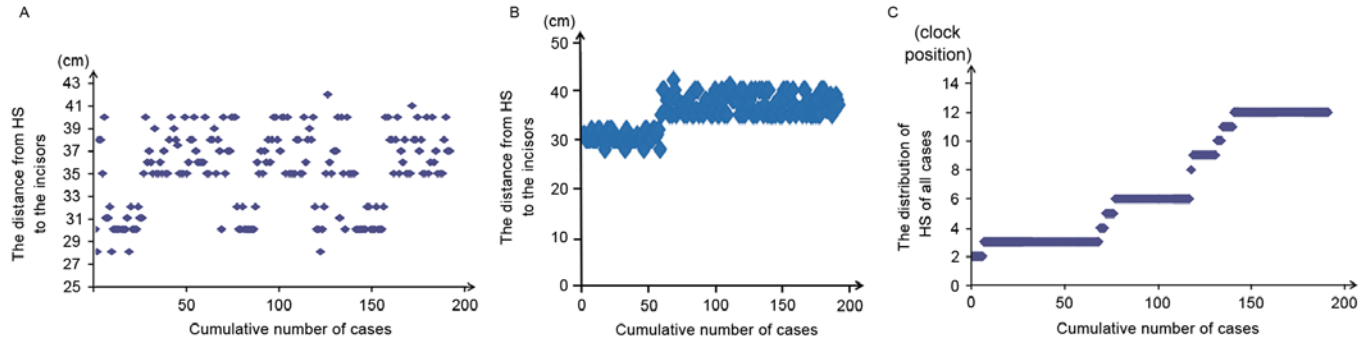

Figure 1. Scatter diagram of the distance and different points/positions in the two groups. (A) Scatter diagram of the distance of the HS from the incisors of all cases; (B) Scatter diagram of the different locations of HS in the ~30 cm group and the 35-40 cm group; (C) Scatter diagram of the different positions of HS in all cases. HS, hemorrhagic stigmata.

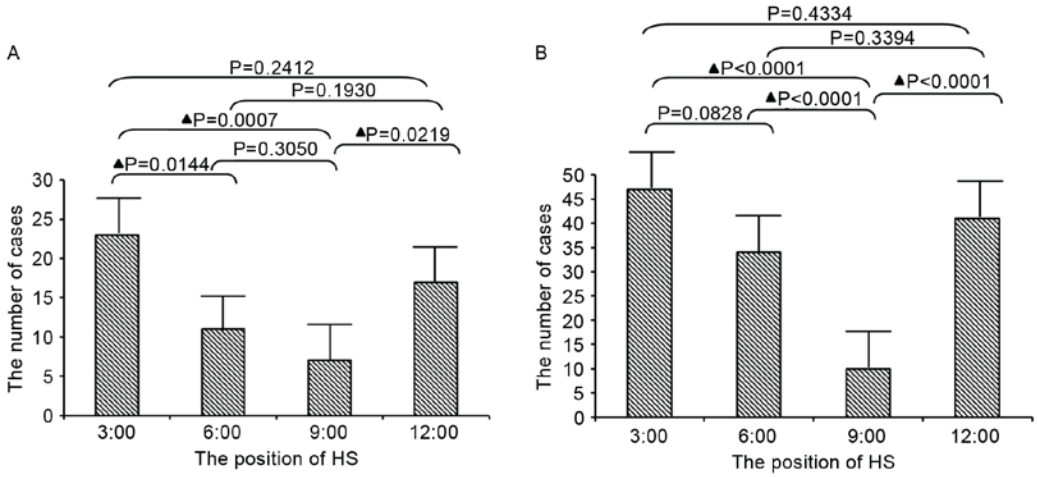

Figure 2. Incidence of HS at different points in the two groups. (A) ~30 cm group and (B) 35-40 cm group. HS, hemorrhagic stigmata.

veins and are also bi-directional (7). The normal vascular network is significantly altered in patients with portal hypertension. Due to the backpressure, the congestion of paraesophageal varices is induced. The pressure is then transferred to blood vessels of the submucosal or epithelial layer through perforating veins or induction of varicose veins (8). Therefore, vascular dilation under epithelium replaces the esophageal venous plexus. The high pressure in the perforating zone influences the blood in the palisade zone, which accommodates the increased gastrosplenic flow by portal hypertension. Consequently, blood flow in the palisade zone is more turbulent in patients with portal hypertension. High pressures and turbulent flow increases the likelihood of superficially located dilated vessels at 5 cm of the distal esophagus to bleed (9,10). In addition, Aharinejad *et al* (11) showed that the number and caliber of submucosal vascular plexuses were decreased from the pharynx to the gastroesophageal junction, which indicated that the lower part of the esophagus is more prone to bleeding in portal hypertension.

Varicosity at 35-40 cm from the incisors is more serious compared with that in the upper and middle parts of the esophagus because of the pressure gradient. However, HS and hemorrhage are likely to appear at ~30 cm. The possible reason is that the azygos and hemiazygos veins are the most important reflux vessels in esophageal varices. The hemiazygos vein flows into the azygos vein at the height of the eighth thoracic vertebrae, which is located at ~30 cm (12). Moreover, the position is at the right side of the esophagus, which is also the 3:00 position under endoscopy (12). Varicosity at the 6:00 and 12:00 position is more serious because of the large amount of anastomoses and perforation of the azygos vein. By contrast, the 9:00 position is the opposite site of the importing point of the azygos or hemiazygos vein and receives less pressure from the communicating vessels, which leads to the lower incidence of HS compared with that at the other points. The incidence of HS at 9:00 position in the 35-40 cm group was significantly lower than that at the other positions due to the entire complex network of the distal esophagus. When portal hypertension occurs, the left gastric vein is the major vessel that causes hemorrhage of gastroesophageal varices (13). Paraesophageal veins at the lower part of the esophagus, also known as the upper esophageal branch of the left gastric vein, mainly import at the top of the vessel arch. Paraesophageal veins ascend along the right rear side of the lower part of the esophagus and issue several branches, which distribute in the anterior and posterior walls of the esophagus and cardia, and then import into the azygous and hemiazygos vein upward through the diaphragm. This drainage channel involves only a small portion of the left esophagus, which resembles the 9:00 position under endoscopy, contributing to the low hemorrhage

rate. Moreover, Ibukuro *et al* (14) demonstrated that one thick vein branch of the left paraesophageal veins, which is known as the anterior esophageal vein, crosses round the descending aorta and drains into the hemiazygos vein, is visible on CT images. The CT during arterial portography showed all of the anterior aortic esophageal veins, which were located between T9 and T11. Thus, it can partially alleviate the pressure of left esophageal varices and simultaneously, the 9:00 position is least likely to bleed. In addition, on CT, the dilated left gastric veins and the varices around the lower part of the esophagus, particularly on the right aspect of the esophagus, were observed in all cases, which also illustrated that there were fewer varices at the 9:00 position. The incidence of hemorrhage in this drainage pathway is ~87.76% (15). This may explain the sharp decrease in the likelihood of hemorrhage at the 9:00 position in the 35-40 cm group.

Of note, the present study had certain limitations. First, it was a retrospective study. Second, the blood flow dynamics were not detected. At last, the portal vein pressure gradient was not investigated. Further study is therefore required to determine the underlying mechanisms.

In conclusion, the occurrence of hemorrhage in esophageal varices was found to be associated with the distance of HS from the incisors and the clock position of HS. The area located 35-40 cm from the incisors is most likely to bleed, followed by that at ~30 cm. The incidence of HS at 9:00 position was lower than that at the others. Therefore, areas of 35-40 and ~30 from the incisors and the 3:00, 12:00 and 6:00 rather than the 9:00 position should be prioritized during endoscopic treatment, particularly in emergency situations.

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