

Risk assessment of first upper gastrointestinal bleeding using computerized tomoscanning in esophageal varices patients with cirrhosis and portal hypertension

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Abstract

To evaluate the risk of first upper gastrointestinal bleeding by computerized tomoscanning (CT) for esophageal varices patients with cirrhotic portal hypertension.

One hundred thirty two esophageal varices patients with cirrhotic portal hypertension who are also complicated with gastrointestinal bleeding were recruited as bleeding group, while another 132 patients without bleeding as non-bleeding group. The diameter of esophageal varices, number of vascular sections, and total area of blood vessels were measured by CT scanning. The sensitivity and specificity of these indicators were calculated, and Youden index was adjusted with the critical point.

The diameter of esophageal varices was 7.83 ± 2.76 mm in bleeding group, and 6.57 ± 3.42 mm in non-bleeding group. The Youden index was 0.32 with the critical point 5.55 mm. The area under the receiver operating characteristics (AUROC) was 0.72. The number of venous vessels was 4.5 ± 2 in bleeding group, whereas being 4 ± 2 in non-bleeding group. The Youden index was 0.35 with a critical point 4, and the area under the curve (AUC) was 0.68. The blood vessel area was 1.73 ± 1.15 cm² in bleeding group, and 1.12 ± 0.89 cm² in non-bleeding group. The Youden index was 0.48 with the critical point being 1.03 cm², and corresponding AUC was 0.82.

Among all 3 indicators of the total area, diameter, and number of sections of the esophageal varices, the total area of esophageal varices showed more accuracy as a potential and novel indicator for bleeding prediction.

Abbreviations: AUC = the area under the curve, AUROC = the area under the receiver operating characteristics, CT = computerized tomoscanning, EV = esophageal varices, EVB = esophageal varices bleeding, ROC = the receiver operating characteristics.

Keywords: computerized tomoscanning, esophageal varices, hepatocirrhosis, the receiver operating characteristics curve

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WX and F-xC have contributed equally to this work.

This study was performed with individual resources.

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1. Introduction

Esophageal varices bleeding (EVB) is one of the serious complications of portal hypertension in cirrhosis, typically with acute onset and high mortality. Rupture bleeding occurs in about 10% to 30% of cirrhotic varices each year.^[1,2] Esophageal varices bleeding caused mortality is relatively higher than gastric varices.^[3,4] Drug and endoscopic treatment, as non-surgical treatments, is the first-priority option for treating portal hypertension caused esophageal variceal bleeding.^[5,6] Today, there's a predilection to determine the extent of esophageal varices using gastroscopie and further assess whether bleeding exists.^[7] Conventional upper endoscopy with moderate to deeper sedation is universally available throughout the western world, Europe, and most of Asia which have been considered safe and secure. It's application in the clinic may be far more popular than computerized tomoscanning (CT) scans which requires administration of multiphasic sequencing and interpretations from qualified radiologists.

The purpose of finding a non-invasive method for predicting esophageal varices bleeding is of urgent needs. Our study utilizes CT scanning to measure and analyze the diameter, number of sections, and area of esophageal varices with portal hypertension. We aimed to determine the sensitivity, specificity, and bleeding threshold of the above esophageal varice indicators, so as to predict their value in esophageal variceal hemorrhage, and evaluate whether they could serve as an early warning signal in upper gastrointestinal bleeding.

2. Materials and methods

2.1. Study subjects

Patients with cirrhosis and portal hypertension were recruited in our hospital from May 2015 to August 2018. Patients were included under the criteria of: patients diagnosed with cirrhosis and portal hypertension based on the results of clinical, biochemical, imaging, and histopathological examination; patients who had undergone gastroscopy, diagnosed as esophagogastric varices with upper gastrointestinal bleeding, and been followed up for 6 months. Exclusion criteria: patients who also had cardiovascular disease, hematologic disease, renal insufficiency, or malignant tumor; patients who had undergone shunt, devascularization, endoscopic esophageal variceal sclerosis, or ligation; patients who had used pituitary vasopressin, growth hormone releasing inhibitory hormone or propranolol within 1 week before hospitalization; patients with upper gastrointestinal bleeding caused by ulcers, gastric mucosal lesions, benign or malignant tumors of stomach; patients who showed upper gastrointestinal bleeding. The study protocol was approved by the ethics committee of the Fourth People's Hospital of Huaian. The study was carried out in accordance with the approved guidelines.

Two hundred sixty four cases with complete clinical data, liver CT scan, together with enhanced scan were selected. Among them, the bleeding group with 132 cases (112 men and 20 women, aged 30–76 years old) were diagnosed as esophageal varices hemorrhage by clinical and digestive endoscopy, with an average age of 54 years old. There were 115 cases of hepatitis B cirrhosis, 14 cases of alcoholic cirrhosis, and 3 cases of hepatitis C cirrhosis within the bleeding group. Meanwhile, a total of 132 cases in non-bleeding group (116 men and 16 women, aged 25–79 years old) were not complicated with esophageal variceal bleeding, with an average age of 54 years old. Accordingly, the non-bleeding group included 125 cases of hepatitis B cirrhosis, 2 cases of alcoholic cirrhosis, and 5 cases of hepatitis C cirrhosis.

2.2. Inspection method

The patient had been on fasting for 6 to 12 hours before SIEMENS Spirit spiral CT scanning was performed. During the examination, the patient was placed in supine position, and parallel liver CT scan was performed first under breath. The scanning range was from 5 cm on the top of the diaphragm to the lower edge of liver and pancreas. The layer thickness was 5 mm. Afterwards, an enhanced scanning was performed: multi-phase scan of arterial phase (23–28 seconds), portal vein phase (60–65 seconds), and delayed phase (180–240 seconds), and the contrast agent was iodized alcohol (300 mg/mL). The total amount of injection was 100 mL with injection rate as 3 mL/s.

2.3. Measurement of indicators

After CT scanning of esophageal varices, measurement of the diameter of esophageal varices, number of esophageal varices, and total area of the section were implemented. The normal movement of diaphragm exerts negative pressure during inhalation, which is a factor in the onset of varicose veins from the upper part of the diaphragm hiatus.^[8] Moreover, the esophageal varices caused by portal hypertension extends from lower segment to the upper. Therefore, images of the esophageal disruption area about 2 to 5 cm above the esophageal hiatus were adopted. Two experienced radiologists in diagnosing liver disease read the film through

workstation image processor using double-blind method. The diameter of blood vessels, number of vascular sections in the portal vein, and cross-sectional area were measured. The area of each blood vessel was added up to obtain the total area of the blood vessel. However, shortest diameter and area in the cross-section of twisted and skewed blood vessels were measured instead. The sensitivity, specificity, and Youden value (Youden index = sensitivity + specificity – 1) of the above indicators were calculated.

2.4. Statistical methods

Statistical analysis was performed by SPSS 21.0 statistical software (IBM Corp, Armonk, NY, USA). The data between 2 groups were analyzed by *t* test. The difference was statistically significant with $P < .05$. According to the method of diagnostic test in clinical research, the sensitivity and specificity of the esophageal variceal section diameter, number of esophageal varices, and total area of the section were calculated, and the receiver operating characteristics (ROC) curve was generated accordingly. The area under the ROC curve, Youden value, and the highest critical point of the Youden index were also determined.

3. Results

3.1. CT findings

Esophageal varices CT exhibited the shape of esophageal varices, which were round, long, and earthworm-like. The shape of the esophagus was irregular, and the wall of esophagus was thickened in a circular manner. The obviously enhanced blood vessels were protruding into the lumen in a nodular fashion.

3.2. Indicators of esophageal varices

The diameter of esophageal varices was 4.6 to 10.8 mm in bleeding group, being 3 to 6 mm in 26 cases (19.7%), and 6.1 to 10.8 mm in 106 cases (80.3%) (Fig. 1). The diameter of



Figure 1. It showed that the esophageal veins in bleeding group were obviously tortuous and dilated, and were nodular and striped protruding into the lumen. The diameter of the vessels increases, with an average diameter of about 7.83 ± 2.76 mm.

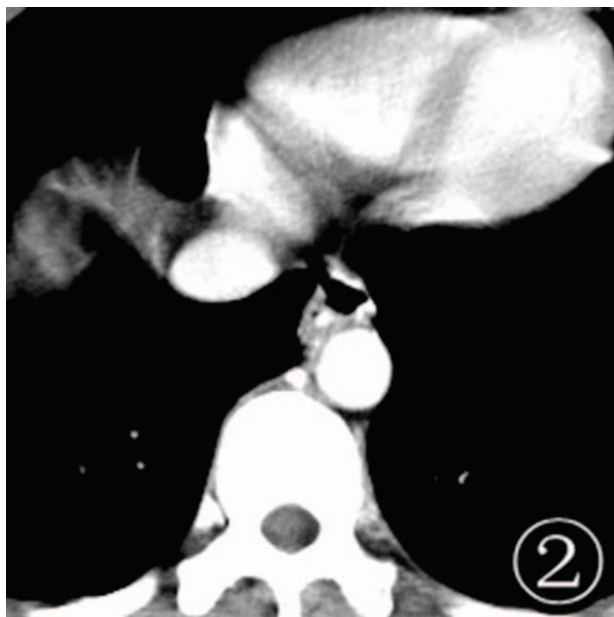


Figure 2. The average diameter of esophageal varices was 6.57 ± 3.42 mm in non-bleeding group.

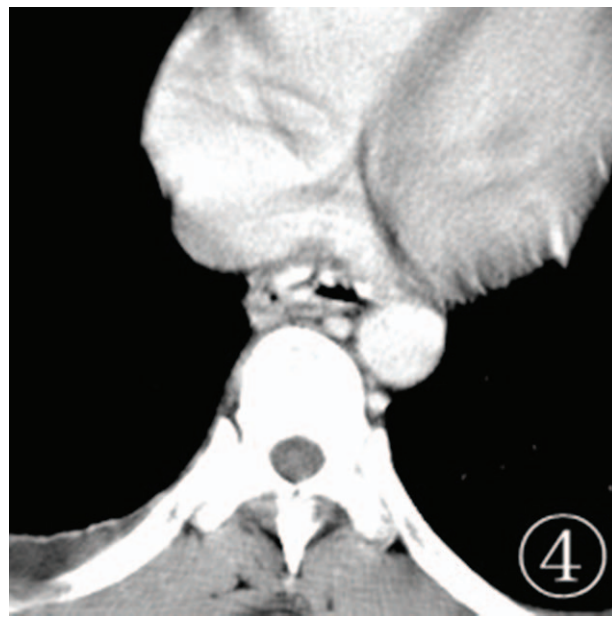


Figure 4. The average number of esophageal varices in non-bleeding group was 4 ± 2 .

esophageal varices in non-bleeding group was 3.1 to 9.8 mm. Sixty three cases were within 3 to 6 mm (47.7%), while the other 69 cases were 6.1 to 10 mm (52.3%) (Fig. 2).

The cross-sectional numbers of esophageal varices were 2 to 7 in bleeding group, 2 in 8 cases (6.1%), 3 in 28 cases (21.2%), 4 in 47 cases (35.6%), and 5 to 7 in 49 cases (37.1%) (Fig. 3). Among non-bleeding group, the cross-sectional numbers of esophageal varices were 2 to 7, 2 in 11 cases (8.3%), 3 in 68 cases (51.5%), 4 in 26 cases (19.7%), and 5 to 7 in 27 cases (20.5%) (Fig. 4).

The total cross-sectional area of esophageal varices was 0.34 to 2.93 cm^2 in bleeding group, with 0.3 to 1.0 cm^2 in 33 cases (25.0%), and 1.1 to 3.0 cm^2 in 99 cases (75.0%) (Fig. 5). In non-bleeding group, it was 0.15 to 1.86 cm^2 , while 96 cases were 0.1 to 1.0 cm^2 (72.7%), and 36 cases were 1.1 to 1.9 cm^2 (27.3%) (Fig. 6).

Table 1 showed the comparisons of diameter of esophageal varices, number of cross-sectional esophageal varices, and total

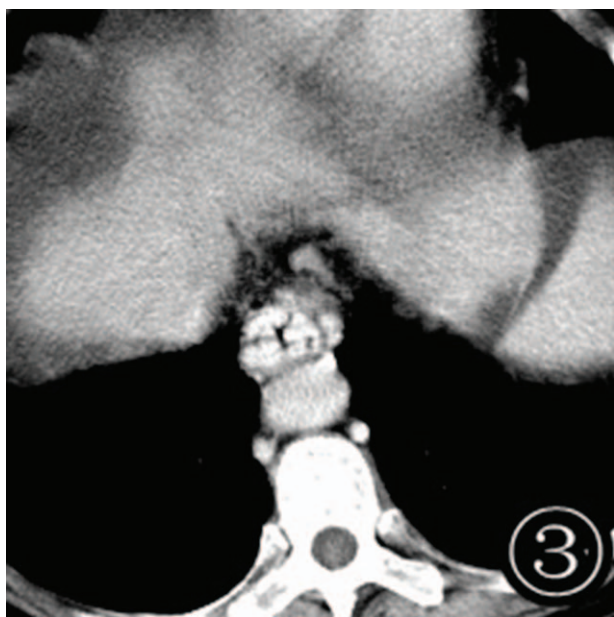


Figure 3. The number of esophageal varices in bleeding group was significantly increased. The esophageal varices were dilated to protrude into the lumen and the average number of vessels was 4.5 ± 2 .



Figure 5. The esophageal varices of bleeding group were with tortuous dilatation, prominent protrusion, narrowed lumen, increased number and diameter of blood vessels, and significantly increased total area of blood vessel section. The average area of blood vessel section was $1.73 \pm 1.15 \text{ cm}^2$.

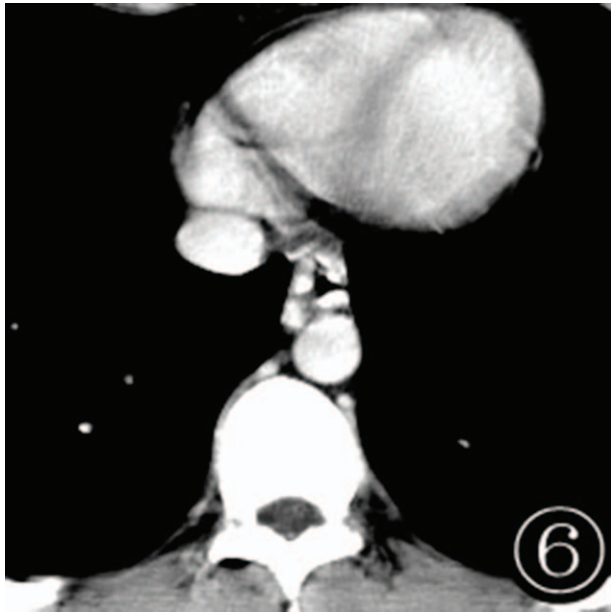


Figure 6. The total area of the cross-section of esophageal varices in non-bleeding group was $1.12 \pm 0.89 \text{ cm}^2$.

cross-sectional area of esophageal varices between the bleeding and non-bleeding group.

3.3. Sensitivity, specificity, and critical point of indicators

We generated the ROC curve, using sensitivity as ordinate, and 1-specificity as abscissa of the measured 3 indicators. We further calculated the AUC and find the cut-off value according to the Youden index. The sensitivity of esophageal vein diameter was 0.8 (106/[106+26]), with specificity being 0.52 (69/[63+69]), Youden index being 0.32, AUC 0.72 (Fig. 7), and a 5.55 mm critical point. The sensitivity of the number of vessels was 0.73 (96/[96+36]), with specificity being 0.6 (79/[53+79]), Youden index as 0.35, AUC 0.68 (Fig. 8), and critical point being 4. The sensitivity of vascular area was 0.75 (99/[99+33]), with specificity in 0.73 (96/[36+96]), Youden index as 0.48, AUC 0.82 (Fig. 9), and the critical point is 1.03 cm^2 .

4. Discussion

Esophageal and gastric variceal bleeding are common complications of liver cirrhosis.^[9] The mortality of primary bleeding is as high as 30% to 50%.^[10] About 5% of cirrhotic patients develop esophageal varices every year, 10% to 20% of them progress from small varices to large varices 1 year later, and the risk of bleeding within 2 years is 20% to 30%.^[11-13] Zoli et al^[14] suggested that the incidence of severe esophageal varices in

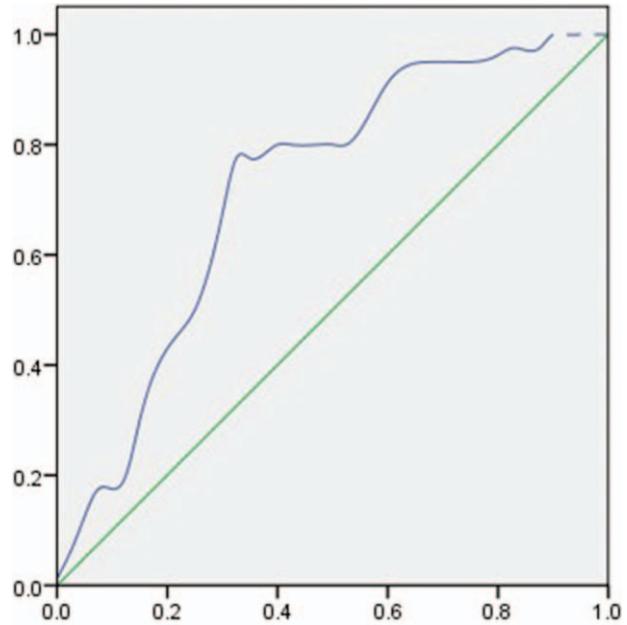


Figure 7. ROC curve of the diameter of esophageal varices. ROC=the receiver operating characteristics.

patients with cirrhosis in the second and fourth years were 21% and 45%, respectively. Therefore, early diagnosis and timely prevention of bleeding from esophagogastric varices is of paramount significance.^[15,16]

Today, endoscopy continues to be the gold standard for diagnosing esophagogastric varices. However, endoscopy is hard to be accepted by patients and it might also increase the possibility of bleeding. Recently, comparing to endoscopy, the application of CT diagnosis of esophageal varices in foreign countries is increasing, it can not only identify submucosal varices, but also find varices around the esophagus. Studies have shown that multi-slice spiral CT display of esophageal varices is highly consistent with gastroscopy, and even superior to gastroscopy in exhibiting gastric varices.^[17-19] CT has become an important tool for evaluating esophageal varices and its hemodynamics.^[20,21]

The diameter of esophageal varices can predict potential upper gastrointestinal bleeding. There will be higher risk of bleeding with higher pressure in varices, larger diameter of esophageal varices and thinner wall. According to the American guidelines for the treatment of esophageal varices with portal hypertension, prophylactic treatment such as endoscopic ligation or non-selective B-blockers is recommended for patients with large esophageal varices (EV) (>5 mm), while prophylactic treatment is not required for patients without or with small EV.^[22,23] In our study, the critical value of esophageal varices diameter was 5.5 mm, indicating that the diagnostic coincidence rate of this index

Table 1
The comparisons of diameter of esophageal varices, number of cross-sectional esophageal varices, and total cross-sectional area of esophageal varices between the bleeding and non-bleeding groups.

Group	Diameter of esophageal varices, mm	Number of blood vessels	Total area of blood vessels, cm^2
Bleeding group	7.83 ± 2.76	4.5 ± 2	1.73 ± 1.15
Non-bleeding group	6.57 ± 3.42	4 ± 2	1.12 ± 0.89
P value	<.01	<.01	<.01

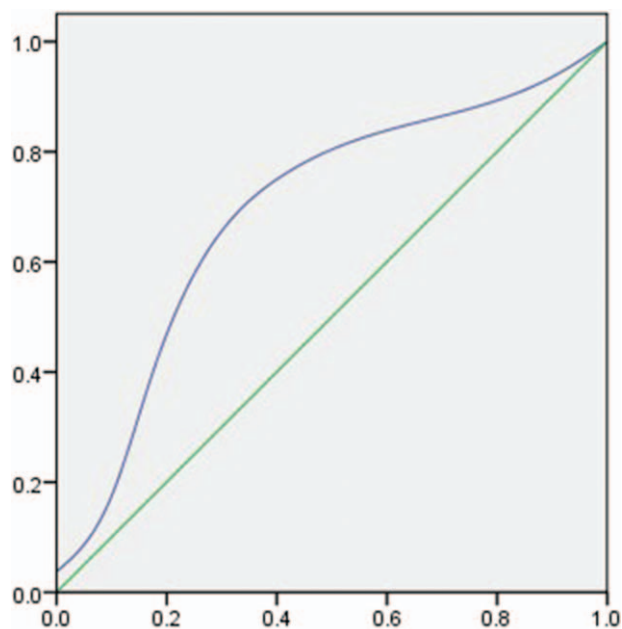


Figure 8. ROC curve of the number of cross-sectional esophageal varices. ROC=the receiver operating characteristics.

with gold standard endoscopy was 90%, which was a good diagnostic index. The AUC^{ROC} of esophageal varices diameter was 0.72 mm, with sensitivity being 0.8, and specificity 0.52, indicating high specificity and low sensitivity with 80% diagnostic accuracy and 48% misdiagnosis rate.

We also predicted the upper gastrointestinal bleeding by the number of cross-sectional esophageal varices. In this study, the critical number of vessels was 4, with sensitivity being 0.73, and specificity 0.6. This indicated CT can predict 73% of

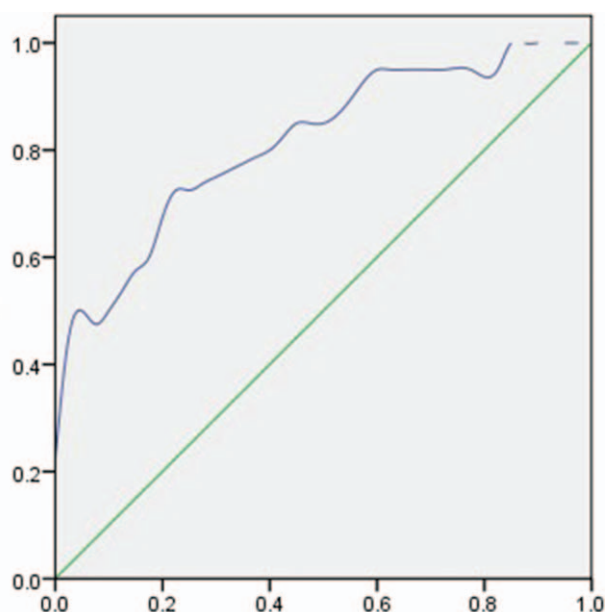


Figure 9. ROC curve of the total cross-sectional area of esophageal varices. ROC=the receiver operating characteristics.

hemorrhagic patients when the number of cross-sectional esophageal varices was >4 , and 40% patients without bleeding may be misdiagnosed as bleeding. The number of cross-sectional esophageal varices in bleeding group was significantly larger than that in bleeding group ($P < .01$). The major reason was that some small vessels were dilated, or some closed vessels were reopened which enabled the CT section easier to display the blood vessels, so the number of vessel sections of bleeding group was much more than that of non-bleeding group.

We predicted the upper gastrointestinal bleeding by the cross-sectional area of esophageal varices. The threshold of the cross-sectional area of esophageal varices was 1.03 cm^2 . The sensitivity and specificity were 0.75 and 0.73, respectively, which indicated that the area of esophageal varices could predict accurate diagnosis of 75% of hemorrhagic patients, whereas 27% of non-hemorrhagic patients might be misdiagnosed as bleeding. Miller et al^[24] proved that there was a positive correlation between the total cross-sectional area of esophageal/gastric varices and the risk of bleeding by ultrasound. Being consistent with their findings, we observed the total area of bleeding group was significantly larger than that of non-bleeding group ($P < .01$). Moreover, the more obvious larger area of the deviation of veins, the more serious of esophageal varices.

Our study has its limitations. It would be better to include a larger sample size with more detailed phenotypic information in future studies, such as size of varices, varying stages of liver disease, hepatic venous pressure gradient, which may portend risks with variceal bleeding.

In conclusion, our study find the diagnostic criteria for upper gastrointestinal bleeding in portal hypertension as follows: 0.82 cm^2 of the total cross-sectional area of esophageal varices, 0.72 mm of the diameters of esophageal varices, and 0.68 of the cross-sectional number of esophageal varices. Collectively, the total cross-sectional area of esophageal varices can serve as an accurate and efficient predictor of first upper gastrointestinal bleeding in patients with cirrhosis and portal hypertension.

Author contributions

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Writing – original draft: Xin Zhang, Li-Yao Zhu.

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