

# Liver stiffness and platelet count to assess the risk of bleeding from esophageal and gastric varices in liver cirrhosis

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# Abstract

## Background

The Baveno VI portal hypertension consensus recommended that liver stiffness measurement (LSM) < 20kPa and platelet count (PLT) > 150×10<sup>9</sup>/L may avoid screening endoscopy in 40% of patients with compensated cirrhosis. We aimed to use transient elastography (TE) to measure liver stiffness, combined with PLT to assess the risk of bleeding from esophageal and gastric varices in patients with liver cirrhosis, and to establish a new standard for Chinese patients.

## Methods

Adult patients with compensated liver cirrhosis treated in 8 clinical research centers from 2018 to 2020 were enrolled and randomly divided into the training cohort and the validation cohort. Patients from the training cohort were used to study the performance of different PLT and LSM, to ensure great endoscopic avoidance rate and very low varicose veins need to be treated (VNT) missed rate. At the same time, the new standard was verified in the validation cohort patients.

## Results

A total of 260 patients (166(63.8%) hepatitis B and 229 (88.07%) Child-Pugh class A) were analyzed. In the training cohort (n = 137) with hepatitis B as the main etiology (63.8%), the LSM < 25kPa and PLT > 120×10<sup>9</sup>/L were the best standards. Under this standard, 23.4% of patients could avoid unnecessary endoscopy screening, and 3.1% of patients missed VNT. In the validation cohort (n = 123), under the TOUCH standard, 24.4% of patients could avoid screening endoscopy, and the risk of missed VNT was within an acceptable range (3.4%).

## Conclusions

The new standard based on instantaneous elastography technology could identify patients with compensatory cirrhosis with low risk of varicose veins and some patients may avoid screening endoscopy.

## Introduction

Portal hypertension is a clinical syndrome of increased portal venous system pressure and extensive collateral circulation caused by obstruction of portal blood flow or abnormal increase in blood flow, including ascites, esophageal varices, and splenomegaly. It is the main manifestation of decompensated liver cirrhosis, among which gastroesophageal varices (GOV) is a common clinical manifestation of

portal hypertension<sup>[1]</sup>. GOV could be seen in about 50% of patients. In case of rupture and bleeding, the condition was dangerous, rapid progress and high mortality. About 20% of patients with GOV rupture die within 6 weeks. If untreated, the long-term rebleeding rate was as high as 60%, which was one of the main causes of death in patients with advanced liver cirrhosis<sup>[2]</sup>. For patients with compensated cirrhosis, although there was no decompensation event, it's not mean GOV doesn't exist. It was reported that about 40% of Child-Pugh Class A patients could develop varicose veins, and the disease progress of these patients was rapid. Therefore, it was extremely important to find out whether GOV exists in time and early intervention for patients with cirrhosis. International guidelines recommended the use of Hepatic Venous Pressure Gradient (HVPG) to measure portal vein pressure<sup>[3]</sup>. However, due to the invasive and high technical requirements of HVPG measurement, a convenient non-invasive method was needed to assess the risk of gastroesophageal varices.

Gastroscopy is the gold standard to evaluate esophageal and gastric varices. However, as an invasive examination, gastroscopy is easy to cause discomfort in patients on the one hand, and most asymptomatic patients in compensatory period are unwilling to cooperate with endoscopy on the other hand. Transient Elastography (TE) is a non-invasive liver detection method that uses ultrasound to display images and calculate liver stiffness measurement (LSM) values. It is easy to operate, repeatable and safe. Studies have shown that TE measurement has potential benefits in the non-invasive diagnosis of portal hypertension, especially when combined with other markers (such as platelet count (PLT) PLT and spleen size). The Baveno VI guidelines<sup>[4]</sup> recommended that patients with compensatory cirrhosis may not need to be screened by endoscopy when  $LSM < 20\text{KPa}$  and  $PLT > 150000\text{ cells}/\mu\text{L}$ , and patients can be followed up for a long time by repeating TE and PLT examination every year. Endoscopy can be performed in time when TE examination and PLT results exceed the standard. However, most of the above standards came from western countries, and most of the included subjects were patients with liver cirrhosis mainly caused by alcohol and hepatitis C, which was different from the etiological spectrum of liver cirrhosis in China, Therefore, it was necessary to find a more suitable decision threshold for our country.

In this prospective multicenter cohort study, we explored and verified the classification criteria more suitable for China based on the LSM value measured by TE and PLT, and explored its screening value for the risk of esophagogastric variceal bleeding in Chinese patients with liver cirrhosis, so that more people can safely avoid screening endoscopy. In addition, Fibroscan is used for TE detection in the establishment and verification of Baveno VI standard. Therefore, we tried to establish the Touch standard through another common TE detection device (Fibrotouch) for the first time.

## Materials And Methods

### Study subjects

This is a prospective study of 260 adult patients with compensatory liver cirrhosis who were treated in 8 clinical research centers from 2018 to 2020 and diagnosed through pathology or clinical diagnosis were

included. The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the ethics committee (NT03778775).

Inclusion criteria are 1) no ascites, hemorrhage, or decompensated events such as hepatic encephalopathy; 2) electronic gastroscopy and liver transient elasticity examination was planned. Exclusion criteria are 1) contraindications of electronic gastroscopy; 2) previous and preventive treatment (NSBB, EVL, EIS); 3) the interval between electronic gastroscopy and liver TE examination was more than 14 days; 4) the Child-Pugh score was greater than 9; 5) diagnosis of liver cancer.

### **Liver TE examination**

iLivTouch - a 2-dimensional image-guided system based on Transient Elastography was used for detection of liver stiffness measurement (LSM). Patients were required fasting for at least 2-3 hours before detection, and kept lying still until the end of detection. The testing process was in strict accordance with the standardized process. An appropriate region was selected to detect through the seventh-ninth intercostal space avoiding the cysts and blood vessels in the liver. When the probe was kept in a vertical position to the skin surface with pressure maintained the appropriate range, reliable data could be collected if the number of successful measurements was  $\geq 10$ , the success rate was  $\geq 60\%$ , and the relative deviation was  $\leq 33\%$ . And then, selected the best image and recorded the LSM value of patient.

### **Standards for varicose veins**

According to the shape and bleeding degree of esophageal and gastric fundus varices, varicose veins could be divided into mild, moderate and severe. Mild: esophageal varices were linear or slightly tortuous without red sign; moderate: esophageal varices were linear or slightly tortuous, with red sign or serpentine tortuous uplift but no red sign; severe: esophageal varices were serpentine tortuous uplift with positive red sign or beaded nodular or tumor like. According to the Baveno VI guidelines, VNT was defined as medium and large varices or small varices with positive red sign.

### **Study methods**

The included patients were randomly assigned to the training cohort and the validation cohort. Gastroscopy and TE were performed in both groups. The general data of patients (age, gender, Child-Pugh classification of liver cirrhosis and etiology of liver cirrhosis) were recorded. At the same time, the laboratory test results (routine blood test, coagulation time, liver function and renal function) and LSM value were collected. The training cohort was used to establish new criteria and the selection criteria of the best cut-off value: the maximum proportion of avoiding screening gastroscopy while missed VNT  $\leq 5\%$ . The validation cohort was used to validate the established new standard.

### **Laboratory examination**

All examinations involved in this study are part of the routine examination. We recorded the basic information of patients, including their age and gender. Etiology and Child-Pugh Class of cirrhosis were collected. Data on liver function (alanine transaminase [ALT] and aspartate aminotransferase [AST]) and blood routine (platelets [PLT]) were included.

## Statistical analysis

SPSS and R statistical platform were used for data statistical analysis. All hypothesis tests were conducted at the significance level of 5% on both sides. The counting data conforming to normal distribution was expressed by mean  $\pm$  standard deviation, the counting data of skew distribution was expressed by median  $\pm$  interquartile spacing, and the count data is represented by the number of cases (n).

# Results

## General characteristics

Among the 260 patients with compensatory cirrhosis, there were 160 males and 100 females, with an average age of 51.66 years. The etiology of the study included chronic hepatitis B infection under maintained viral suppression with antiviral treatment (HBV, n=166 (63.8%)), chronic hepatitis C infection (HCV, n=35 (9.6%)), alcohol related liver disease (ALD, n=13 (5%)), and other (n=56 (21.5%)). Among the patients with compensated cirrhosis, there were 229 cases of Child-Pugh class A, accounting for 88.1%, and the average LSM was 18.38kPa, there were 89 patients with VNT through the examination by gastroscopy, accounting for 34.2%. The average value of PLT was  $94 \times 10^9/L$ , which was lower than the lower limit of normal value. The average values of ALT and AST were within the normal range. Among the 260 patients included, there were 137 in the training cohort and 123 in the validation cohort. The basic characteristic data of patients in the two cohorts are shown in Table 1.

## Study cut-off value

Table 2 showed the data and performance of new criteria based on the Baveno VI criteria by increasing the LAM or decreasing PLT in the training cohort. In the training cohort, under the condition of ensuring the maximum rate of avoiding screening endoscopy and the rate of missed VNT was less than 5%, the best cut-off value was the LSM  $< 25kpa$  and PLT  $> 120 \times 10^9/L$ . Under this cut-off value, 32 (23.4%) of the 137 patients evaluated could avoid screening endoscopy, and only 1 (3.1%) patient missed VNT. We propose the criteria for the new classification rule.

The cut-off value was further verified in the validation cohort. The performance of the new standard in the validation cohort was also shown in Table 2. Overall, the risk of missed VNT was 3.4%, and endoscopy was avoided in 24.4% of patients. The risk of missed VNT and avoiding endoscopy in validation cohort is almost similar to that in training cohort.

## Performance of new criteria in patients with HBV and Child-Pugh A

Because the patients with HBV and child-pugh A accounted for the largest proportion in our study, we re-evaluated the performance of the new criteria separately for these two patients (Table 3). The application had a similar performance in these two parts. Both the patients with HBV and Child-Pugh A in training cohort have 25% spared endoscopies rate and no missed VNT. The missed VTN rate the verification group also did not exceed 5%. Spared endoscopies rate in patients with HBV and Child-Pugh A were 23.3% and 23.9%, respectively.

### Screening process

Figure 1 showed the screening process of whether there was VNT in patients with compensatory cirrhosis based on TE detection. After blood routine examination and liver cirrhosis examination for patients with compensatory cirrhosis, patients with LSM < 25kpa and PLT > 120×10<sup>9</sup>/L could temporarily not undergo endoscopy, and blood routine and LSM values examination were followed up dynamically. Once the examination values were outside the scope of this standard, gastroscopy should be performed in time to judge whether the patient needs prevention and treatment.

## Discussion

Esophageal and gastric variceal bleeding (EGVB) is one of the most common complications and one of the main causes of death in patients with liver cirrhosis. It is the key to improve the survival rate of patients with liver cirrhosis to early predict the risk of esophageal and gastric variceal bleeding and actively take preventive measures. As the "gold standard" for the diagnosis of EGVB, gastroscopy leads to poor patient compliance due to its invasive operation. Therefore, how to early apply non-invasive indexes to predict the risk of variceal rupture is the focus of current research.

Early studies found the predictive value of the ratio of PLT to spleen diameter, because varicose veins and hypersplenism were the results of portal hypertension, and splenomegaly was the main clinical manifestation of hypersplenism. In addition, the PLT of patients with liver cirrhosis was affected by many factors, except hypersplenism, the number of thrombopoietin would be greatly reduced when hepatocytes were damaged<sup>[5]</sup>. Through a prospective study of 150 patients, Baig et al. showed that the ratio of PLT to spleen diameter is more accurate than the two alone<sup>[6]</sup>.

In the earlier study, Giannini et al. believed that the ratio of PLT and spleen longest diameter could predict whether patients with liver cirrhosis have esophageal varices, and that the ratio 909 is an effective index to predict the presence or absence of esophageal varices. When the ratio is lower than 909, the positive predictive value and negative predictive value reach 96% and 100% respectively<sup>[7]</sup>. Subsequently, a large number of studies have verified it. In addition, Albreedy et al. found that the area ratio of platelet and spleen can reflect EGVB, showed good sensitivity (100%) and specificity (88%)<sup>[8]</sup>.

In the early days, ultrasonic Doppler was the main examination equipment, which could indirectly evaluate the risk of EGVB by measuring the diameter of liver and spleen. With the development of TE, it has been widely accepted because of its advantages of non-invasive, simple, fast, repeatability and safety, and has become one of the important non-invasive methods for evaluating liver fibrosis<sup>[9]</sup>. However, the application of TE in patients with ascites needed to be carefully explained. Therefore, more studies tended to predict the risk of esophagogastric varices in cirrhotic patients without ascites in the compensatory period through the indicators measured by TE<sup>[10]</sup>. The study confirmed that TE technology was a valuable and meaningful non-invasive examination for the diagnosis of esophageal varices, and the LSM value was closely related to the degree of esophageal varices. In a prospective cohort, Kazemi et al. reported that 13.9 kPa and 19.0 kPa are the critical values of varices and VNT<sup>[11]</sup>. Li et al. study results showed that through evaluation by TE and gastroscopy, 22.8 kPa, 30.6 kPa and 34.6 kPa were the best critical values of LSM for mild, moderate and severe esophageal varices<sup>[12]</sup>. Since then, several studies have been published on the LSM prediction critical values, but the reported results vary widely.

The 2015 Baveno VI Consensus introduced the important innovations in the management of patients with compensated liver cirrhosis<sup>[4]</sup>. The guidelines proposed that LSM<20 kPa combined with PLT>150,000/mm<sup>3</sup> can be used as a new standard to identify varicose veins with a lower risk of bleeding. In this part of patients, endoscopy screening could be avoided. Since then, a number of studies have confirmed the effectiveness of this risk classification rule based on this standard. However, there were still studies that have not reached the same conclusion. A meta-analysis was conducted to integrate the evidence of LSM and PLT for the identification of esophageal varices, and 15 studies were included<sup>[13]</sup>. The results suggested that compared with patients with high LSM value or low PLT, patients with low LSM value and normal PLT had low risk of varicose veins, and the heterogeneity between the studies was low. It was confirmed that PLT combined with LSM value could be used to identify the risk of venous bleeding.

However, according to this standard, only about 20% of the patients did not need endoscopy. Therefore, in the recent study<sup>[14]</sup>, the American Liver Research Association proposed a new standard that endoscopy is not required when the LSM<25kpa and the PLT>110×10<sup>9</sup>/L. Subsequently, different studies verified the diagnostic value of the two standards<sup>[15]</sup>. In a study of 1035 patients with compensatory advanced chronic liver disease, the extended standard (51.7%) could avoid more endoscopy than the original standard (27.6%), but the extended standard also missed more high-risk varices (6.8%, 3.8%). According to the etiological stratification of liver diseases (hepatitis B, hepatitis C, alcoholic fatty liver and nonalcoholic fatty liver), the negative predictive values of the original Baveno VI standard were 0.92, 1.00, 1.00 and 1.00, and the negative predictive values of the extended standard were 0.92, 0.96, 0.92 and 0.93<sup>[16]</sup>. Similarly, in a large meta-analysis of 1000 patients with chronic liver disease, the Baveno VI standard would allow 262 patients to avoid screening endoscopy, but 6 patients would be missed. On the contrary, using the expanded Baveno VI standard would result in 428 patients avoided screening endoscopy, but 20 HRV patients will be missed<sup>[17]</sup>. Subsequently, Vilar et al. added the spleen diameter to the index. By enrolling 518 patients with compensated chronic liver disease from 5 clinical research

centers in Europe and Canada, all patients measured the LSM value by TE. The study showed that when liver stiffness  $\times$  spleen diameter/PLT (LSPS) $<1.33$ , the risk of VET in patients is  $<5\%$ <sup>[18]</sup>. In addition, there are several validation studies performed in the Asian cohort especially in the recent years<sup>[19-23]</sup>. We summarized and presented these studies in table 4. These studies are mainly concentrated in China, Singapore, and Korea. The etiology of the involved patients in different studies is different, including viral hepatitis and/or fatty liver. The endoscope spare rate in expanded Baveno VI standard (40%-60%) was significantly higher than that in Baveno VI standard (20%-40%). But missing rate in expanded Baveno VI standard is correspondingly higher.

However, the current standards were mostly derived from Western countries, and the subjects included in the study were mostly alcohol and hepatitis C patients with liver cirrhosis. The etiology spectrum of liver cirrhosis was not the same in our country. Therefore, it was necessary to find a more suitable decision threshold for our country. In this large multi-center cohort study, based on the BAVENO VI guidelines, we combined the LSM value detected by TE and PLT to explore the best standard and best cut-off value (LSM $<25$ kpa, PLT $>120 \times 10^9$ ) to identify patients with compensatory cirrhosis with low risk of clinically significant varicose veins, so as to safely avoid screening endoscopy in 23.4% of patients.

However, our study also has certain limitations. First, although our data came from multiple clinical research centers, the number of study patients with compensated liver cirrhosis were much smaller than that of domestic patients, and larger data were needed to explore and verify the standard. In addition, our study did not provide instantaneous elastography. Fibrotouch detection was closely related to the technique of the inspector. In addition, factors such as obesity and alcohol consumption may have a certain impact on the LSM value, which would increase the LSM value. In such cases it may cause differences in our study standards. Therefore, whether the standards we were exploring can be applied to clinical practice still needs to be further improved and verified.

In short, the combination of TE and PLT can identify patients with compensatory cirrhosis with low risk of varicose veins. When the LSM  $<25$  kPa and PLT  $>120 \times 10^9$ /L, endoscopy screening was avoided in 23.4% of patients.

## Declarations

**Ethics approval and consent to participate:** The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the ethics committee of the First Hospital of Lanzhou University (NT03778775). All patients gave written informed consent before participation in this study.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets generated and/or analysed during the current study are not publicly available because the public data has not obtained the consent of the participants' guardian, but the data acquisition and analysis have obtained the consent of the participants' guardian. But they are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

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## Tables

**Table 1. Baseline characteristics of study cohort.**

	Total (n=260)	Training cohort (n=137)	Validation cohort (n=123)
Age (year), mean (SD)	51.66 (10.97)	53.00 (11.41)	50.59 (10.39)
Male, n (%)	160 (61.5%)	82 (59.9%)	78 (63.4%)
LSM, kpa	18.38 (11.92)	15.50 (9.63)	20.98 (12.23)
VNT, n (%)	89 (34.2)	52 (37.9)	37 (30.1%)
Etiology, n (%)			
HBV	166 (63.8%)	80 (58.4%)	86 (69.9%)
HCV	25 (9.6%)	7 (5.1%)	18 (14.6%)
Alcoholic liver disease	13 (5.0%)	11 (8.0%)	2 (1.6%)
Other	56 (21.5%)	39 (28.5%)	17 (13.8%)
Child-Pugh Class, n (%)			
Class A	229 (88.1%)	116 (84.7%)	113 (91.9%)
Class B	31 (11.9%)	21 (15.3%)	10 (8.1%)
Laboratory, median (IQR)			
PLT (10 <sup>9</sup> /L)	94.00 (67.50)	97.00 (60.75)	93.00 (78.75)
ALT (U/L)	36.00 (46.00)	28.00 (24.00)	50.60 (98.80)
AST(U/L)	40.00 (37.38)	32.00 (32.00)	48.00 (84.20)

SD, standard deviation; IQR, interquartile range; LSM, liver stiffness measurement; VNT, varices needing treatment; PLT, platelet count; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

**Table 2. Performances of TOUCH criteria in the training and validation cohort.**

	Missed VNT	Spared endoscopies
Training cohort (n = 137)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	1/32 (3.1%)	32 (23.4%)
Validation cohort (n = 123)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	1/30 (3.4%)	30 (24.4%)

Data are presented as n (%) or n/N (%), where N is the total number of related cases, the unit of platelets was  $\times 10^9/L$ . VNT, varices needing treatment.

**Table 3. Performances of TOUCH criteria in the patients with hepatitis B infection and Child-Pugh A.**

	Missed VNT	Spared endoscopies
HBV		
Training cohort (n = 80)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	0/20 (0.0%)	20 (25.0%)
Validation cohort (n = 86)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	1/20 (5.0%)	20 (23.3%)
Child-Pugh A		
Training cohort (n = 116)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	0/29(0.0%)	29 (25.0%)
Validation cohort (n = 113)		
TOUCH criteria		
LSM < 25.0 + PLT > 120	1/27 (3.7%)	27 (23.9%)

Data are presented as n (%) or n/N (%), where N is the total number of related cases, the unit of platelets was  $\times 10^9/L$ . VNT, varices needing treatment.

Table 4 is not available with this version

## Figures

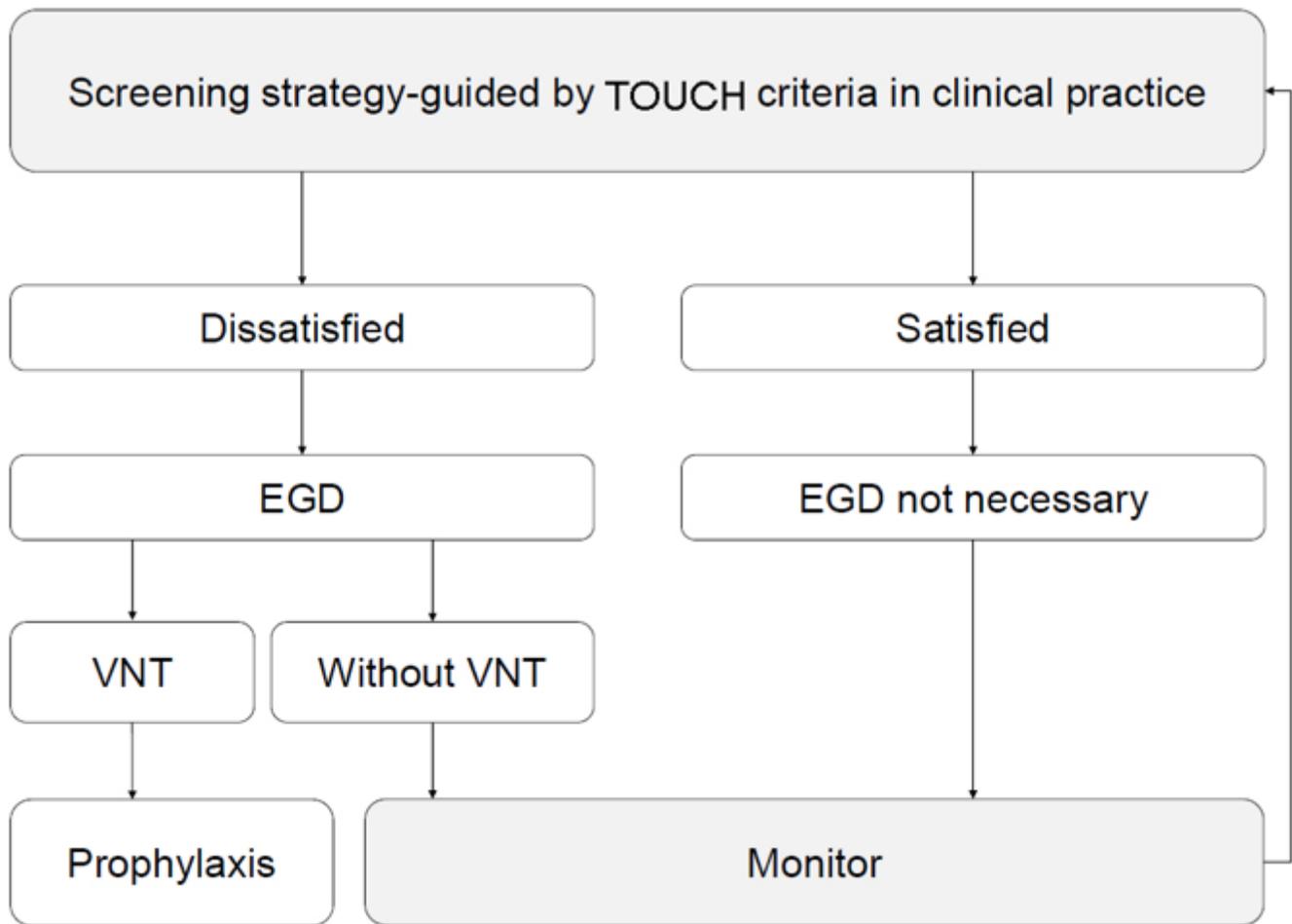


Figure 1

Screening strategy-guided by TOUCH criteria