DR. ÉLIO CUNHA CASTRO FILHO (Orcid ID : 0000-0003-3670-9911)

DR. HUGO PERAZZO (Orcid ID : 0000-0003-0931-6418)

Article type : Original Articles

Handling Editor: Christophe Bureau

Reliability and safety of transnasal compared to conventional endoscopy for detecting esophageal varices in cirrhotic patients

Author Names:

Elio C Castro Filho[1]; Hugo Perazzo[2]; Raquel Al-Cici P Guimaraes[1]; Lilian Machado[1]; Flavia F Fernandes[3]; Renata M Perez [1,4,5]

Department/Institution Names:

[1] University of the State of Rio de Janeiro (UERJ), Gastroenterology Department, Rio de Janeiro, Brazil

[2] Evandro Chagas National Institute of Infectious Disease (INI) - Oswaldo Cruz Foundation (FIOCRUZ), Laboratory of clinical research on STD/AIDS, Rio de Janeiro, Brazil.

[3] Bonsucesso Federal Hospital, Gastroenterology Department, Rio de Janeiro, Brazil

[4] Federal University of Rio de Janeiro (UFRJ), Internal Medicine Department, Rio de Janeiro, Brazil

[5] D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil

Corresponding Author:

Elio C Castro Filho; MD

Hospital Pedro Ernesto / UERJ. Gastroenterology Department – 3º floor

Blv 28 de Setembro, 77 - CEP: 20551-030 - Vila Isabel - Rio de Janeiro, RJ – Brazil

E-mail: elio.filho@cremerj.org.br / emailproelio@yahoo.com.br

Tel: +55 21 2868-8654 / +55 21 2868-8258. Fax: +55 21 2868-8222

List of abbreviations in the order of appearance: GIE, gastrointestinal endoscopy; EV, esophageal varices; IRB, institutional review board; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; SE, standard error; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; INR, international normatized ratio; CC, correctly classified; FN, false negative; FP, false positive; IQR, interquartile range; PO, peroral; TN, transnasal

Conflict of interest: The authors have no conflict of interest to disclose.

Financial support:

This work was supported by funding from Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Rio de Janeiro, Brazil.

Author Contributions: Elio C Castro Filho (ECCF): performance and video-recording of transnasal and conventional endoscopies, data collection, interpretation of data, manuscript drafting and critical revision; Hugo Perazzo (HP): statistical analysis and interpretation of data, draft and critical revision of the manuscript; Raquel Al-Cici P Guimaraes (RAPG) &

Lilian Machado (LM): blinded-evaluation of recorded videos from transnasal and conventional endoscopies, data collection, interpretation of data and critical revision of the manuscript; Flavia F Fernandes (FFF): data collection, interpretation of data, critical revision of the manuscript; Renata M Perez (RMP): study concept and design, study supervision, interpretation of data, critical revision of the manuscript.

ABSTRACT

Background & Aims: Unsedated transnasal endoscopy may be used for detecting esophageal varices. However, few studies evaluated feasibility and accuracy of this technique. We aimed to evaluate accuracy, interobserver agreement and safety of the transnasal ultrathin compared to conventional endoscopy in patients with cirrhosis.

Methods: This cross-sectional study included consecutive patients referred for screening or surveillance of esophageal varices. Patients underwent unsedated transnasal and sedated conventional endoscopies at the same day, which were recorded in a digital video file and randomly analyzed by two double-blinded endoscopists. High-risk varices were defined by presence of large caliber or red wale marks. Accuracy, interobserver agreement and safety of transnasal were compared to conventional endoscopy.

Results: 133 cirrhotic patients [48% male, aged of 60 ±5, 34% Child-Pugh B/C and 71% of cases for variceal screening] were included .The prevalence of esophageal varices and high-risk esophageal varices were 59% (n=79) and 29% (n=39), respectively. For presence of esophageal varices, transnasal GIE yielded sensitivity of 94% [95%Confidence Interval, CI 88-99], specificity of 89% [81-97], as well as positive and negative predictive value of 93% and 91%, respectively. A satisfactory interobserver agreement was observed for presence of esophageal varices (kappa=0.89) and high-risk varices (kappa=0.65). No serious adverse

events were recorded, transnasal GIE was safe and significantly associated with lower rates of hypoxemia ($p<0.0001$) and hypotension ($p<0.0001$) compared to conventional endoscopy.

Conclusions: Unsedated transnasal endoscopy was safe and had an excellent accuracy and high interobserver agreement for detecting esophageal varices and for identifying high-risk varices in cirrhotic patients.

Electronic word count of abstract: 250 **Keywords:** cirrhosis; portal hypertension; esophageal varices, diagnostic performance, transnasal ultrathin endoscopy.

KEY POINTS BOX:

1 – Sedation may trigger hepatic encephalopathy in decompensated cirrhosis.

2 – Transnasal endoscopy is well tolerated and reliable for the assessment of gastrointestinal tract. Limited studies evaluated the role of this method for detecting esophageal varices in cirrhotic patients.

3 – Our study showed that transnasal endoscopy without sedation is reliable for detecting EV and High-risk EV, regardless of severity of cirrhosis.

4 – Unsedated transnasal endoscopy might be an alternative for variceal screening in cirrhotic patients with high risk of sedative adverse events.

Introduction

Portal hypertension is mostly associated with cirrhosis and may lead to development of gastroesophageal varices and life-threatening adverse events.[1] Esophageal varices may be present in up to 40% of patients with compensated cirrhosis and bleeding from esophageal varices has been associated with high mortality risk.[2] Early diagnosis of esophageal varices

and implementation of prophylactic measures to prevent variceal bleeding are mandatory to increase survival of patients with cirrhosis.[3]

Conventional gastrointestinal endoscopy (GIE) has been used for screening or surveillance of esophageal varices in cirrhotic patients. However, this method has been challenged by high direct and indirect costs [4] which is augmented by the necessity of having endoscopy repeated at one to three years for surveillance.[3] In addition, conscious sedation with midazolam may trigger hepatic encephalopathy in cirrhotic patients.[4] Unsedated transnasal GIE, first described by Shaker et al [5], has been proposed as an alternative modality that could eliminate certain direct costs, such as need of monitoring, oxygen supplementation and administration of sedative drugs, as well as indirect costs, including time lost from work.

Esophageal assessment with transnasal GIE seems to be comparable to conventional GIE in overall quality allowing the use of this technique for identification of esophageal varices.[6] In a pilot study, unsedated esophagoscopy with ultrathin endoscopes was safe, well tolerated and may give cost benefits for the diagnosis of esophageal varices in patients with cirrhosis.[7] Further studies have reported the feasibility and high accuracy of unsedated small−caliber endoscopy in comparison to conventional GIE for evaluating esophageal varices.[8-11] However, most of them had considerable limitations, such as small sample size, lack of evaluation of the interobserver agreement and not acknowledging the potential impact of the severity of cirrhosis in the diagnostic performance of this method. In addition, those studies used different approaches (peroral vs transnasal GIE; sedated vs unsedated protocols) and distinct endoscopic technologies challenging results interpretation. This study aimed to evaluate the accuracy, interobserver agreement and safety of transnasal ultrathin GIE in

unsedated cirrhotic patients for detecting esophageal varices compared to conventional endoscopy under sedation.

Patients and Methods

Study design

This cross-sectional study was conducted from January 2014 to the end of 2016 at the University of the State of Rio de Janeiro. Consecutive patients with cirrhosis (diagnosed by physical examination, imaging studies or liver biopsy) scheduled to undergo upper GIE for screening or surveillance of esophageal varices were included. Screening was considered for patients without previous diagnosis of varices, and surveillance for those with known varices in follow-up for primary or secondary prophylaxis.[3] Previous history of epistaxis, nasal obstruction, surgery or nasal trauma, coagulation disturbance (use of anticoagulant or platelet count lower than $30x10^3/mm^3$) and suspicion of acute variceal bleeding were exclusion criteria. The study protocol was approved by the Ethical Committee from Pedro Ernesto University Hospital (IRB number 501.923) and all participants signed the informed consent on enrollment at the study.

Study procedures

Patients were submitted to transnasal ultrathin GIE immediately followed by conventional GIE under sedation by the same experienced operator (ECCF). Transnasal ultrathin GIE was performed without sedation using a 5.9 mm caliber insertion gastroscope (Fujinon® EG-530N, Tokyo, Japan). Before transnasal ultrathin GIE, a vasoconstrictor solution (nafazolin 0.5 mg/ml) was administered at left or right nostril followed by local anesthesia with 2% lidocaine gel (by inhalation and insertion of an 18 Fr catheter covered with lidocaine jelly for 5 minutes). Conventional GIE was performed using a 9.0 mm caliber

gastroscope (Fujinon® EG-450 HR or EG-490 WR5, Tokyo, Japan) after local anesthesia with 10% lidocaine spray and under conscious sedation with midazolam (0.05 mg/kg up to 5 mg) plus meperidine (up to 50 mg). Propofol (titrated doses of 0.25 mg/kg) was administered by a second physician in patients who required more sedation for performance of an adequate exam. Supplementary Table S1 describes technical aspects of transnasal and standard caliber endoscopes used in the study.

Transnasal and conventional GIEs were recorded (Archos® 605, Igny, France) in a high-definition file and coded using a random number generator. The recorded videos were randomly analyzed separately by two endoscopists (RAPG and LM) who were blinded for clinical data. They should describe the following GIE findings for each exam of transnasal and conventional GIE: (i) presence of esophageal varices [yes vs no]; (ii) varices sizes [small (≤ 5mm) vs large (> 5mm)]; (iii) presence of red wale marks [yes vs no] and presence of band ligation sequelae [yes vs no].[12] High-risk esophageal varices were defined as large varices or presence of red wale marks.[2,3] Both endoscopists underwent a training program for video analysis previously to this study. In a second step, conventional GIEs were assessed by both endoscopists for consensus of each finding that was used as the gold standard.

Safety of GIE procedures

Oxygen saturation, blood pressure and heart rate were recorded using a multiparameter monitor (GE Healthcare® Carescape Monitor B650, Helsinki, Finland) before, during [every 5 minutes] and after transnasal and conventional GIEs. The following cardiopulmonary adverse events were assessed during procedure or recovery time: (i) hypoxemia [oxygen saturation < 90% for more than 10 seconds, refractory to airway rectification measures, requiring oxygen supplementation or use of antagonist drugs (flumazenil or naloxone); (ii) hypotension [20% decrease in mean blood pressure or systolic

pressure < 90mmHg and/or diastolic pressure < 50 mmHg] and (iii) bradycardia [25% decrease in initial heart rate or heart rate < 55 beats/minute]. In addition, minor adverse events, such as epistaxis gagging or pain and major adverse events, such as digestive bleeding, perforation or deathwere recorded.

Statistical Analysis

A sample size of 114 was calculated considering the following parameters: diagnostic accuracy of transnasal GIE as binary test outcome with an estimated sensitivity of 95%, confidence interval (CI) with 5% of alpha error, as well as 5% of precision for estimates of sensitivity and 64% of prevalence of esophageal varices in patients with cirrhosis.[13,14] Continuous variables were reported as mean ± standard deviation or as median (range or interquartile range). Discrete variables were reported as absolute (n) and relative frequency (%). Comparisons between groups were assessed by *t* student's test or Mann-Whitney for quantitative comparisons and chi-square or the Fisher exact test for qualitative comparisons. Repetitive measures were compared and assessed by paired *t* student's test or Wilcoxon signed-rank for paired continuous variables and McNemar for paired discrete variables.

The diagnostic performance of transnasal ultrathin GIE by the senior endoscopist (LM) was assessed by reporting its sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR+) using the consensus of conventional GIE as the reference. Interobserver agreement for presence of esophageal varices, high-risk varices or band ligation sequelae were assessed by kappa (k) reliability values (standard error, SE). Significance level was determined by p value ≤ 0.05 assuming two-tailed tests. Statistical analyses were performed using STATA statistical package for Windows (2017; StataCorp LP, College Station, TX, USA).

Results

A total of 139 patients with cirrhosis were eligible and six subjects were excluded by refusing to participate (n=2), coagulation disturbance (n=1), recent episode of epistaxis (n=1) and inadequate video recording (n=2) (Figure 1). Therefore, 133 patients [48% male, mean age 60±5, 75% with chronic viral hepatitis and 34% with Child-Pugh B or C] were included (Table 1). In 71% (n=94) of cases the endoscopies were performed for screening of gastro-esophageal varices. The prevalence of esophageal varices and high-risk esophageal varices were 59% (n=79) and 29% (n=39), respectively. All patients with presence of red wale marks (n=14) had large esophageal varices and 17% (n=23) of sample had band ligation sequelae.

Accuracy of transnasal GIE

The diagnostic performance of transnasal ultrathin GIE was estimated using the consensus of two endoscopists for endoscopic findings of conventional GIE as the reference. Transnasal ultrathin GIE yielded sensitivities and specificities of 94% [95%CI 88-99] and 89% [81-97] for presence of esophageal varices and 90% [80-99] and 90% [85-96], respectively for presence of high-risk varices. A very good performance was reported for patients submitted to transnasal ultrathin GIE for screening of esophageal varices (Se=92% [85-99] / Sp=91% [83-99] for presence of esophageal varices and Se=87% [73-99] / Sp=94% [89-99] for high-risk varices). In addition, the accuracy of transnasal ultrathin GIE for detection of esophageal varices (Se=92% [84-99]; Sp=98 [93-100]; PPV=98%; NPV=91%) or high-risk varices [Se=89% [76-99]; Sp=93% [87-99]; PPV=77%; NPV=97%) was satisfactory in patients with Child-Pugh A cirrhosis (n=88). Similar results were observed for detection of high-risk varices in patients with decompensated cirrhosis (Se=90% [77-100]; Sp=84% [70-98]; PPV=82%; NPV=91%). Despite an excellent Se (97% [91-100]), this sub-group had lower Sp (62% [35-88]) for detection of esophageal varices. Table 2 summarizes

the diagnostic performance of transnasal ultrathin GIE compared to conventional gastrointestinal endoscopy by two experienced endoscopists.

Interobserver agreement for transnasal and conventional GIE

Interobserver agreement of transnasal and conventional GIEs for presence of esophageal and high-risk esophageal varices were assessed between the random video evaluations of two blinded endoscopists. Considering the transnasal ultrathin GIE, the k values (SE) for presence of esophageal varices, high-risk varices and band ligation sequelae were 0.83 (0.09), 0.65 (0.08) and 0.89 (0.09), respectively. Interobserver agreement was higher in the screening group (n=94) [k=0.89 (0.10) for presence of esophageal varices and k=0.72 (0.10) for high-risk varices] compared to patients submitted to GIE for surveillance (n=39) [k=0.60 (0.15) for presence of esophageal varices and k=0.49 (0.15) for high-risk varices]. Regarding to the conventional GIE, agreement was satisfactory for presence of esophageal varices [k=0.86 (0.09)], high-risk varices [k=0.63 (0.09)] and band ligation sequelae [k=0.74 (0.08)]. The concordance between endoscopists were slightly lower in the surveillance setting compared to screening for both procedures. In addition, interobserver agreement for detection of esophageal varices and high-risk varices of transnasal and conventional GIE were similar according to Child-Pugh classification. Table 3 summarizes the prevalence of gastrointestinal findings and interobserver agreement (k values) of transnasal and conventional GIE.

Feasibility and safety of transanasal GIE

Transnasal and conventional GIEs were completed in all included patients. The proportion of minor cardiopulmonary adverse events, such as hypoxemia (22% vs 1%; $p<0.0001$) and hypotension (14% vs 3%; $p < 0.0001$), was significantly higher in

conventional compared to transnasal ultrathin GIE. None of the patients needed oxygen supplementation during transnasal ultrathin GIE and oxygen saturation before and after the endoscopy were similar (p=0.568). On the other hand, in conventional GIE oxygen saturation was significantly lower post-procedure compared to baseline (p=0.0011) and 23% of patients needed oxygen supplementation. Patients had higher mean blood pressure (p=0.044) and higher heart rate after transnasal (p=0.0001) compared to before transnasal ultrathin GIE. After conventional GIE, mean blood pressure [91mmHg (range; 51-124) vs 98mmHg (59-132); p<0.0001] and heart rate [75 beats/minute (47-130) vs 78 beats/minute (49-173); p=0.0281] were significantly lower when compared to before the procedure. The prevalence of at least one minor adverse event was significantly lower in transnasal compared to conventional GIE (8% vs 33%; p<0.0001) (Table 4). No major adverse events were observed during both procedures, a single patient did not tolerate nasal introduction of ultrathin endoscopy and another subject had a self-limited epistaxis after the transnasal ultrathin GIE.

Discussion

To the best of our knowledge, this is the largest study that evaluated the accuracy and interobserver agreement of unsedated transnasal ultrathin endoscopy for the detection of esophageal varices in patients with cirrhosis. Our findings highlighted the excellent accuracy of this method to detect esophageal varices and to identify high-risk varices compared to conventional GIE, as well as its high interobserver agreement for endoscopic findings between blinded endoscopists. In addition, transnasal ultrathin GIE was safe, well tolerated and had high sensitivities to identifying esophageal varices regardless of the severity of cirrhosis.

Some studies have been describing high sensitivities and specificities of small-caliber or ultrathin GIE for identifying esophageal varices in cirrhotic patients (Table 5).[10,11,15-17] However, these limited sample size studies have used different technologies and distinct tube insertion routes. The present study reported similar results for detecting esophageal varices using a transnasal ultrathin gastroscope in unsedated patients with cirrhosis (Table 4).

In a sensitivity analysis, the accuracy remains satisfactory regardless of the indication of the procedure (screening or surveillance) and the severity of liver disease (Table 2). The detection of high-risk varices, characterized by large size and/or red-wale marks, represents anincreased risk for variceal bleeding[18] and lead to indication of pharmacological treatment or endoscopic band ligation to prevent future adverse events.[3] The present study confirmed the high accuracy of the transnasal ultrathin endoscopy for identifying high-risk varices. Most cases of discordance between ultrathin and conventional GIE were related to overestimation of presence of esophageal varices (false-positive) by the transnasal endoscopy.

A single large study in the United States of America reported a satisfactory interobserver agreement and high accuracy for detecting high-risk varices by small-caliber endoscopy compared to conventional GIE in patients with cirrhosis (n=115; 71% Child-Pugh B/C). However, the peroral route was used in both types of endoscopy and all patients underwent conscious sedation in this study, challenging the validation of these results for transnasal endoscopy in unsedated patients.[11]

Promising results were described by Huynh et al in 48 Australian unsedated cirrhotic patients (79% Child-Pugh A) using a peroral ultrathin disposable gastroscope.[16] However, the technology used by those authors is slightly different from that used in our study: their device

consists of a disposable probe with capacity for insufflation and it stills a proof-of-concept for upper endoscopic examination in Asia.[17] These results reinforced the feasibility of ultrathin or small-caliber endoscopes GIE for detection of esophageal varices and the need to perform further studies to validate this method for clinical-practice.

Two small-sample size studies have evaluated the interobserver agreement of ultrathin endoscopies in the presence of cirrhosis.[15,16]Our results were aligned with previous publications reporting an excellent (k=0.83) interobserver agreement for detection of esophageal varices in a higher sample-size . In addition, similar results were observed in the setting of variceal screening and in patients with compensated cirrhosis.. On the other hand, variability was higher in endoscopies for surveillance and Child-Pugh B/C sub-group. The higher discordance between endoscopists for detection of high-risk varices was not a phenomenon exclusive to transnasal GIE because similar variability was also observed with conventional GIE. This higher discrepancy in both methods might be rather associated with intrinsic operator variability than related to the type of endoscopic technique.

Transnasal GIE has been described as a safe[19] and well tolerated procedure.[20] However, cardiorespiratory safety in cirrhosis was assessed in only two limited studies.[10,21] Feasibility studies reported that transnasal GIE was completed from 88% to 96% of cases.[22] A multicenter trial confirmed the feasibility, safety and tolerability of transnasal GIE renforcing that this method can be used for screening of esophageal diseases. [23] In our sample, duodenal intubation was achieved in all patients by transnasal GIE and none serious adverse events were observed during or after endoscopies. Despite platelet count lower than 100 $x10^3/mm^3$ in 41% of cases, self-limited epistaxis post-transnasal GIE was registered in a single patient (0.75%). On the other hand, conventional GIE was significantly associated with

higher proportion of hypoxemia and hypotension compared to transnasal GIE. We acknowledge that higher rates of cardiovascular adverse events might be rather associated with use of sedative drugs than the endoscopic technique.[24] The prevalence of adverse events was not different according to severity of liver disease or risk of cardiovascular disease (Supplementary Table S2). Cirrhotic patients might be more susceptible to adverse events related to conscious sedation than general population[25] and hepatic encephalopathy might be triggered by sedative drugs in patients with cirrhosis.[4] In the present study we did not assess minimal hepatic encephalopathy by psychometric and electrophysiologic tests after conventional GIE under conscious sedation. However, there is a good rationale to recommend unsedated transnasal GIE for variceal screening or surveillance, especially in elderly or those patients with more severe liver disease. In a sample of Brazilian patients with cirrhosis, our study confirmed that unsedated transnasal ultrathin GIE for esophageal varices identification is feasible, well-tolerated and safe. This method can be performed without oxygen supplementation or monitoring of vital signs due to low rates of hemodynamic adverse events.

Major limitations of the present study might be the relative low prevalence of Child-Pugh C patients (6%) as well asthe lack of satisfaction survey after procedures and assessment of the intraobserver variability of transnasal ultrathin GIE. The low prevalence of patients with end-stage liver disease might affect drawing conclusion for the use of transnasal GIE in clinical practice for detection of esophageal varices in this sub-group. This fact may be minimized by the relatively high prevalence of high-risk varices (29%) in our sample confirmed by the consensus meeting between the two experienced endoscopists on the conventional GIE. Another potential criticism might be quality image of transnasal endoscopy. However, image quality of transnasal seems to be similar to standard caliber

endoscopes. [26,27] In addition, we used the same processor (Fujinon® EPX-4400, Tokyo, Japan) in all procedures to minimize the risk of bias and very few patients (<2%) were excluded due to inadequate image quality (Figure 1).

Our major strengths were the sample size, the design of the study and the fact that we assessed the interobserver variability of transnasal GIE.. We prospectively included 133 patients whom screening or surveillance of esophageal varices was indicated and both endoscopic procedures were performed and video-recorded by a single endoscopist (ECCF) at the same day. Anonymous videos from endoscopic procedures were randomly assessed by two experienced endoscopists (LM and RAPG) who were blinded for clinical data and the gold standard for endoscopic findings was defined in a consensus by re-evaluation of video-files from conventional GIE.

In conclusion, transnasal ultrathin endoscopy without sedation is reliable, safe and accurate for identification of esophageal varices in patients with cirrhosis regardless of severity of liver disease. Further studies, must be performed to analyze cost-effectiveness of transnasal GIE compared to the current standard-of-care. However, unsedated transnasal GIE may be recommended for patients more susceptible to adverse events related to sedative drugs and those with decompensated liver disease.

References

1. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. *J Hepatol*. 2008; 48 Suppl 1: S68-92.

2. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med.* 2010; 362: 823-832.

3. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015; 63: 743-752.

4. Haq MM, Faisal N, Khalil A, Haqqi SA, Shaikh H, Arain N. Midazolam for sedation during diagnostic or therapeutic upper gastrointestinal endoscopy in cirrhotic patients. *Eur J Gastroenterol Hepatol*. 2012; 24: 1214-1218.

5. Shaker R. Unsedated trans-nasal pharyngoesophagogastroduodenoscopy (T-EGD): technique. *Gastrointest Endosc.* 1994; 40: 346-348.

6. Crews NR, Gorospe EC, Johnson ML, Wong Kee Song LM, Katzka DA, Iyer PG. Comparative quality assessment of esophageal examination with transnasal and sedated endoscopy. *Endosc Int Open*. 2017; 5: E340-E44.

7. Darwin P, Zangara J, Heller T, Haluszka O, Laurin J. Unsedated esophagoscopy for the diagnosis of esophageal varices in patients with cirrhosis. *Endoscopy*. 2000; 32: 971-973.

8. Saeian K, Staff D, Knox J, et al. Unsedated transnasal endoscopy: a new technique for accurately detecting and grading esophageal varices in cirrhotic patients. *Am J Gastroenterol.* 2002; 97: 2246-2249.

9. Madhotra R, Mokhashi M, Willner I, Hawes RH, Reuben A. Prospective evaluation of a 3.1-mm battery-powered esophagoscope in screening for esophageal varices in cirrhotic patients. *Am J Gastroenterol.* 2003; 98: 807-812.

10. Choe WH, Kim JH, Ko SY, et al. Comparison of transnasal small-caliber vs. peroral conventional esophagogastroduodenoscopy for evaluating varices in unsedated cirrhotic patients. *Endoscopy.* 2011; 43: 649-656.

11. Pungpapong S, Keaveny A, Raimondo M, et al. Accuracy and interobserver agreement of small-caliber vs. conventional esophagogastroduodenoscopy for evaluating esophageal varices. *Endoscopy.* 2007; 39: 673-680.

12. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology.* 2007; 46: 922-938.

13. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform* 2014; 48: 193-204.

14. Pu K, Shi JH, Wang X, et al. Diagnostic accuracy of transient elastography (FibroScan) in detection of esophageal varices in patients with cirrhosis: A meta-analysis. *World J Gastroenterol.* 2017; 23: 345-356.

15. Aedo MR, Zavala-Gonzalez MA, Meixueiro-Daza A, Remes-Troche JM. Accuracy of transnasal endoscopy with a disposable esophagoscope compared to conventional endoscopy. *World J Gastrointest Endosc.* 2014; 6: 128-136.

16. Huynh DK, Toscano L, Phan VA, Ow TW, Schoeman M, Nguyen NQ. Ultrathin disposable gastroscope for screening and surveillance of gastroesophageal varices in patients with liver cirrhosis: a prospective comparative study. *Gastrointest Endosc.* 2017; 85: 1212-1217.

17. Sami SS, Ragunath K, Wilkes EA, et al. The detection of oesophageal varices using a novel, disposable, probe-based transnasal endoscope: a prospective diagnostic pilot study. *Liver Int.* 2016; 36: 1639-1648.

18. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology.* 1995; 22: 332-354.

19. Yagi J, Adachi K, Arima N, et al. A prospective randomized comparative study on the safety and tolerability of transnasal esophagogastroduodenoscopy. *Endoscopy.* 2005; 37: 1226-1231.

20. Alexandridis E, Inglis S, McAvoy NC, et al. Randomised clinical study: comparison of acceptability, patient tolerance, cardiac stress and endoscopic views in transnasal and transoral endoscopy under local anaesthetic. *Aliment Pharmacol Ther.* 2014; 40: 467-476.

21. Chung JW, Park S, Chung MJ, et al. A novel disposable, transnasal esophagoscope: a pilot trial of feasibility, safety, and tolerance. *Endoscopy.* 2012; 44: 206-209.

22. Preiss C, Charton JP, Schumacher B, Neuhaus H. A randomized trial of unsedated transnasal small-caliber esophagogastroduodenoscopy (EGD) versus peroral small-caliber EGD versus conventional EGD. *Endoscopy.* 2003; 35: 641-646.

23. Peery AF, Hoppo T, Garman KS, et al. Feasibility, safety, acceptability, and yield of office-based, screening transnasal esophagoscopy (with video). *Gastrointest Endosc.* 2012; 75: 945-953.

24. Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc.* 2008; 68: 815-826.

25. Correia LM, Bonilha DQ, Gomes GF, et al. Sedation during upper GI endoscopy in cirrhotic outpatients: a randomized, controlled trial comparing propofol and fentanyl with midazolam and fentanyl. *Gastrointest Endosc.* 2011; 73: 45-51.

26. Ai ZL, Lan CH, Fan LL, et al. Unsedated transnasal upper gastrointestinal endoscopy has favorable diagnostic effectiveness, cardiopulmonary safety, and patient satisfaction compared with conventional or sedated endoscopy. *Surg Endosc*. 2012; 26: 3565-3572.

27. Shariff MK, Bird-Lieberman EL, O'Donovan M, et al. Randomized crossover study comparing efficacy of transnasal endoscopy with that of standard endoscopy to detect Barrett's esophagus. *Gastrointest Endosc*. 2012; 75: 954-961.

Table 1. Clinical and demographic characteristics of patients with cirrhosis submitted to transnasal and conventional gastrointestinal endoscopies

	All (n=133)
Male gender [a]	64 (48)
Age, years [b]	60 (±5)
Etiology [a]	
HCV	95 (71)
HBV	5 (4)
Alcoholic liver disease	16 (12)
Others	17 (13)
Indication of endoscopy [a]	
Variceal screening	94 (71)
Primary surveillance	10 (8)
Secondary surveillance	29 (21)
Severity of disease	
Child-Pugh score [b]	5 (5-7)
Child-Pugh B/C [a]	45 (34)
MELD score [b]	9 (7-13)
MELD score > 20 [a]	4 (3)
Co-morbidities [a]	
Type-2 diabetes	41 (31)
Blood hypertension	46 (35)
History of hepatocellular carcinoma	4 (3)
Biochemistry [b]	
Total bilirubin, mg/dL	1.1 (0.8-2.0)
Albumin, mg/dL	3.8 (3.2-4.2)
INR	1.2 (1.1-1.3)
Platelet count, $x10^3/mm^3$	115 (82-158)
Creatinin, mg/dL	0.9 (0.8-1.0)

Data expressed as [a] n (%) and [b] median (interquartile range); HCV, hepatits C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; INR, international ratio.

Table 2. Diagnostic performance of transnasal gastrointestinal endoscopy by blinded endoscopist compared to conventional gastrointestinal endoscopy by two experienced endoscopists

	Prevalence, n (%)	Se % [95%CI]	Sp % [95%CI]	PPV,%	NPV,%	LR+	CC, %	FN, n (%)	FP, n (%)
All patients (n=133)									
Esophageal varices	79 (59)	94 [88-99]	89 [81-97]	93	91	8.4	92	5 (6)	6 (11)
High-Risk EV	39 (29)	90 [80-99]	90 [85-96]	80	96	9.4	90	4 (10)	9 (10)
Variceal screening (n=94)									
Esophageal varices	52 (55)	92 [85-99]	91 [83-99]	92	91	10.4	92	4 (8)	4 (9)
High-Risk EV	23 (25)	87 [73-99]	94 [89-99]	83	96	15.4	93	3 (13)	4 (6)
Surveillance (n=39)									
High-Risk EV	27 (69)	94 [82-100]	78 [61-95]	75	95	4.3	85	1 (6)	5 (12)
Band ligation sequelae	16 (41)	82 [66-98]	94 [83-100]	95	80	13.9	87	4 (18)	1 (6)
Child-Pugh A (n=88)									
Esophageal varices	47 (53)	92 [84-99]	98 [93-100]	98	91	37.5	94	4 (9)	1 (2)
High-Risk EV	19 (22)	89 [76-99]	93 [87-99]	77	97	12.3	92	2 (11)	5 (7)
Child-Pugh B/C (n=45)									
Esophageal varices	32 (71)	97 [91-100]	62 [35-88]	86	89	2.5	87	1 (3)	5 (38)
High-Risk EV	20 (44)	90 [77-100]	84 [70-98]	82	91	5.6	87	2 (10)	4 (16)

CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; CC, correctly classified; FN, false negative; FP, false positive; EV, esophageal varices

Table 3. Interobserver agreement of transnasal and conventional gastrointestinal endoscopies for detection of esophageal varices in patients with cirrhosis (n=133)

	Transnasal ultrathin GI endoscopy			Conventional GI endoscopy		
	Prevalence		Agreement	Prevalence		Agreement
	First examinator	Second examinator	Kappa (SE)	First examinator	Second examinator	Kappa (SE)
All patients (n=133)						
Esophageal varices	75 (56)	80 (60)	0.83 (0.09)	81 (61)	82 (62)	0.86 (0.09)
High-Risk EV	29 (22)	44 (33)	0.65 (0.08)	35 (26)	41 (31)	0.63 (0.09)
Band ligation sequelae	24 (18)	20 (15)	0.89 (0.09)	30 (23)	21 (16)	0.74 (0.08)
Variceal screening (n=94)						
Esophageal varices	48 (51)	49 (52)	0.89 (0.10)	54 (58)	54 (58)	0.91 (0.10)
High-Risk EV	17 (18)	24 (26)	0.72 (0.10)	21 (22)	23 (25)	0.64 (0.10)
Surveillance (n=39)						
Esophageal varices	27 (69)	31 (79)	0.60 (0.15)	27 (69)	28 (71)	0.69 (0.16)
High-Risk EV	12 (31)	20 (51)	0.49 (0.15)	14 (36)	18 (46)	0.58 (0.16)
Band ligation sequelae	23 (59)	19 (49)	0.80 (0.16)	24 (62)	19 (49)	0.75 (0.16)
Child-Pugh A (n=88)						
Esophageal varices	42 (48)	44 (50)	0.86 (0.11)	48 (55)	48 (55)	0.91 (0.11)
High-Risk EV	14 (16)	22 (25)	0.66 (0.10)	18 (21)	18 (21)	0.65 (0.11)
Child-Pugh B/C (n=45)						
Esophageal varices	33 (73)	36 (80)	0.69 (0.15)	33 (73)	34 (76)	0.71 (0.15)
High-Risk EV	15 (33)	22 (49)	0.60 (0.14)	17 (38)	23 (51)	0.56 (0.14)

GI, gastrointestinal; EV, esophageal varices; SE, standard error

Table 4. Safety of transnasal ultrathin and conventional gastrointestinal endoscopies

	Transnasal ultrathin GIE	Conventional GIE	p value
At least one adverse event, n (%)	11 (8)	44 (33)	< 0.0001
Necessity of oxygen supplementation, n (%)	0 (0)	31 (23)	<0.0001
Oxygen saturation			
Oxygen saturation before GIE [a]	98 [87-100]	96 [90-100]	< 0.0001
Lowest oxygen saturation during GIE [a]	97 [87-100]	91 [56-100]	< 0.0001
Oxygen saturation after GIE [a]	97 [90-100]	95 [83-100]	< 0.0001
p value for before vs after GIE	0.568	0.0011	
Hypoxemia, n (%)	1 (1)	29 (22)	< 0.0001
Blood pressure			
Mean blood pressure before GIE [a]	101 [60-142]	98 [59-132]	0.0091
Lowest mean blood pressure during GIE [a]	108 [66-152]	93 [43-143]	< 0.0001
Mean blood pressure after GIE [a]	106 [67-431]	91 [51-124]	<0.0001
p value for before vs after GIE	0.044	<0.0001	
Hypotension, n (%)	4 (3)	19 (14)	0.0011
Pulse			
Heart rate before GIE [a]	72 [48-132]	78 [49-173]	0.0094
Lowest heart rate during GIE [a]	82 [48-167]	76 [49-126]	0.0001
Heart rate after GIE [a]	78 [48-160]	75 [47-130]	0.0074
p value for before vs after GIE	0.0001	0.0281	
Bradycardia, n (%)	7 (5)	13 (10)	0.110
Sedation			
Midazolam, mg [b]	-	4 [4-5]	NA
Meperidine, mg [b]	-	40 [35-50]	NA
Necessity of propofol, n (%)	-	41 (31)	NA
Propofol, mg [b]	-	40 [30-50]	NA
Necessity of sedative reversion, n (%)	-	2 (2)	NA

Data expressed as [a] mean [range] and [b] median [interquartile range]; continuous and discrete variables compared by paired *t* tests and Chi-square, respectively. GIE, gastrointestinal endoscopy

Table 5. Studies that evaluated the diagnostic performance of small-caliber endoscopy for detection of esophageal varices in patients with cirrhosis

Authors	Year	Country	N	Route	Equipament	Child-Pugh A/B/C, n	Esophageal varices			High-risk EV		
							Prevalence	Se	Sp	Prevalence	Se	Sp
Saeian et al[9]	2002	USA	15	TN	Ultrathin endoscope (Pentax EG-1540)	NA	67%	100%	100%	-	-	-
Madhotra et al[10]	2003	USA	28	PO	Ultrathin battery-powered endoscope (Olympus XEF-DP)	6/15/7	50%	100%	93%	-	-	-
Pungpapong et al[12]	2007	USA	115	PO	Small−caliber endoscope (Olympus GIF−N180)	33/47/35	-	-	-	29%	100%	95%
Choe et al[11]	2011	Korea	84	TN	Small-caliber endoscope (Olympus GIFN260)	40/32/12	67%	100%	93%	-	-	-
Aedo et al[14]†	2014	Mexico	23	TN	Disposable probe (E.G. Scan I - IntroMedic)	NA	96%	95%	97%	-	-	-
Sami et al[16]	2016	UK	45	TN	Disposable probe (E.G. Scan II- IntroMedic)	34/10/01	49%	82%	78%	-	-	-
Huynh et al[15]	2017	Australia	48	PO	Disposable probe (E.G. Scan II- IntroMedic)	35/13/00	54%	96%	86%	21%	90%	100%
Present study	**2017**	**Brazil**	**133**	**TN**	**Ultrathin endoscope (Fujinon EG-530N)**	**88/37/8**	**59%**	**94%**	**89%**	**29%**	**90%**	**90%**

† study including n=96 participants who 24% (n=23) were patients with cirrhosis; EV, esophageal varices; TN, transnasal; PO, peroral; NA, not available; Se, sensitivity; Sp, specificity. Transnasal endoscopies were performed without sedation in all studies except for Pungpapong et al.

Figure legend

Flow-chart of inclusion of patients with cirrhosis referred for screening or surveillance of esophageal varices