

# Outcome of patients undergoing early versus late endoscopic intervention for acute oesophageal variceal bleeding at Air Force Hospital, Egypt. A population based cohort study

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## ABSTRACT

**Background:** Whether on-call gastroenterologists should perform emergency endoscopic treatment or delay endoscopy the next day has not been investigated. This study aims to investigate the effect of timing of endoscopy on patients with acute esophageal variceal bleeding. **Patients and Methods:** We included 167 patients with acute variceal bleeding in the gastroenterology unit of the air force hospital, Cairo, Egypt, from 15 January till 15 July 2010. Endoscopy was scheduled once the patient's hemodynamics permitted. Time from admission to endoscopy was recorded. Patients were stratified into 2 groups: **Early endoscopy:** when done  $\leq 12$  hours and **late endoscopy:** when done  $> 12$  hours. Patients were followed up for 42 days. **Results:** The study included 102 males (61.1%) and 65 females (38.9%) (mean age  $54 \pm 11$  years). 151 patients received endoscopic treatment. Early endoscopy group included 85 patients (56.3%), and the late endoscopy group included 66 patients (43.7%) ( $p = 0.14$ ). Early endoscopy patients were transfused a mean of  $2.9 (\pm 1.8)$  units of blood versus  $4.3 (\pm 0.14)$  units in the late endoscopy patients  $p = 0.001$ . Mean hospital stay was  $7.1 (\pm 3.3)$  days versus  $9.3 (\pm 4.6)$  days in the early and late groups respectively  $p: 0.001$ . 5-day mortality was reported in 6 ( $\pm 7$ ) cases in the early endoscopy group and 23 ( $\pm 34.8$ ) cases in the late endoscopy group  $p: 0.001$ . **Conclusion:** Early endoscopic intervention for patients with acute variceal bleeding is associated with a more favorable

outcome in terms of morbidity and mortality. On call gastroenterologists should comply with the 12-hour period rather than delaying cirrhotic patients with acute variceal bleeding to the following day.

## KEYWORDS

Bleeding Varices; Early Endoscopy; Late Endoscopy

## 1. INTRODUCTION

Portal hypertension is a common disease among Egyptian patients due to schistosomiasis and the hepatitis C virus endemicity [1-4]. The timing of endoscopic intervention for patients presenting with acute variceal bleeding has not been properly evaluated. The near equivalence in efficacy of pharmacological treatment and endoscopy in achieving initial hemostasis, reducing mortality and re-bleeding rates raised the question of whether on-call gastroenterologists should perform emergency endoscopic treatment in the middle of the night or start pharmacological treatment and delay endoscopy until the optimal patient and working conditions the next morning? Some studies have advocated delaying endoscopic treatment until the next morning as the most reasonable practical approach [5]. However, the AASLD guidelines recommended performing upper endoscopy within 12 hours of variceal hemorrhage, both for diagnosis and management, either with endoscopic band ligation "EBL" or endoscopic injection sclerotherapy EIS [6]. In Baveno IV, it was clear that endoscopy should be performed as soon as possible after admission (within 12 hrs), especially in patients with clinically significant

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bleeding or in patients with features suggesting cirrhosis [7].

### 1.1. Aim of the Work

This study aims to investigate the effect of timing of endoscopic intervention in patients presenting with acute esophageal variceal bleeding.

### 1.2. Patients and Methods

This study was approved by the Hepato-gastroenterology Department and the Research Board of Cairo University. It included 167 patients with acute bleeding from esophageal varices. Patients were admitted to Gastroenterology Unit of Air force Hospital, Cairo, Egypt, during the period from 15 January till 15 July 2010. Patients with bleeding gastric varices, bleeding portal hypertensive gastropathy, gastritis, duodenitis and/or duodenal ulcers were not included in the study as well as patients with hepatocellular carcinoma or those who developed hepatic coma prior to hospital admission.

All patients were resuscitated after relevant history taking and clinical examination. Blood was transfused according to the severity of bleeding and hemodynamic status, with a transfusion target of hematocrit 24% or hemoglobin 8 g/dl. Octreotide was started whenever indicated in a dose of 50 µg IV bolus, followed by continuous infusion of 50 µg/hr for 2 - 5 days. Further assessment was done including laboratory investigations and imaging studies. Endoscopy session was scheduled once the patient's hemodynamics improved. Time from admission (time zero) to endoscopic treatment was recorded. Upper endoscopy was done after both written and informed consent. Varices were assigned grades according to their shape and size: grade F1, small straight veins; grade F2, slightly enlarged tortuous veins occupying less than one-third of the esophageal lumen; and grade F3, large coil-shaped varices that occupied more than one-third of the esophageal lumen [8].

All patients were planned for EBL using the Saeed multi-band ligator, manufactured by the Wilson-Cook Medical GI endoscopy company, or EIS using 5% ethanolamine oleate depending on technical feasibility. Patients with circumstantial evidence to have esophageal variceal bleeding (e.g. chronic liver disease patients with previous documented esophageal varices) who died few hours after admission (*i.e.* before endoscopy) were included as esophageal variceal bleeding. Time was calculated from admission to endoscopy and patients were stratified into 2 groups:

- Early endoscopy: when done  $\leq$  12 hours;
- Late endoscopy: when done  $>$  12 hours.

The assessment for treatment side-effects was performed daily during hospital stay. All basic investiga-

tions were repeated 5 days after acute bleeding episode and/or when needed (CBC, liver function tests and kidney function test). All available patients were followed up for 42 days for clinical assessment, variceal re-bleeding, hepatic de-compensation, and laboratory investigations.

### 1.3. Definitions of Applied Terms

- **The acute (Index) bleeding episode:** is represented by an interval of 48 hours from time zero (time of admission to the first hospital) with no evidence of clinically significant bleeding between 24 and 48 hours [9].
- **Esophageal varices were considered as the source of bleeding** by visualizing bleeding varix or by the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding [9].
- **Failure to control active bleeding** Failure to control active bleeding was considered according to the **UK guidelines** as transfusion requirement of 4 units or more and inability to achieve an increase in systolic blood pressure by 20 mm Hg or to 70 mm Hg or more, and/or inability to achieve a pulse rate reduction to less than 100 beat/min or a reduction of 20 beat/min from baseline pulse rate (within the first six hours). Or the occurrence of haematemesis from the six hour point, reduction in blood pressure of more than 20 mm Hg from the six hour point and/or increase in pulse rate of more than 20 beat/min from the six hour point on two consecutive readings an hour apart, transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the haematocrit to above 27%, or haemoglobin to above 9 g/dl [10].
- **Early re-bleeding:** was considered according to **de Franchis** [9] as the occurrence of new haematemesis or melena after a period of 24 hours or more of stable vital signs and hematocrit/hemoglobin following an episode of acute bleeding within the first 5 days of admission.
- **Late re-bleeding:** was considered when there was recurrent bleeding between 5 - 42 days [11].
- **Bleeding-related mortality:** was considered whenever death was reported during the period of six weeks from time zero, regardless of the mode of death (as stated by De Franchis [7]). It can be divided into mortality within 5 days and within 42 days [11].
- **The severity of bleeding was considered as:** mild when pulse rate  $<$ 100/min., orthostatic hypotension or cold extremities, moderate when pulse rate 100 - 120 beats/min. with restlessness or severe when pulse rate  $>$ 120 beats/min, systolic blood pressure  $<$ 60 mmHg, severe pallor or oliguria [12].

- **Stoppage of bleeding:** was considered when there was no hematemesis, stable hemoglobin concentration without blood transfusions, stable hemodynamic conditions at the beginning of the first 24-hour interval from time zero [7,9,13-15].
- Patients' data were tabulated and processed using SPSS (10.0) statistical package. Quantitative variables were expressed by means and standard deviation. While qualitative data were expressed by frequency and percent. Qualitative variables were analyzed using Chi-square or Fisher's exact test when appropriate. Quantitative variables were analyzed using student's T-test or Friedmann's test when appropriate. In all tests P value was significant when <0.05. Statistical analysis was done in by a specialized office.

## 2. RESULT

This study included 167 patients with acute esophageal variceal bleeding (first or recurrent attack) who were admitted to Air Force Hospital, from January to July 2010. They were 102 males (61.1%) and 65 females (38.9%) with a mean age of  $54 \pm 11$  years (range of 32 - 68 years). Most of the patients were Child class C (53.2 %) while 38.9% were Child class B and only 7.8% were Child A (38.9%). Sixteen patients died before endoscopy due to failure to control the acute bleeding episode. The remaining 151 patients received endoscopic treatment. The base line features of the studied patients are shown in **Table 1**, stratification of patients according to the time of intervention is shown in **Figure 1**. **Figure 2** shows endoscopic sclerotherapy for bleeding oesophageal varices.

The characteristics of patients according to the time of intervention are shown in **Table 2**. Patients undergoing late endoscopy had a significantly lower Hemoglobin at day 1 and 5, a larger number of transfused packed RBCs, with a longer duration of hospital stay and worse outcome in terms of early and late re-bleeding as well as development of spontaneous bacterial peritonitis and mortality. Both groups were comparable regarding the severity of bleeding episodes, mild variceal bleeding was seen in 41 (48.2%) patients in the early endoscopy group versus 19 (28.8%) patients in the late endoscopy group ( $p = 0.73$ ) (**Table 2**, **Figure 3**).

## 3. DISCUSSION

Bleeding from esophageal varices is a life-threatening complication of portal hypertension which accounts for most cirrhosis-related mortalities [16]. Mortality from variceal bleeding has decreased substantially from 42% as reported by Graham and Smith [17] to around 20% as a result of more effective therapies [18,19].

**Table 1.** Base-line characteristics of the studied (151) patients.

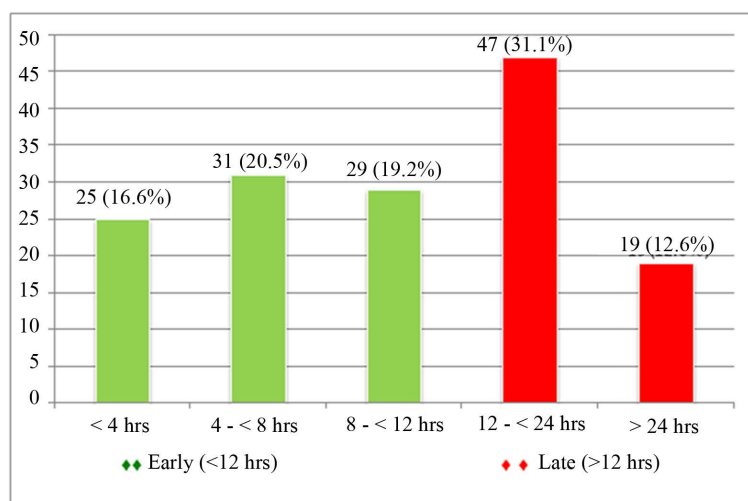
|   | No/Mean | SD/%       | P    |
|---|---------|------------|------|
| <b>History of Previous bleeding</b>               |         |            |      |
| Present   | 81      | 70.4%      | 0.05 |
| Absent  | 34      | 29.5%      |      |
| <b>Grade of Varices</b>                           |         |            |      |
| F1  | 12      | 7.9%       |      |
| F2  | 70      | 46.3%      | 0.04 |
| F3  | 69      | 45.6%      |      |
| <b>Severity of bleeding</b>                       |         |            |      |
| Mild  | 60      | 39.7%      |      |
| Moderate  | 63      | 41.7%      | 0.04 |
| Severe  | 28      | 18.5%      |      |
| <b>Time from admission to stabilization (hrs)</b> | 9.5     | $\pm 6.5$  |      |
| <b>Mean hemoglobin (g/dl)</b>                     |         |            |      |
| Day 1   | 8.4     | $\pm 0.36$ |      |
| Day 5   | 8.6     | $\pm 0.31$ | 0.1  |
| <b>Units of packed RBCs</b>                       | 3.9     | $\pm 1.2$  |      |
| <b>Timing of Endoscopy</b>                        |         |            |      |
| Early ( $\leq 12$ hrs)                            | 85      | 56.3%      |      |
| Late ( $> 12$ hrs)                                | 66      | 43.7%      | 0.14 |
| <b>Hospital stay in days</b>                      | 9.1     | $\pm 1.9$  |      |

Endoscopic therapy is an integral component of the management of acute variceal bleeding [6,18]. Thriving to optimize endotherapy in bleeding patients has been continually progressing. This has evolved at different levels, first improving the general condition of the patient to undergo the procedure, second, optimizing the type of the procedure, the practiced technique as well as the post procedural care.

One of the debatable, not-yet solved issues is the timing of the procedure. The debate is not only on being early or late, but also on the exact definition of either terms "early" or "late". There are 2 opposing opinions, the first states that with the near-equivalence of pharmacotherapy to endotherapy (in terms of efficacy, mortality and re-bleeding), it is better to not to call for emergency intervention and delay endoscopy for the following day when the patients' conditions and the working set up are more favorable [5,20]. The second debate advocates that early intervention would improve mortality and decrease morbidity after adequate control of the bleeding episode [21].

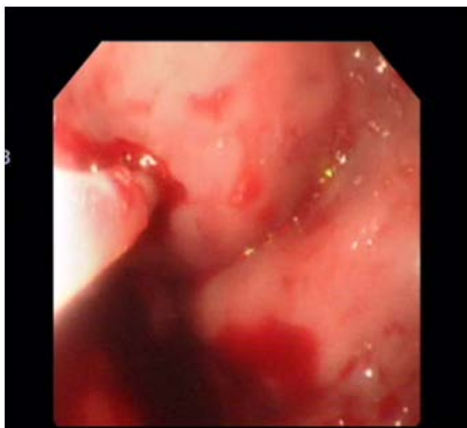
**Table 2.** Characteristics of patients according to the timing of intervention.

| Variables                                   | Early endoscopy |      | Late endoscopy |      | P     |
|---|-----------------|------|----------------|------|-------|
|   | No/Mean         | %/SD | No/Mean        | %/SD |       |
| <b>Cases of early versus late endoscopy</b> | 85              | 56.3 | 66             | 43.7 | 0.14  |
| <b>Severity of bleeding</b>                 |                 |      |                |      |       |
| Mild  | 41              | 48.2 | 19             | 28.8 | 0.73  |
| Moderate                                    | 31              | 36.5 | 32             | 48.5 |       |
| Severe                                      | 13              | 15.3 | 15             | 22.7 |       |
| <b>Child Pugh class A</b>                   | 9               | 11   | 4              | 6    | 0.06  |
| <b>Child Pugh class B</b>                   | 47              | 55   | 15             | 23   |       |
| <b>Child Pugh class C</b>                   | 29              | 34   | 47             | 71   |       |
| <b>Serum creatinine &lt;1.7 mg/dl</b>       | 54              | 63   | 34             | 51   | 0.02  |
| <b>Mean Hemoglobin at Day 1 (gm/dl)</b>     | 8.3             | 0.29 | 7.9            | 0.54 | 0.03  |
| <b>Mean Hemoglobin at Day 5 (gm/dl)</b>     | 8.8             | 0.43 | 8.4            | 0.72 | 0.001 |
| <b>Units of transfused packed RBCs</b>      | 2.9             | 1.8  | 4.3            | 0.14 | 0.001 |
| <b>Days in hospital</b>                     | 7.1             | 3.3  | 9.3            | 4.6  | 0.001 |
| <b>Managed by sclerotherapy</b>             | 35              | 41.2 | 23             | 34.8 | 0.142 |
| <b>Managed by band ligation</b>             | 50              | 58.8 | 43             | 65.2 |       |
| <b>Early re-bleeding</b>                    | 14              | 16.5 | 16             | 24.2 | 0.012 |
| <b>Late re-bleeding</b>                     | 5               | 5.8  | 8              | 12.1 | 0.05  |
| <b>SBP</b>                                  | 6               | 7.1  | 11             | 16.7 | 0.005 |
| <b>5 days mortality</b>                     | 6               | 7    | 23             | 34.8 | 0.001 |
| <b>Mortality between 5 - 42 days</b>        | 11              | 12.9 | 12             | 18.2 | 0.05  |

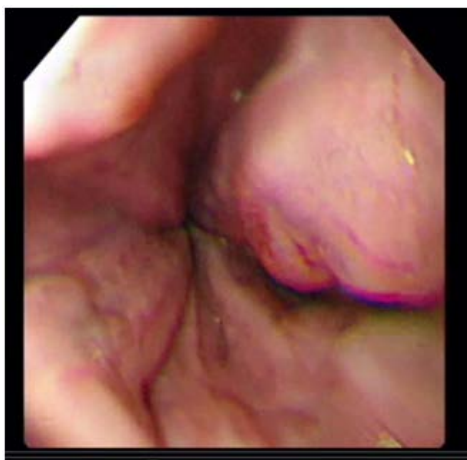
**Figure 1.** Classification of patients according to timing of endoscopic intervention (p NS).

Villanueva *et al.*, [11] and Banares *et al.*, [22] preferred therapeutic endoscopy <12 hours after admission; while Bosch *et al.* preferred endoscopy within 6 hours [23]. Also, AASLD guidelines for management of acute

vaiceal bleeding recommend performing endoscopy within 12 hours [6]. Baveno IV stated that, endoscopy should be performed as soon as possible after admission (within 12 h), especially in patients with clinically



**Figure 2.** Injection sclerotherapy for bleed varices.



**Figure 3.** Large sized (F3) mild variceal bleeding at the time of endoscopy

significant bleeding or in patients with cirrhosis [7]. Although Sarin and co-workers [24] found no significant difference between early and late endoscopy in terms of mortality, need for surgery or transfusion requirements, it is worth mentioning that their study population included patients with suspected and actual upper GI bleeding without essentially being variceal bleeding. Wysocki and co-workers [25] found in a retrospective analysis that if patients did not receive an early endoscopy, mortality increased from 8.25% to 15.3% in patients with acute variceal bleeding. However, they referred to early endoscopy in this situation as being within 24 hours from hospital admission. It is clear from these data that studies are heterogenous; some have included both variceal and non-variceal bleeding, others didn't reach standardization about the exact studied time.

We believe that in our country, and based on the Egyptian culture, the outcome of patients presenting with acute variceal bleeding is not only dependent on the time of endoscopy as calculated from the onset of hospital

admission. A hidden part of ice-berg exists; this is the time between the onset of bleeding and presentation to the hospital. This requires adequate patient education of the potential risk of variceal bleeding and its impact on morbidity. It also depends on how close is the nearest center to the patient. Since endoscopic service is not provided in all centers the need to transfer the patient to a relatively far specialized center might be needed in some situations and adds to the miscalculations. In our community not all patients agree to perform surveillance endoscopy, although they are well informed about the potential risks and the need for primary prophylaxis of variceal bleeding. This makes the situation perplexed when a first attack of variceal bleeding occurs. While patients presenting with recurrent bleeding are rather trained and experienced about their medical condition and are well aware about which medical center to present to. These 2 examples about one group presenting with a long gap and another presenting with a relatively short gap between the onset of bleeding and the time of hospital admission, makes time zero calculation at the time of admission confusing. Also, patient education about the necessity to report early to the nearest hospital in case of bleeding is highly mandatory and needs to be emphasized.

Another point worth mentioning concerns the study design: Some of the similar studies were randomized, some were retrospective and in some the study design was not clear. This is a population based cohort prospective study. Due to ethical considerations, patients were not randomized to fall in an early or late endoscopy groups, endoscopy was performed whenever the patients' general condition permitted undergoing the procedure, irrespective of time. Later on, patients were sub-grouped according to the exact time they underwent the procedure.

To what extent time altered the outcome of our patients, remained to be investigated. So this study was designed at the Air Force hospital, on 167 patients with acute variceal bleeding. All patients were subjected to combined vasoactive drugs and endoscopic therapy (either EBL or EIS). Patients underwent endoscopy according to the UK guidelines which stated that timing of upper gastrointestinal endoscopy is recommended to be as soon as the patient is hemodynamically stable [10]. This explains why patients in the early endoscopy group had better hemodynamic stability and more reported incidence of mild bleeding attacks as compared to patients among the late endoscopy group.

Patients undergoing early endoscopy had a more favorable outcome than those undergoing late endoscopy in terms of better renal function, less anemia on days 1 and 5, decreased need for transfusion, shortened hospitalization, low liability to both early and late re-bleeding, low susceptibility to peritonitis and improved patients

survival within 5 and 42 days. Cooper *et al.* [26] compared early endoscopy to delayed endoscopy and found that early endoscopy was associated with clinically significant reductions in recurrent bleeding and the need for surgery. Hsu *et al.* [27] found that delayed endoscopy for more than 15 h, high MELD score, failure of the first endoscopy and hematemesis are independent risk factors for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage. According to Rollhauser and Fleischer [28] early endoscopy allows endoscopists to alter the natural course of patients at high risk for recurrent bleeding through the various haemostatic techniques used to reduce the rate of re-bleeding, morbidity as well as mortality.

Cheung *et al.* [20] evaluated the association between the timing of endoscopy and outcomes of stable acute variceal bleeding patients. Outcome comparisons were also performed for three different urgency times (< or = vs. > 4 h, < or = vs. > 8 h, and < or = vs. > 12 h), and found that the time to endoscopy does not appear to be associated with mortality. Again this study included both variceal and non variceal bleeding patients which might explain the discrepancy in results. Similarly, Bjorkman *et al.* [29] didn't show any significant differences in urgent endoscopy (*i.e.* performed within hours of presentation) in terms of patients' outcomes, compared with routine endoscopy. Yan and Lee [5] raised the question of whether on-call gastroenterologists should perform emergency endoscopy in the middle of the night or start pharmacological treatment and delay endoscopy until optimal patient and working condition the next morning? The authors admitted difficulty in answering this question because studies were too heterogenous, however, they assumed that given the similar efficacy for hemostatic control and mortality between pharmacological therapy and endoscopic therapy, it seems reasonable to delay endoscopic treatment until optimal conditions or pharmacological failure occurs. It is worth mentioning that the authors withdrew their statement from only one study that they considered as "truly addressing the issue of timing", this study dated back to 1990 and used only sclerotherapy before the advent of EBL and before the recommendation of routine pharmacotherapy which are known to have altered the outcome of variceal bleeding.

Furthermore, In 2006 Lee [30] explained that the reasons for the lack of a significant impact of early endoscopy in the previous studies (in terms of cost and patients' outcome) by the fact that the decision to perform blood transfusion is often made on admission to hospital before endoscopy and the greatest costs of caring for a patient with bleeding are mostly spent at the pre-endoscopy phase of admission and finally, re-bleeding is determined by the effectiveness of endoscopic therapy rather than by the timing of endoscopy. He added that early endoscopy

(within 24 h) is performed, only because of its potential to improve outcome in the subset of patients who require endoscopic hemostasis, and because it is a routine clinical practice in the US. The conclusions made by Lee cannot fit to our study, this is a prospective study and so all patients were entitled to fit into pre-determined criteria, only patients with variceal bleeding were included, the severity of liver disease as assessed by the Child-Pugh score was comparable among early and late groups, the routine standards of care applied to the patients as blood transfusion and somatostatin infusion were standardized to all cases based on their needs whether in the pre-endoscopic or post endoscopic phase, even the procedure was done by a single endoscopist, the procedure was done whenever the patients' condition permitted without any delay, and although both EBL and EIS were used, both techniques were comparable among early and late groups. Also, in our local protocol there is no role for discharging patients immediately after endoscopy. This leaves no place that relatively low risk patients might have been discharged, or that transfusion or pharmacotherapy were uncontrollably instituted or that there is disparity of outcome of patients' outcome due to multiplicity of the working hand.

Although our study was not designed as a cost-effective analysis, yet it is clear from our data that on call gastroenterologist would save their hospitals not only time but money as well. Endoscopic intervention would definitely intercept the cycle of pouring packed blood units, somatostatin ampoules, bed occupation and consequently a huge hospital bill. This is evidenced by the significantly higher number of transfusion units of blood, longer duration of hospital stay and higher incidence of co-morbidity among patients undergoing late endoscopic intervention. This is can be used as a mirror image of the economic aspects of this condition and so the economic perspective on early treatment of acute variceal bleeding should be emphasized.

#### 4. CONCLUSION

Early endoscopic intervention for patients with acute variceal bleeding is associated with a more favorable outcome in terms of morbidity and mortality on one hand and probably with less expense on the other hand. Since endoscopy mandates patient stabilization as a pre-requisite, rapid patient resuscitation and stabilization immediately after hospital admission are mandatory. Finally, improvement of the prognosis of acute variceal bleeding is reachable and we can do much effort in this way, so when dealing with variceal bleeding and cirrhotic patients, on call gastroenterologists should comply with the 12-hour period rather than delay their patients to the following day.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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