Re: 41836

Timing of upper GI endoscopy does not influence short-term outcomes in patients with acute variceal bleeding

October 15, 2018

Andrzej S Tarnawski
Editors-in-Chief, *World Journal of Gastrotenterology*

Dear Editor,

We appreciate the reviewers' helpful comments and we are pleased to have an opportunity to make this paper to be a better one. We have carried out the revisions according to the reviewers' comments and provided a point-by-point response to all of the reviewers' comments. Changes within the revised manuscript have been highlighted (underlined and in blue).

We hope that our revised manuscript will be acceptable for publication in *World Journal of Gastrotenterology.*

With best regards,

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Responses to the Reviewer A's Comments

1) Comment #1: I read with interest this study by Yoo J-J et al regarding the optimal timing to preform endoscopy in patients presented with acute variceal bleeding. The manuscript is well written, but some changes have to be made in order this paper is ready for publication. Firstly the authors have to describe in more details in which factors the doctors decided not to perform an endoscopy within the first 12 hours.

Response: We appreciate the reviewer's helpful comments. The physician decided to perform endoscopy within the first 12 hours according to the presence of poor prognostic factors such as (1) advanced age, (2) presence of comorbidities such as renal failure, or cardiopulmonary disease, (3) hemodynamic instability, and (4) laboratory abnormalities including coagulopathy, lactic acidosis and anemia. If patients did not exhibit poor clinical factors or they had signs of hepatic encephalopathy more than grade III, delayed endoscopic examination was considered. We described the physician's clinical decision making in more detail as follows.

"Then, the GI specialist determined the timing of the endoscopy, considering each patient's age, presence of comorbidities such as renal failure or cardiopulmonary disease, presence of hepatic encephalopathy, hemodynamic instability, and laboratory abnormalities including anemia, lactic acidosis and coagulopathy. If patients did not exhibit poor clinical factors or they had signs of hepatic encephalopathy more than grade III, delayed endoscopic examination was considered." (page 6, lines 22-28)

2) Comment #2: There is an important finding showing that patients in the non-urgent

endoscopy group had significantly longer in-hospital duration as compared with the urgent-endoscopy group. How the authors explain this difference between the two groups.

Response: Following the reviewer's helpful comments, we revised the discussion section as follows.

"Consistent with previous reports, the length of hospital stay was statistically different between the urgent group and non-urgent group. [10, 28-30] It may be due to more accurate diagnosis and earlier hemostasis of the bleeding source by urgent endoscopy, leading to decrease in the subsequent resource use including the length of stay and total hospitalization costs." (page 13, lines 16-20)

3) Comment #3: In both groups there is significant number of patients having HCC (>50%) and this may be an important difference from other similar studies.

Response: As noted in the reviewer's valid comments, about half of the patients had HCC in our study population. The goal of this study was to investigate the actual aspects of variceal bleeding in the real clinical practice setting, and acute decompensation induced by variceal bleeding occurs frequently in patients with HCC. Therefore, patients with HCC were not excluded in this study. In addition, previous studies also have included HCC patients in the assessment of acute variceal bleeding.[1-3] As the concomitant presence of HCC may significantly affect the long-term prognosis of cirrhotic patients with acute variceal bleeding, we assessed only short-term outcome (e.g. 6-week mortality) rather than overall survival.

References

1 Chen PH, Chen WC, Hou MC, Liu TT, Chang CJ, Liao WC, Su CW, Wang HM, Lin HC, Lee FY, Lee SD. Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: a cohort study. *Journal of hepatology* 2012; **57**(6): 1207-1213 [PMID: 22885718 DOI: 10.1016/j.jhep.2012.07.038]

2 Hsu YC, Chung CS, Tseng CH, Lin TL, Liou JM, Wu MS, Hu FC, Wang HP. Delayed endoscopy as a risk factor for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage. *Journal of gastroenterology and hepatology* 2009; **24**(7): 1294-1299 [PMID: 19682197 DOI: 10.1111/j.1440-1746.2009.05903.x]

3 Ardevol A, Ibanez-Sanz G, Profitos J, Aracil C, Castellvi JM, Alvarado E, Cachero A, Horta D, Minana J, Gomez-Pastrana B, Pavel O, Duenas E, Casas M, Planella M, Castellote J, Villanueva C. Survival of patients with cirrhosis and acute peptic ulcer bleeding compared with variceal bleeding using current first-line therapies. *Hepatology* 2018; **67**(4): 1458-1471 [PMID: 28714072 DOI: 10.1002/hep.29370]

4) Comment #4: Minor English language is needed.

Response: We appreciate the reviewer's helpful comments. We used the language editing service and did our best to achieve the level of English required by the reviewer.

Responses to the Reviewer B's Comments

1) Comment #1: This is an interesting and well written paper regarding the impact of early G.I. endoscopy on the outcome of cirrhotic patients with acute variceal bleeding. However, some issues should be addressed by the authors. How many pts were excluded, and which were the reasons (based on their exclusion criteria)?

Response: We appreciate the reviewer's helpful comments. We added the exact number of excluded patients in the method section as follows:

"Exclusion criteria were as follows: (a) patients who did not undergo endoscopic examination during ER stay (n=38); (b) UGIB from other than variceal bleeding (e.g. peptic ulcer bleeding, portal hypertensive gastropathy bleeding) (n=165); or (c) if endoscopy had been performed within 7 days prior to admission (n=7). In total, 484 patients met the inclusion criteria and 210 patients were excluded as above. Finally, 274 patients were analyzed." (page 6, lines 8-14)

2) Comment #2: Did the authors exclude the patients with portal gastropathy?

Response: We appreciate the reviewer's valid comment. As described in the revised method section, we excluded patients with bleeding from portal hypertensive gastropathy.

3) Comment #3: Which was the standard of care (protocol therapy)?

Response: Following the reviewer's helpful comment, we added the information of standard of care in the method section as follows:

"When a cirrhotic patient with UGIB arrived at the ER of each hospital, adequate fluid resuscitation, a prophylactic antibiotic, and a vasoactive drug with terlipressin were immediately administered at the time of admission. If peptic ulcer bleeding could not be ruled out, a proton pump inhibitor was also administrated. An emergency medical specialist first examined the patient, and consulted a GI specialist about whether an endoscopy was to be performed. Then, the GI specialist determined the timing of the endoscopy, considering each patient's age, presence of comorbidities such as renal failure or cardiopulmonary disease, presence of hepatic encephalopathy, hemodynamic instability, and laboratory abnormalities including anemia, lactic acidosis and coagulopathy. If patients did not exhibit poor clinical factors or they had signs of hepatic encephalopathy more than grade III, delayed endoscopic examination was considered. (In both hospitals, a GI specialist with technical expertise in the use of endoscopic devices is on call 24 hours a day, 7 days a week.) Therapeutic endoscopy was performed using standard video-endoscopes (GIF-Q260 or GIF-Q290; Olympus, Tokyo, Japan). When EVL failed, salvage treatments including endoscopic variceal obturation (EVO) using n-butyl-2-cyanoacrylate (NBC), insertion of a Sengstaken–Blakemore (SB) tube, transjugular intrahepatic portosystemic shunt, variceal embolization, or a combination of multiple treatment modalities were performed. When EVO was performed, NBC (Histoacryl®; B. Braun Dexon, Spangenberg, Germany) was mixed with ethiodized oil (Lipiodol; Guerbert, Roissy, France) and was injected as a bolus dose of 0.5 to 2 mL, depending on the amount of bleeding." (page 6, lines 17-page 7, lines 8)

4) Comment #4: The urgent endoscopy group showed a shorter mean hospital

admission duration than that of the non-urgent endoscopy group (7.8 vs. 16.5 days, P<0.001). A comment in the discussion is needed (e.g. cost etc). Why did the patients without urgent endoscopy stay longer?

Response: We appreciate the reviewer's valid comment. Following the reviewer's comment, we revised the discussion section as follows:

"Consistent with previous reports, the length of hospital stay was statistically different between the urgent group and non-urgent group. [10, 28-30] It may be due to more accurate diagnosis and earlier hemostasis of the bleeding source by urgent endoscopy, leading to decrease in the subsequent resource use including the length of stay and total hospitalization costs." (page 13, lines 16-20)

5) Comment #5: In Table 3 no lab tests were included

Response: We appreciate the reviewer's thoughtful comment. Actually, we analyzed laboratory factors associated with survival, and found that individual components of MELD score (*e.g.* serum creatinine, serum bilirubin, and prothrombin time) were related with survival. We also found that MELD score was an independent prognostic factor for survival. Considering the multicollinearity between MELD score and its individual components, only MELD score, the most relevant prognostic parameter in patients with cirrhosis, was included in the final model. We added the information to the method section, and foot notes of Table 3 as follows.

"If multicollinearity occurred between the individual components in the univariate analysis,

only the most relevant prognostic parameter was included in the final multivariable model." (page 8, lines 11-14)

"* Considering the multicollinearity between MELD score and its individual components, only MELD score, the most relevant prognostic parameter in cirrhosis, was included in the final multivariable model." (page 27, Table 3 foot notes)

6) Comment #6: In Table 1, SD for time is too high (4.7 ±3.1 vs 26.6 ± 16.7). Median values are more proper

Response: Following the reviewer's valid comment, we changed the summary statistics of the variables showing nonparametric distribution from mean to median ones as follows:

Table 1. Baseline characteristics of patients before and after inverse probability weighting

Endoscopy								
Time to endoscopy, hours, median (IQR)	12.7 (2.8-16.5)	4.0 (2.1-6.8)	19.5 (15.0-35.5)	<0.001	12.5 (2.8-16.4)	4.0 (2.2-6.8)	19.5 (15.1-35.4)	<0.001

Table 2. Clinical outcomes of the patients

Outcomes	**All patients (N=274)**	**Urgent endoscopy (N=173)**	**Non-urgent endoscopy (N=101)**	***P***
Hospital admission duration, days, median (IQR)	4.0 (3.0-9.5)	4.0 (2.0-9.0)	4.0 (3.0-11.0)	0.033

"Although the median hospital admission duration was similar in both groups, significant differences observed in the mean rank scores (i.e., Mann-Whitney U test), suggesting that the data for the non-urgent group were more right skewed (*P*=0.033).[15]" (page 10, lines 2-5)

7) Comment #7: 26.3 hours was the mean time for non-urgent group, i.e. roughly during the first 24 hours. A comment in the discussion is needed.

Response: Following the reviewer's comment #6, we changed the summary statistics from mean to median. The median time to endoscopy in the non-urgent group was 19.5 hours (interquartile range, 15.0-35.5) and that of the urgent group was 4.0 hours (interquartile range, 2.1-6.8). Accordging to the reviewer's comment, we revised the discussion section as follows:

"In our study, the median door-to-endoscopy time in the non-urgent group was 19.5 hours which was much longer than the recommended time. Although most guidelines recommend that endoscopy should be performed within 12 hours of presentation, various clinical and facility factors may hamper guideline implementation in the real clinical settings.[4, 5, 26, 27] To overcome these baseline imbalances, we used IPW method. After IPW, there were no significant differences in the short-term outcomes between two groups." (page 12, lines 26-page 13, lines 2)

Responses to the Reviewer C's Comments

1) Comment #1: To the authors, I read with interest your manuscript and I do not have any concerns. It is well written. The limitation is the retrospective design as you mentioned. I recommend your manuscript for publication.

Response: We appreciate the reviewer's encouraging comments.