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Editors-in-Chiefs

World Journal of Clinical Cases

7041 Koll Center Parkway, Suite 160

Pleasanton, CA 94566

RE: The Safety of Gastrointestinal Endoscopy in Patients with Acute Coronary Syndrome and Concomitant Gastrointestinal Hemorrhage

Dear Dr. Bloomfield, Dr. Peng, and Dr. Vento:

We have attached a manuscript describing the safety and outcomes associated with the performance of gastrointestinal endoscopy in patients with acute coronary syndrome and concomitant gastrointestinal bleeding. The study spanned 10 years and includes over 250,000 admissions with acute coronary syndrome (ACS) and concomitant gastrointestinal bleeding (GIB). 183,409 patients with ACS and concomitant GIB underwent at least one endoscopic procedure during the same admission and 86,073 did not undergo an endoscopic procedure. The outcomes of the group undergoing at least one GI endoscopic procedure were compared to the group not undergoing an endoscopic procedure. The performance of an endoscopic procedure positively impacted both mortality and length of stay.

It is our opinion the information contained in this manuscript would be of significant interest to the readership of the *World Journal of Clinical Cases* as clinical gastroenterologists are regularly faced with the dilemma as regards the safety of endoscopic procedures in patients with acute coronary syndrome. This large and "real-world" study of over 250,000 admissions with acute coronary syndrome and concomitant gastrointestinal bleeding confirms the safety of proceeding with GI endoscopic procedures during the same admission. This manuscript was initially submitted to the *World Journal of Gastroenterology* (manuscript 58290) and the editorial office indicated a preliminary decision to accept the article for publication in the *World Journal of Clinical Cases* pending receipt of an appropriately revised manuscript.

The authors would first like to thank the publisher, editors, and reviewers for the very timely review of the manuscript and the valuable comments by the reviewers. The authors especially appreciate that all five of the reviewers rated the scientific quality of the manuscript as very good (2) or good (3) and that only one of the 5 reviewers recommended the manuscript be rejected.

As per the recommended revisions:

- An Article Highlights Section has been added at the end of the main text.

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- The STROBE check list has been completed.
- Requirements 4.4 – 4.8 have been addressed.
- Response to Comments by Reviewer 5 – The authors appreciate the reviewer's recommendation the article be published and the reviewer's comments regarding the study being well-designed and our fluent writing style. Thank you for the insightful and valuable comments.
- Response to Comments by Reviewer 4 – The authors appreciate the reviewer's recommendation the article be published and the reviewer's opinion as regards the valuable information contained in the manuscript to the field of gastroenterology. Thank you for the insightful and valuable comments.
- Response to Comments by Reviewer 3 – The author's appreciate the reviewer's recommendation the article be published after minor revision and the positive comments on our writing style. The authors agree it is important to validate the findings in another cohort and that additional references should be cited. Six additional references have been added to the introduction and the discussion sections (references 1, 7, 14, 19, 20, 26). Some of these are somewhat similar database cohort studies evaluating the safety of endoscopic procedures within 30 days of an acute cardiac event and others are small series of consecutive patients with acute cardiac events who underwent endoscopic procedures. The discussion section has been expanded to include additional information about these somewhat similar studies. However, our study of over 183,000 patients with acute coronary syndrome and gastrointestinal hemorrhage who underwent at least one endoscopic procedure during the same hospitalization is unique in that it is larger than any previously reported study evaluating the safety of performing an endoscopic procedure during the same hospitalization as an acute cardiac event.
- Response to Comments by Reviewer 2 – The authors appreciate the comment regarding the manuscript being well written. The reviewer makes multiple excellent points regarding the reasons for not performing endoscopic procedures in some patients, stratification for the type of endoscopy, and the success of endoscopic interventions. However, the aim of the study was not to evaluate these factors. The primary aim was to determine if endoscopic procedures could be safely performed in patients with acute coronary syndrome ... that is the question endoscopists want to know the answer to. Other studies evaluate the success of various endoscopic interventions, the safety of upper compared to lower procedures, etc. The study herein clearly answers the question. Endoscopic procedures were performed during the same admission with an acute coronary event and the mortality was low – 3.8%. In selecting the most appropriate population as a comparator the authors considered comparing the mortality in patients with acute coronary syndrome but determined a more appropriate population for comparison would be to compare the mortality rate to a large group of patients (86,073) with acute coronary syndrome and concomitant GI bleeding. Thank you for the insightful and valuable comments.

- Response to Comments by Reviewer 1 – The authors appreciate the reviewer's recommendation the manuscript be returned for revision and not rejected. The authors agree a randomized study would definitely be desirable however, given the low complication rates associated with endoscopic procedures combined with the data from the current and other studies it appears the number of patients needed to be randomized would not only be prohibitive but many investigators might consider it unethical to withhold performance of an endoscopic procedure in an actively bleeding patient. Similarly, if non-bleeding patients with acute coronary syndrome were randomized to a non-indicated endoscopic procedure this too would raise significant ethical concerns. Large database/observational studies like the one detailed in this manuscript are designed to provide insight into questions that randomized controlled trials are not likely to ever resolve as the trials would be prohibitively large. Virtually all database studies regularly generate more questions than they answer. This is especially true when an administrative database is queried as the data elements to answer the clinical questions reviewer 1 & 2 would like addressed are not included in the database and with the deidentified data the source documents are not available for review. Thank you for the insightful and valuable comments.

This manuscript has not been published or submitted elsewhere for publication, or consideration for publication. An abstract of the data was accepted for presentation at Digestive Disease Week – 2019.

Thank you in advance for your time and efforts as you evaluate this manuscript for publication in the prestigious *World Journal of Clinical Cases*. Please contact either of us if any supplemental materials are needed as you evaluate this manuscript.

Sincerely,



Donald R. Campbell, MD



Ahmed A. Elkafrawy, MD

Answering reviewers for re-review:

December 19, 2020 Editors-in-Chiefs World Journal of Clinical Cases 7041 Koll Center Parkway, Suite 160 Pleasanton, CA 94566 RE: The Safety of Gastrointestinal Endoscopy in Patients with Acute Coronary Syndrome and Concomitant Gastrointestinal Hemorrhage Dear WJCC editors and reviewers: We would like to thank the reviewer for providing us with these insightful comments. We appreciate giving us the chance to revise the manuscript and helping the authors to present their work in a better way. As per the recommended revisions: 1) I understand the limitations of this study, which are inherent to its nature and the impossibility to provide detailed information and explanation for the findings. In the primary question set by the authors, whether performance of GI endoscopy in patients with acute coronary syndrome and GI hemorrhage is safe their answer is yes. I am a little bit concern regarding the message conveyed to the readers. In my opinion the limitations of the study and the influence of other factors should be stretched more in the discussion. In this context, in the statistics it should be clear that multivariate analysis included only statistically significant factors detected by univariate analysis. The multivariate analysis paragraph in the results section should be extended and include the impact and significance of other factors as well. A short comment on this topic should be also included in the discussion especially when their HR is higher than that of GIE (see presence of shock and mechanical ventilation). We thank the reviewer for the thorough review of the manuscript and for understanding the nature and the limitation of using de-identified national databases. • The main aim of the study was to evaluate the safety and the impact of performing GI endoscopy in patients with ACS and GI bleeding, not investigating the predictors of morbidity and mortality in this specific population. The multivariate analysis included all the factors that may have a confounding effect on the outcomes of performing endoscopy in this group of patients. Univariate analysis was not performed as we did not want to eliminate any variable that can be a possible confounding factor to our results. In that context, we included all variables that we thought it could influence the outcomes of performing GIE in patients with ACS and GI bleeding. Of note, the practice of screening risk factors by univariate analysis before performing multivariate analysis is debatable, and some authors even consider it risky in certain situations (1-2). • Results and discussion sections were expanded to include comments on other independent predictors of mortality and prolonged length of stay as shock and mechanical ventilation. These variables were strong predictors of higher mortality. The fact that they were included in the multivariate analysis supports our conclusion that performing GIE is associated with less mortality. The sentence "One of the challenges in this study ... an endoscopic procedure performed" should be further commented. The sentence "A temporal relationship not be evaluated in this database" in the discussion is not clear and should be

detailed (see Table 1, proportion of patients in shock or under mechanical ventilation). • Both mentioned sentences were further detailed in the discussion section. 2) Table 1. Please correct “2 groups regarding undergoing” in the head and “Patients underwent endoscopy” in the heading of the second column. Not all variables are shown as n(%), there are also variables shown as mean±SD (please clarify in the footnote). • Table 1 heading and footnote have been changed and edited as suggested by the reviewer. 3) Tables 2 and 3. I wonder if these tables present uni- or multivariate analysis. It is hard to believe that all these variables were significant independent determinants of mortality or LOS. If these are the results of multivariate analysis then only statistically significant independent prognostic factors should be given and the results of univariate analysis should be mentioned in the results section of the manuscript. As seen in the tables, GIE has the lowest OR with mechanical ventilation and presence of shock being the strongest predictors for both mortality and LOS (see comments above). Please use uniform headings (predictors - factors, OR 95%CI - Beta Weight, 95% CI for LOS, Female - Sex (Female)) and remove “Label” from Table 3. Other points needing clarification; age as a continuous variable or with a cut-off set at some age point, female vs male, Caucasian vs not Caucasian, and all other variables as present vs absent. • Tables 2 and 3 represent a multivariate, not a univariate analysis. The reason of having many variables included in the analysis was explained above in the response to point 1. The huge number of patients included in the cohort (269483 patients) may also have contributed to some extent in more statistically significant results by overpowering the results. Some variables in the analysis were statistically insignificant predictors for the outcomes (for example, sex in mortality and anemia in LOS). • We used Odds Ratio for the multivariate analysis of the mortality as it's a nominal value, while we used the Beta - Weight factor for the length of stay being a continuous variable. • Requested heading changes and clarifications were addressed. 4) Please give abbreviations in full when first mentioned (see EGD and GIE in the Abstract, GIB and EGD in the Introduction). • Abbreviations were explained in full at first mention in the abstract and in the introduction section. References: (1) Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. *J Clin Epidemiol.* 1996;49(8):907-916. doi:10.1016/0895-4356(96)00025-x (2) Lo SK, Li IT, Tsou TS, See L. [Non-significant in univariate but significant in multivariate analysis: a discussion with examples]. *Changeng Yi Xue Za Zhi.* 1995 Jun;18(2):95-101. Chinese. PMID: 7641117. Thank you in advance for your time and efforts as you evaluate this manuscript for publication in the prestigious World Journal Clinical Cases. Please contact either of us if any supplemental materials are needed as you evaluate this manuscript. Sincerely, Donald R. Campbell, MD Ahmed A. Elkafrawy, MD