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Prof. Lian-Sheng Ma

Editor-in-Chief

World Journal of Gastroenterology

Manuscript No.: 86144

Title: Changing trends and characteristics of peptic ulcer disease: a multicenter study from 2010 to 2019 in Korea.

Dear Editor

Thank you for reviewing our manuscript and inviting revision. We are resubmitting our manuscript after making a new version according to your recommendations. Revised contents were highlighted with yellow in the text in addition to last revision. Let us address referees' comments as followings:

Reviewer(s)' Comments to Author:

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: In the last two decades, special attention of gastroenterologists has been focused on the problem of gastroesophageal reflux disease. At the same time, the number of studies and publications on the problem of epidemiology, etiology, features of the clinical course and treatment of peptic ulcers has significantly decreased. The authors studied the peculiarities of the course of peptic ulcer disease in the Korean population, depending on the etiology and age aspects. The data of 26 785 patients from 7 hospital bases in the period from 2010 to 2019 were analyzed. It should be noted the correct distribution of patients into three groups depending on the etiological factor. Important scientific and practical data on peptic ulcer caused by drug-induced

factors were obtained. The article is illustrated with figures and tables, which significantly improves the perception of the material. The authors outline the prospects for further research into the relationship between idiopathic ulcer and chronic liver diseases.

Answer) Thank you for your positive response.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Authors I read with interest the paper showing trends of PUD from an Asian country. The concept of studying trends is interesting and I agree that lessons can be learned by such epidemiologic observations and data trends are under reported by medical fraternity. Thus, this study is not only of clinical but also of epidemiologic and scholarly interest. I am in active clinical practice as a general and acute surgeon and my comments or critics will likely give the flavor of my views and opinions about PUD and while they in general are given with intent to improve the manuscript, its scientific outlook, and reader friendliness on the topic, please feel free to ignore my comments if authors deem them too incisive with logical explanations in the response letter. I have put my comments in Major, Intermediate and Minor categories for clarity of communication.

<Major comments:>

1. You classified PUD as 3 categories - hpylori, drug and idiopathic. What about smoking-related? (PMID: 28138363). Even if we exclude rare aetiology like ZE syndrome, MEN1 syndrome, Hypercalcemia from parathyroid issues, etc but smoking cannot and should not be ignored from causation/aetiology. Either put this as a limitation or if possible supply the data and tabulate it.

Answer) Thank you for your valuable comments. Unfortunately, we could not extract data about smoking from the limitation of database. We added limitation in DISCUSSION as below.

Lastly, we could not include smoking-related data; therefore, it could not be evaluated as a cause of idiopathic PUD.

2. In abstract and introduction section you state that there are not many reports on PUD trends. Than in discussion you report "several studies have reported trends". I find this puzzling, conflicting and a problem that should be addressed.

Answer) I'm sorry for the ambiguous expression. Actually, recent study (Xie X et al. The global, regional and national burden of peptic ulcer disease from 1990 to 2019: a population-based study. BMC Gastroenterol 2022; 22(1): 58) analyzed the global trend of PUD. However, the clinical characteristics were not fully evaluated in previous studies. To avoid the confusion, we corrected abstract as below.

The clinical trend and characteristics of peptic ulcer disease (PUD) have not fully been investigated in the past decade.

<Intermediate comments>

1. In the introduction section I see citations 2-12 commenting on something that is actually common public knowledge i.e. h pylori related PUD is reducing and old age and medication-induced PPU is increasing. I suggest retaining about 2-3 citations and not so many citations to only endorse a theme that is widely observed and agreed upon. So many citations are unnecessary.

Answer) We removed citations, and revised introduction. Please check the revised version.

2. 12.7% of PUD patients are on steroids. This, considering a report from Asia, is essentially too high. I have reported <1% steroid use even in perforated peptic ulcer population. Some explanation is warranted for this substantial high number of steroids. Is this a coding problem?

Answer) Thank you for your point. A recent Korean study (our reference) about the trend of PUB also showed similar figure in proportion of steroid. The diagnostic code of steroid also includes all ingredients including inhaler. We added the Figure of reference below.

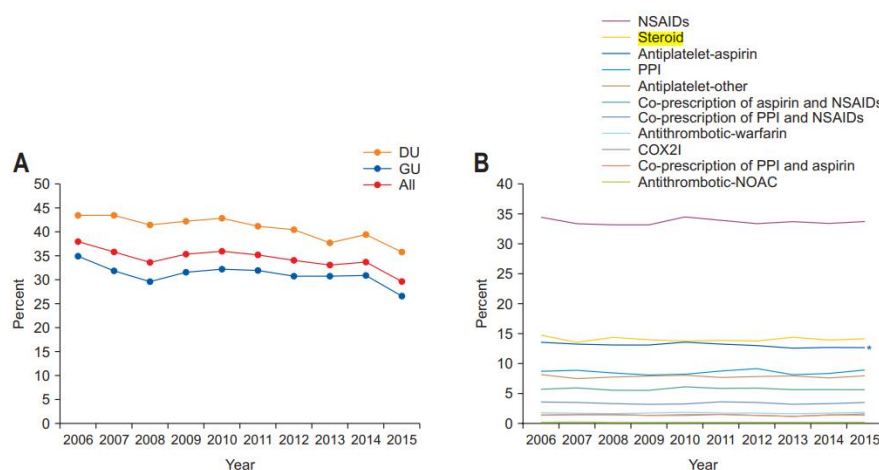


Fig. 3. *Helicobacter pylori* infection rate and drug exposure according to year. (A) Annual trends in the *H. pylori* infection rate in patients with peptic ulcer bleeding (PUB) between 2006 and 2015. (B) Annual trends in the rates of exposure to protective and risk-enhancing drugs in patients with PUB between 2006 and 2015.

Kim YS et al. A Nationwide Cohort Study Shows a Sex-Dependent Change in the Trend of Peptic Ulcer Bleeding Incidence in Korea between 2006 and 2015. *Gut Liver* 2021; 15(4): 537-545

3. Without data on smoking - i can postulate that alcoholics are more likely to be smokers also and thus develop PUD. So the association of chronic liver disease in alcoholic patients is not true association as smoking status is unreported. (We all agree that this is for sure not a causation).

Answer) Thank you for your comment. As you mentioned, the association between chronic liver disease and

idiopathic PUD is not clear, so we added the limitation in DISCUSSION as below.

Moreover, we demonstrated that alcoholic liver disease was more prevalent in idiopathic PUD, suggesting that alcohol may be another risk factor for idiopathic PUD, although the causal relationship is uncertain.

4. In the discussion segment it is not sufficient to mention that H Pylori-related PUD reported by others was lower due to flaws in their diagnostic test selection/reporting etc. More meaningful is to report and comment about how H Pylori is a public health concern, how public knowledge and awareness is improved or lacking (PMID: 33656211), how the utility of technology has enabled H Pylori eradication initiatives (PMID: 35363943) and what it means for your study results to have >40% Hpylori aetiology.

Answer) Thank you for your valuable comments. We agree with your opinion. We revised DISCUSSION as below.

Our proportion of H. pylori-related PUD also included patients who had H. pylori eradication therapy, which suggests that the knowledge and awareness of the public was improved in the past decade. A recent meta-analysis also revealed that technology-enhanced communication initiatives effectively improve compliance to the H. pylori eradication regimen and increase the eradication rate. [21]

<Minor comments>

1. In the abstract you mention no trends reported and, in the introduction, you mention no trends reported from "Asia". I invite you to please perform a quick and fairly detailed check and confirm if non-Asians also have not reported trends and if so omit the "Asia" and be bold and report that "no trends are reported" (internationally nobody has reported). But pls check first.

Answer) As I mentioned above, global trend study exists, and the study includes Asian data.

Xie X, Ren K, Zhou Z, Dang C, Zhang H. The global, regional and national burden of peptic ulcer disease from 1990 to 2019: a population-based study. BMC Gastroenterol 2022; 22(1): 58 [PMID: 35144540 PMCID: PMC8832644 DOI: 10.1186/s12876-022-02130-2].

Therefore, I removed the phrase "in Asia" and I emphasized our study was large-scaled and the efforts to investigate distinct characteristics according to etiology of ulcer as below.

To date, few large-scale studies have comprehensively investigated the recent changing trends and clinical characteristics of PUD, including the multiple risk factors. Therefore, we investigated the trends and characteristics of PUD according to age and etiology in Korea between 2010 and 2019.

2. Introduction is too short and does not do justice to your manuscript. Pls enhance why studying trends are not only important but essential in epidemiology and how your study bridge the knowledge gaps. For example, can add on NOACs or newer NSAIDs and Hpylori eradication, increase in endoscopy access and affordability etc or other relevant trends that are either reported or in common knowledge.

Answer) We revised INTRODUCTION as your suggestions. Please check the highlighted version.

3. I am unclear why tracheostomy patients have a separate and special mention in PUD report. Why have you

reported this operation - is there an association between tracheostomy and PUD? If so, what about whipples or bariatric procedures that cause risk of marginal ulcers or burns causing Curlings ulcer etc. Please only report what is relevant and not just because your database contains or you can retrieve such variables.

Answer) Thank you for your comment. We removed contents about tracheostomy throughout the paper. Please check the revised version.

4. In the discussion segment about drug induced PUD, i suggest to include more points from the 2020 GUTLIVER guidelines paper PMID: 33191311 to enhance the discussion on this theme and how it relates to your data/results.

Answer) We added more comments referring to the guideline.

Clinical practice guidelines for the appropriate treatment and prevention of drug-related PUD have been recently developed. [26, 27] The guidelines recommend high-risk patients who are on long-term NSAID medications receive low-dose PPIs to prevent PUD and its complications; however, evidence in patients who take multiple ulcerogenic drugs remains lacking. [26]

Our results suggest that drug-induced PUD may have more severe clinical outcomes; therefore, further strategies should be investigated to prevent complications in elderly patients.

5. The subgroup analysis table 3 most of the data is not matched to 100% and i dont think this is due to error but this is due to reporting not being clear. Pls revise the table to tell readers so data interpretation is easy

Answer) Sorry for misunderstanding. We put denominator in the Table 3. Please check the revised version.

6. There has to be a mention than old age defined as 65 is only one way and many people consider 70 yrs or 75 years as old age.

Answer) Thank you for your comment. We added the definition of old age in MATERIALS AND METHODS as below.

We defined old age group as 65 or older, and young age group as < 65 years.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

These two authors contributed equally to this work and should be considered co-first authors (Authorship) - Designation of co-first authors and co-corresponding authors is not permitted (please see Guidelines for Manuscript Preparation and Submission).

Answer) We corrected Yoon Jin Choi as single first author.

H. pylori infection rate was 34.37% (Discussion) - please use 34.4% PUB (Page 13, used twice) - PUD is right. CDM (Page 15) - please use this term in full. Refs 23 and 35 - please use abbreviated Titles (as in PubMed) Cirrhosis of liver (Tables 2 and 3) - liver cirrhosis is a more common term.

Answer) Thank you for your comments. We corrected 34.4%.

-But, the reference “Kim YS et al. A Nationwide Cohort Study Shows a Sex-Dependent Change in the Trend of Peptic Ulcer Bleeding Incidence in Korea between 2006 and 2015. Gut Liver 2021; 15(4): 537-545” included only PUB patients, therefore, we mentioned PUB as abbreviation.

-The abbreviation “CDM” is mentioned in MATERIALS AND METHODS as below.

We analyzed seven hospital databases converted into the Observational Medical Outcomes Partnership–Common Data Model (OMOP-CDM)

-References were corrected as your suggestion.

(reference 18. Stud Health Technol Inform / reference 31. Scand J Gastroenterol)

-Cirrhosis of liver was revised to “liver cirrhosis” in Table 2 and 3. Please check the revised version.

The article as a whole is well written, and significant results were obtained in this study. However, I cannot understand in any way why the authors included tracheostomy as a risk factor for peptic ulcer disease in the analysis? Why not a cholecystectomy or appendectomy? This decision looks extremely illogical and unnatural. It seems to me that it is better to remove this information from the tables altogether, or at least to justify its inclusion more carefully.

Answer) Thank you for your comment. We removed information about tracheostomy throughout the paper. Please check the revised manuscript.

JOURNAL EDITORIAL BOARD'S REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 86144

Title: Changing trends and characteristics of peptic ulcer disease: A multicenter study from 2010 to 2019 in Korea

Journal Editor-in-Chief/Associate Editor/Editorial Board Member: Mitsushige Sugimoto

Country/Territory: Japan

Editorial Director: Jin-Lei Wang

Date accepted review: 2023-10-24 22:30

Date reviewed: 2023-10-24 22:55

Review time: 1 Hour

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION |
|---|---|--|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D: Fair | | <input type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> Major revision |

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

General: In this study, the authors evaluated the changing trends and characteristics of peptic ulcer according to age and etiology using seven hospital databases. H. pylori-related peptic ulcer exhibited a decreasing trend after 2014 ($P=0.01$), drug-related peptic ulcer demonstrated an increasing trend, and idiopathic peptic ulcer showed an increasing trend in the old-age group during 10 years. This study was well written and may have potential. Major comments: 1. Antibiotic investigated peptic ulcer from 2010 to 2019, 10 years. This is Not so long periods. The fact suggested by this 10-years will be limited. 2. As exclusion criteria, authors raised gastric cancer and benign gastric neoplasm before the index date. Authors should include those patients. 3. What is benign gastric neoplasm? 4. Authors checked H. pylori infection by RUT and IgG-test. IgG test-positive does not mean current infection of H. pylori. 5. non-vitamin K antagonist oral anticoagulants (NOAC) → direct oral anticoagulants

(DOAC) 6. Please divide patients into three group: age >65 years, >75 years and >85 years. 7. If possible, please add data of smoking and drinking.

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

General: In this study, the authors evaluated the changing trends and characteristics of peptic ulcer according to age and etiology using seven hospital databases. H. pylori-related peptic ulcer exhibited a decreasing trend after 2014 ($P=0.01$), drug-related peptic ulcer demonstrated an increasing trend, and idiopathic peptic ulcer showed an increasing trend in the old-age group during 10 years. This study was well written and may have potential.

Major comments: 1. Antibiotic investigated peptic ulcer from 2010 to 2019, 10 years. This is Not so long periods. The fact suggested by this 10-years will be limited.

Reply: Thank you for your comments. We agree with your opinion. In fact, the period of 10-years may not be so long- period, however, we aimed to show the recent changing trend of peptic ulcer disease. In addition, our study was based on electronic health record data of 7 hospitals which were converted to OMOP-CDM. There might be data quality issue in the process of data conversion when we use the outdated data from multiple hospitals. Please note our aims and limitations.

2. As exclusion criteria, authors raised gastric cancer and benign gastric neoplasm before the index date. Authors should include those patients.

Reply: Thank you for your comment. As we mentioned in DISCUSSION, our study used the operational definition of PUD based on a previous Korean validation study, which showed optimal operational definition of peptic ulcer for big data analysis with high sensitivity and specificity (Reference 19 as below). In the reference study, the authors excluded post EMR/ESD ulcer to minimize the false-positive case in defining true peptic ulcer bleeding. In reference to the validation study, we excluded patients diagnosed with gastric cancer and benign gastric neoplasm before index date. The change of entire cohort definition might be difficult at this time. Please consider our background. 19. Lee JW, Kim HK, Woo YS, Jahng J, Jin YR, Park JH, Kim YS, Jung HY. [Optimal Operational Definition of Patient with Peptic Ulcer Bleeding for Big Data Analysis Using Combination of Clinical Characteristics in a Secondary General Hospital]. Korean J Gastroenterol 2016; 68: 77-86 [PMID: 27554214 DOI: 10.4166/kjg.2016.68.2.77]

3. What is benign gastric neoplasm?

Reply: It includes gastric adenoma and submucosal tumors including gastrointestinal stromal tumor, which is not related to peptic ulcer disease. As mentioned above answer, we excluded the concept to define the peptic ulcer disease more accurately in reference to previous Korean validation study of PUD.

4. Authors checked H. pylori infection by RUT and IgG-test. IgG test-positive does not mean current infection of H. pylori.

Reply: Thank you for your comment. The IgG test-positive does not mean current infection, but we all use IgG test as serologic testing. IgM has been found to have little diagnostic utility for H. pylori



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infections and is elevated only acutely after infection, whereas *H. pylori* infections are generally chronic. The serologic testing is not affected by recent antibiotics or proton pump inhibitors, so it can be useful in the setting of peptic ulcer bleeding.

5. non-vitamin K antagonist oral anticoagulants (NOAC) → direct oral anticoagulants (DOAC) : We revised as suggested. 6. Please divide patients into three group: age >65 years, >75 years and >85 years.

Reply: Thank you for your suggestion. Our study defined old age as >65 years, and we could not analyze extreme older age in detail. Unfortunately, it is difficult to perform further re-analysis currently, because our study included 26785 patients from 7 different hospital databases. Please note our study points that we focused mainly on the etiology of peptic ulcer disease as well as age and sex. 7. If possible, please add data of smoking and drinking.

Reply: Thank you for your comment. We also received similar comments from other reviewers, and we added comments about alcohol in limitations of DISCUSSION as below. "Lastly, we could not include exact data on smoking or alcohol consumption; therefore, it could not be evaluated as a cause of idiopathic PUD." The information on the smoking and drinking is limited in our study, however, we tried to overcome the limitation with detailed baseline characteristics including alcoholic liver disease, which reflects alcohol consumption indirectly. We are sorry for our limitations. Please understand our efforts and consider the fact that there have been few studies on the changing trend of peptic ulcer disease focusing etiology and age in multicenter study.