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Dear Dr. Schemmer:

We are submitting the revised manuscript, "Burden of Gallstone Disease in the United States Population: Prepandemic Rates and Trends" (manuscript NO.: 89732, Clinical and Translational Research) for consideration for publication as an original article in the *World Journal of Gastrointestinal Surgery*. The paper was previously submitted to the *World Journal of Gastroenterology* (invited manuscript # 05843136) and we have made revisions in response to the previous reviewers' and editors' comments. In this submission, we present graphically 15-year trends in health care utilization and mortality with gallstone disease in the overall United States population and by age, sex, race-ethnicity, and geographic region. We also present trends in ambulatory and inpatient laparoscopic and open cholecystectomy. In addition, we provide event counts and rates for the most recent year of data overall by demographic group. National data sources include the National Ambulatory Medical Care Survey, National Inpatient Sample, Nationwide Emergency Department Sample, Nationwide Ambulatory Surgery Sample, and Vital Statistics of the U.S. Claims data sources include Optum Clinformatics® Data Mart and Centers for Medicare and Medicaid Services (CMS) Medicare 5% Sample and Medicaid files which provide claims-based prevalence and information on commercially insured persons, older adults, and lower income persons, respectively.

No part of the manuscript has been published, already accepted for publication, or simultaneously submitted elsewhere. Both authors have approved the contents of the manuscript. Neither author has financial interests that might affect the conduct or reporting of this work. The work was supported by a contract from the National Institute of Diabetes and Digestive and Kidney Diseases (75N94022F00050). An earlier version of the manuscript was posted as a preprint on medRxiv (<https://medrxiv.org/cgi/content/short/2022.07.08.22277386v1>). The current version has been updated with newer years of data and Medicare Advantage and Medicaid have been included as data sources.

We think that our manuscript contributes to a better understanding of the growing public health burden of gallstone disease in the United States and would be of great interest to your readers. Thank you in advance for your kind consideration.

Our response to the *WJG* reviewers' and editors' comments follows:

Reviewer #1:

There are still some questions for the authors:

1. In this article, the result shows that " Women had higher medical care rates with a gallstone disease diagnosis, but mortality rates were higher among men. Hispanics had higher ambulatory care visit and hospital discharge rates compared with Whites, but not mortality rates. Blacks had lower ambulatory care visit and mortality rates, but similar hospital discharge rates compared with whites". What are the reasons causing such results? What is the guiding significance of these findings in the aspect of practice pattern monitor?

Higher medical care rates in women, but higher mortality in men. Sex differences in gallbladder disease severity may be a factor. Men were found more likely to present with complicated gallbladder disease suggesting a more advanced stage of disease while women were more likely to present with uncomplicated gallbladder disease (Bailey KS et al, *Am Surg* 2022; 88: 201). This has been added to the discussion (p. 16).

Higher medical care rates in Hispanics, but lower mortality rates. The Hispanic population in the U.S. is younger compared with the non-Hispanic White population. Hispanics experience lower mortality than non-Hispanic Whites overall (Fenelon et al, *SSM Popul Health* 2017; 3: 245). In addition, Hispanics may die of other causes first and gallstone disease may not be captured even among all-listed causes of death. This has been added to the discussion (p. 16).

Lower ambulatory care visit and mortality rates among Blacks, but similar hospital discharge rates. Blacks may be in lower socioeconomic groups and have less access to care. They may also receive care in later stages of gallstone disease that may require inpatient hospitalization. This has been added to the discussion (p. 17).

We expanded on explanations for these findings within each data source available since there may be some differences among health care utilization. The U.S. prevalence data may inform health care needs of populations groups in relation to gallstone disease.

2. The conclusion of this article is "the gallstone disease burden in the United States is substantial and increasing, particularly among women, Hispanics, and older adults with laparoscopic cholecystectomy as the mainstay treatment" . However, this finding is not novel, similar conclusion has been proposed in past articles. I would like to see more unique and novel findings in this article.

We agree with the reviewer that the prevalence of gallstone disease in the U.S. has been significant over decades, and we continue to monitor differences among population groups and analyze risk factors toward better management of this disease.

3. I am not quite familiar with the medical insurance system of the United States, so I don't know why the data were different between different kinds of insurance types, for example, "blacks had a lower prevalence compared with Whites among Medicare and Medicaid beneficiaries, but not private insurance enrollees". Does the type of insurance influence the medical behaviors, for example, people's health seeking or physical examination behaviors, or diagnosis & treatment methods selection, so as to influence the statistical results ?

The insurance types used in our analyses differ based on age and socioeconomic status of insured persons. Medicare beneficiaries consisted of persons 65 years or older as is stated in the statistical analysis section of the methods (p. 10). Medicaid eligibility is based on income below a certain level that varies among states, so Medicaid beneficiaries represent a low-income population. This has been added to the methods (p.8) to clarify for readers less familiar with the U.S. health care system. Most commercial insurance enrollees are employed persons who receive health insurance through their employer. This has been added to the methods (p. 8). Because age and socioeconomic status influence health there may be differences in health care utilization among these three claims data sources. For example, the effect of different insurance types on claims-based prevalence is discussed in response to Reviewer #2, comment #4 and has been added to the discussion (pp. 15-16).

4. The discussion part of this article is not deep enough. For example, the burden and the morbidity of gallstone disease are different in different population, including age, agenda and insurance types. What causes these differences? Are the reasons helpful for disease prevention in order to lighten the burden? I would like to see more related discussions in this article.

Additions to the discussion have been made in response to this and other reviewers' comments.

5. It is the end of 2023 now. The data used in this article were not new enough. As we know, after the COVID-19, the medical pattern, disease spectrum and the medical conscious of people may have changed in many countries. Is the analysis of old data much helpful for current medical situation? If the authors can analyze recent data or give a trend forecast, the article may have more guiding significance for gallstone disease.

The data used in this article were those most recently available. There is a 2–3-year lag between the end of a calendar year and our national data sources becoming available for research use. We agree that it will be important to continue to monitor current practice patterns post-pandemic as additional years of data become available. This will clarify whether small decreases in medical care use with gallstone disease and increases in gallstone disease mortality between 2019 and 2020 represent only temporary fluctuations or the beginning of trends.

6. Why does the laparoscopic cholecystectomy, as one of the curing method of gallstone disease, cause "doubling of gallstone disease" ?

The publication referenced (Unalp-Arida et al, *Hepatology* 2023; 77: 1882) used National Health and Nutrition Examination Survey data and defined gallstone disease as either a gallstone disease diagnosis without gallbladder surgery or a history of gallbladder surgery. The growth of the lower risk laparoscopic cholecystectomy procedure has resulted in changing indications for gallbladder surgery. This has contributed to an increased cholecystectomy prevalence and in the report referenced to an increased prevalence of gallstone disease overall.

Reviewer #2:

1. Please give the full spelling for GSD if appeared first time.

We now write out “gallstone disease” throughout the manuscript rather than using the abbreviation.

2. These data from different period from different sources used in this report. How about the bios?

It is unclear what the review means by “bios.” Does it mean a description of the data? If so, this is provided in the methods section on pages 6-9. If the editor can clarify, we would be happy to respond to this comment.

3. The numbers of patient were set on the "thousand" as a unit for measurement, it is better to describe in the section of method.

In Tables 1 and 5 for national data, event counts are shown as ‘Number in thousands’ which is the column heading. This has been added to the Statistical Analysis section of the Methods on page 10.

4. Could you explain the main reasons for the different results of claims-based prevalence from different sources?

Claims-based prevalence was highest among Medicare beneficiaries (2.09%). This is as expected given that Medicare beneficiaries in our analyses consisted of persons 65+ years or older age is a risk factor for gallstone disease. Claims-based prevalence was higher among Medicaid beneficiaries compared with commercial insurance enrollees (1.03% vs. 0.70%). Medicaid beneficiaries represent a lower income group compared with persons with private health insurance and gallstone disease was associated with lower socioeconomic status in the U.S.(Unalp-Arida et al., *Hepatology* 2023; **77**: 1882). This has been added to the 1st paragraph of the discussion (pp. 15-16).

5. Ambulatory laparoscopic rates were higher among Whites compared with Blacks and why? Please tell the possible reasons in the discussion.

Racial-ethnic differences in ambulatory laparoscopic cholecystectomy rates are consistent with gallstone disease prevalence among racial-ethnic groups. Gallstone disease is more common in Whites compared with Blacks and is most common in Hispanics and least common in Asians. Ambulatory cholecystectomy rate differences could also reflect disparities in access to care. Racial and ethnic minorities may have a higher likelihood of receiving inpatient as compared to ambulatory cholecystectomy due to delayed access to care and more advanced disease (Janeway et al, *J Surg Res* 2021; **266**: 373). This may contribute to lower ambulatory laparoscopic cholecystectomy rates among Blacks compared with Whites. This has been added to the discussion (pp. 17-18).

6. Please shorten the content in the text where possible.

We have shortened the content of the methods and results text.

Reviewer #3: No comments requiring response.

Thank you for reading our manuscript.

Reviewer #4:

The language needs to be refined. The following were some sentences (not all indicated). In the US population, persons with gallstone disease had increased mortality overall and from cardiovascular disease and cancer over a 20-year period and this relationship was found for both ultrasound-diagnosed gallstones and cholecystectomy. All privately insured enrollees with a single consistent birth year recorded in CDM who resided in the U.S. and were continuously enrolled for at least one full calendar year were included. The claims-based prevalence was calculated as the percentage of privately insured enrollees each year who qualified as gallstone disease patients. It was highest among 54.4 million Medicare beneficiaries, of whom 1.1 million had a gallstone disease diagnosis for a claims-based prevalence of 2.09% (2019). and was lowest among Asians was highest among American Indians/ Alaska natives, followed by Hispanics, Whites, Hawaiians/Pacific Islanders, and Blacks, and was lowest among Asians. Ambulatory care visit and hospital discharge rates were highest among Hispanics. In contrast to national hospitalization data that includes persons regardless of health insurance status, among commercial insurance enrollees hospitalization rates increased. Mortality data are dependent on the accuracy of death certificates that may vary by condition and chronic diseases that contribute to mortality are frequently underreported.

The sentences listed above have been divided into shorter sentences to simplify. Throughout the manuscript we made refinements and highlighted those in the revised manuscript.

Editorial office comments:

4 Specific comments:

(1) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A,B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

The figures have been converted to PowerPoint. All figures were original images created for this manuscript. Figure legends have been revised to include the lettered subtitles as part of the main titles as shown in the publisher's guidelines.

(2) Please provide the filled conflict-of-interest disclosure form.

Completed conflict-of-interest disclosure forms have been submitted.

(3) Please add the Core tip section. The number of words should be controlled between 50-100 words.

The Core tip section has been added.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References).

The Article Highlights section has been added.

(5) Please provide the PMID numbers and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

PMID numbers and DOI citation numbers have been added. All authors are included.

(6) Please provide the primary version (PDF) of the Institutional Review Board's official approval, prepared in the official language of the authors' country.

Not applicable. The study used only secondary de-identified data. Because there were no experimental protocols including human subjects, our study does not qualify as human subjects research. Consequently, there were no institutional approval requirements.

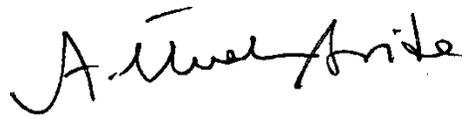
(7) Please provide the Clinical trial registration statement.

Not applicable. The study is not a clinical trial.

(8) Please provide the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors' country.

Not applicable. The study used only secondary de-identified data. Because there were no experimental protocols including human subjects, our study does not qualify as human subjects research. Consequently, there were no individual patient consent requirements.

Yours truly,

A handwritten signature in black ink, appearing to read "Aynur Unalp-Arida". The signature is fluid and cursive, with a horizontal line underneath it.

Aynur Unalp-Arida, M.D., Ph.D.

National Institute of Diabetes and Digestive and Kidney Diseases

Constance E. Ruhl, M.D., Ph.D.

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