

Date: May 8th, 2020

To:

Ramdas G. Pai MD, FACC, FRCP

Editor in chief

World Journal of Cardiology

Subject: Manuscript revision (Manuscript No. 52493)

Dear Dr. Pai,

We greatly appreciate your and the reviewers' thoughtful and insightful assessment of our manuscript titled "Morbidity and Mortality Associated with Atrial Fibrillation in Liver Cirrhosis" to be considered for publication in the World Journal of Cardiology. We have addressed each of the concerns outlined in the point-by-point response below. We believe your and the reviewers' concerns has substantially improved the quality and content of the manuscript to merit publication in the World Journal of Cardiology.

Atrial fibrillation (AF) is the most encountered arrhythmia in clinical practice but there is controversial data about its influence in patients with liver cirrhosis. In this study we analyzed 696,937 patients from the National Inpatient Sample (NIS), the largest publicly available US inpatient database, with the primary diagnosis of hepatic cirrhosis; 45,745 of those with a concomitant diagnosis of AF (representing 6.6% of patients with liver cirrhosis). After accounting for covariates using propensity score matching to patients without AF, we found that patients with AF had a higher in-hospital mortality, clinical stroke, and acute kidney injury ($p < .001$), and a lower rate of gastrointestinal bleeding, and blood transfusion ($p < .001$). Furthermore, the length of hospital stay in days and cost in dollars were higher in the atrial fibrillation patients ($p < .001$). They were also less likely to be discharged home and more likely to go to a rehabilitation or acute care facility.

This study highlights the clinical and the economic impact AF has in patients with liver cirrhosis. It is important to realize that AF is an adverse prognostic indicator in this population in order to provide them with appropriate management strategy.

This original manuscript is not under consideration for publication elsewhere, nor has it been previously published. All authors have made an important contribution to the study, approve the manuscript, and are responsible for its contents. There are no special financial or other relationships, nor conflicts of interest to disclose.

We hope to receive positive news from you in due course.

Sincerely,

Yousef Darrat, MD

Reviewer #1: In my previous review, major corrections were requested. Unfortunately, many of these corrections were not completed. These were as follows:

Your comments were not sent to us during the previous first revision review process.

We will now address the comments as follows:

1) There are many similar clinical studies in the medical literature.

We recognize that there are several studies investigating the general topic of AF in liver cirrhosis and we have already mentioned that in the manuscript. However, our study is different from the others since we specifically investigated in-hospital mortality and morbidity. Furthermore, our study is by far the largest and it has included 696,937 hospitalizations for cirrhosis; 45,745 patients with liver cirrhosis and AF.

2) There is no new or interesting information in the manuscript.

We respectfully disagree with this comment. The manuscript has shown that inpatient mortality, stroke, acute kidney injury is higher in hospitalized patients with liver cirrhosis and atrial fibrillation compared to those without the arrhythmia. Also, interestingly GI bleeding and need for transfusion is lower in liver cirrhosis patients with AF. In addition, we have shown that AF in liver cirrhosis is associated with prolonged hospitalization and cost. All the above were not shown in previously published studies since none have investigated the inpatient database.

3) There are many writing and grammar errors in the manuscript. These should be corrected by a native English speaker.

We have corrected the grammatical errors in the manuscript, please see the updated version.

4) The major limitation of the study is its retrospective design. These may lead to bias in the reported results. What is CHA2DS2-VASC score of the POAF patients? Is there any correlation between this score and clinical outcomes (i.e., hospital stay, time to surgery, mortality)?

We concur with the reviewer that this a retrospective study, with inherent limitations similar to any retrospective study including biases. We have already mentioned that in the limitations section.

We have added CHA2DS2-VASC score in the most recent revised version of the manuscript as requested by another reviewer. We have found that patients with CHADSVASC score of 2 and above have higher stroke and need for blood transfusions.

5) More detail should be provided for echocardiographic findings. What are the mean values for ejection fraction, left ventricular dimensions, left ventricular wall thicknesses, atrial dimensions, E/E' ratio and pulmonary artery pressure? Is there any correlation between these parameters and clinical outcomes?

The NIS database does not contain echocardiographic findings and therefore we will not be able to present such findings. Furthermore, it is beyond the scope of this study.

6) References should be rewritten according to the Journal's style.

We have revised the references and are now definitely compatible with the journal style.

7) Since they are related to the manuscript, the studies of Bahçivan et al (Anadolu Kardiyol Derg. 2008 Oct;8(5):354-9) and Cho et al (Korean Circ J. 2019 Nov 19. doi: 10.4070/kcj.2019.0219) should be mentioned in the discussion section. Unless these corrections are completed, the manuscript is not suitable for publication.

Your first article by Bahçivan et al (Bahçivan M, Gülel O, Kolbakir F. The effect of preoperative circadian blood pressure pattern on early postoperative outcomes in patients with coronary artery bypass graft surgery. Anadolu Kardiyol Derg. 2008 Oct;8(5):354-9.) is not related to our manuscript in any form or manner. Therefore, we will not be able to cite it. The second article by Cho et al (Clinical Implications of Preoperative Nonvalvular Atrial Fibrillation with Respect to Postoperative Cardiovascular Outcomes in Patients Undergoing Non-Cardiac Surgery. Korean Circ J. 2019 Nov 19. doi: 10.4070/kcj.2019.0219) investigates postoperative cardiovascular

outcomes in patients with preoperative diagnosis of AF. Although this article does not specifically include patients with liver cirrhosis we are happy to cite it in our article as follows:

“As seen in other studies (Cho et al) a CHA₂DS₂-VASc of 2 or more is associated with higher risk of stroke.”

The above statement was added to the discussion section on page 12.

Reviewer#2:

The manuscript is interesting and well written (it needs only minor copyediting for few typos). I have two major comments:

1) Authors should better describe the population hospitalized with liver cirrhosis AND atrial fibrillation. The prevalence of AF among liver cirrhosis patients by gender and age group should be presented: how does it compare with estimates for the general US population?

We appreciate the reviewer's comment and feel that it is of importance. The prevalence of AF among hospitalized liver cirrhosis patients by age and gender is represented in table 5 (see below) and is very similar to that in the general population. We have added a statement in the discussion on page 11 to describe how the prevalence of AF in liver cirrhosis compares to the general population as follows:

“In our study the prevalence of AF in patients with liver cirrhosis is 6.6%, it is very similar to that based on estimates in the general population according to age and gender as shown in table 5. This indicates that liver cirrhosis per se is not associated with an increased risk of AF. “

Table 5: The prevalence of AF according to age and gender for in-patients with liver cirrhosis compared to the general in-patient population.

Age (years)	Gender	AF in Liver Cirrhosis	AF National Estimates
<45	Male	1.70%	1.76%
	Female	0.90%	0.88%
46-65	Male	5.90%	5.91%
	Female	3.20%	3.16%
66-85	Male	20.00%	20.03%
	Female	16.00%	15.99%
>86	Male	34.10%	34.18%
	Female	33.50%	33.60%

2) Authors should provide some further insight into possible mechanisms of higher mortality in liver cirrhosis patients with AF. They speculate about a role of stroke and AKI. However, they have data at hand to test such hypothesis; for example, they could perform a mediation analysis, or , to keep it simple, they could assess if an increased mortality is found also among liver cirrhosis patients with atrial fibrillation AND WITOUT mention of stroke/ AKI.

We appreciate the reviewer comment. As suggested by the reviewer, we simply performed a regression analysis for in hospital mortality in patients with liver cirrhosis and AF and found that age 66-85 years (2.014), age above 86 years(OR 2.449), HF (OR 1.587) and vascular disease (OR 1.218) significantly predicted mortality.

We have added a statement regarding that as follows in the results section on page 10:

“We performed a regression analysis with excluding stroke and acute kidney injury and found that predictors of in-hospital mortality in patients with liver cirrhosis AF include older age (66-85 years; OR 2.014, above 86 years; OR 2.449), congestive heart failure (CHF) (OR 1.587) and vascular disease (OR 1.218).”

Reviewer#3:

In this manuscript, the authors examined morbidity and mortality of patients with concomitant atrial fibrillation (AF) and liver cirrhosis from the National Inpatient Sample (NIS) database. They found that these patients had higher mortality, stroke, and acute kidney injury compared to those who did not have the cardiac arrhythmia. My comments are as follows:

- 1) This was an interesting and highly scientific study.

We appreciate the reviewer's comment.

- 2) The major limitation of the study was its retrospective design. This might lead to bias in the reported results.

We agree with reviewer that this is a retrospective analysis and has inherent limitations and bias. We have explained that in the limitations section of the manuscript.

- 3) References should be rewritten according to the Journal's style.

We have corrected the references and are now compatible with the Journal's style.

Reviewer#4:

The paper entitled “Morbidity and Mortality Associated with Atrial Fibrillation in Liver Cirrhosis” is a good one, showing that Atrial fibrillation (AFib) is a predictor of increased in-hospital-mortality in patients with liver cirrhosis and is associated with a

higher risk of stroke and AKI but interestingly less GI bleeding and need for blood transfusion due to the lower use of anticoagulants in this kind of patients. Besides the limitation of this study as retrospective, in my opinion, this study brings additional knowledge in the field and encourages to make better research in this field. My only concern could be related to knowing the CHADSVASC and HASBLED score of the population and the influence on his prognosis specially for the AFib patients. As a peer reviewer, I do not have any further concerns

We appreciate the reviewer's insightful comments. We have divided liver cirrhosis and AF patients into two groups according to CHA₂DS₂-VASc score with a score of 2 as cut off. Those with CHA₂DS₂-VASc score of 2 or more had more strokes compared to CHA₂DS₂-VASc of 0 and 1 (<0.001). There was more need for blood transfusion in patients with CHA₂DS₂-VASc score of 2 or more ($P=0.018$). We have added a statement in the results section as follows on page 10:

"In AF patients with a CHA₂DS₂-VASc score of 2 or higher, there were more clinical stroke ($P <0.001$) and need for blood transfusion ($P=0.018$)."

However, we could not calculate a HAS-BLED score since in the NIS database does not provide medications (such aspirin, NSAIDs) or INR values and both are part of the score. Therefore, it is not feasible to generate a HAS-Bled score in this study.