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April 30, 2024

To the Editorial Staff:

Thank you to your staff and the reviewers for a critical review of our manuscript. We sincerely appreciate the constructive feedback to help improve our study "**Preoperative Hepatology and Primary Care Visits Improve Postoperative Outcomes in Patients with Cirrhosis Undergoing Surgery**." We have done our best to comprehensively address the reviewer comments and incorporated the suggestions into a revised manuscript, which has been uploaded. We have also submitted a point-by-point response to the reviewer comments as requested. We hope you find our work suitable for publication in *Clinical Gastroenterology and Hepatology*.

Thank you again for your consideration and please do not hesitate to contact us with questions.

Sincerely,

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Response to Reviewer Critiques

Reviewer #1 Comments:

1. The authors state that the patients without pre-operative visits were more likely to have significant cardiac comorbidities including atrial fibrillation, CAD and heart failure. Although this possible source of confounding is addressed in their propensity score, it is a surprising deviation from real world practice, where cardiac disease routinely necessitates pre-operative medical clearance from a PCP. It would be beneficial to comment on this in the discussion.

Thank you very much for a thorough critique of our manuscript, and for this important comment. As noted, in our unmatched cohort there was a higher proportion of cardiac comorbidities among those without preoperative visits as compared to those with preoperative visits. Given that we did not capture preoperative visits with specialists other than GI/Hep in our study, it is possible that patients with significant cardiac comorbidities could have been preferentially seen by a cardiologist rather than their PCP to obtain preoperative clearance. This would likely bias results towards a null hypothesis, and we now address this potential limitation in the discussion. Another potential explanation is that patients with multiple medical comorbidities such as coronary artery disease, depression, and/or substance have been demonstrated to have higher rates of appointment no-shows (PMID: 29482948). Nonetheless, differences in baseline comorbidities were very well balanced in the propensity matched cohort.

2. A possible source of confounding that isn't addressed is the impact of other specialty pre-operative risk factor modification, as patients seeing their PCP and hepatologist pre-operatively may be more likely to be seeing their cardiologist, nephrologist, etc.. Including this data in your Table 1 could be informative.

Thank you for your comment. We agree that this is an important potential source of residual confounding. In this study we chose to focus on GI/Hep and PCP outpatient visits, which we expected would be most salient to operative risk in a cohort of patients with cirrhosis. However, we agree that specialty preoperative visits, in particular cardiology, may impact operative risk as well. To address your comment, we have discussed this potential source of confounding in the limitations section of the discussion and highlight this as an important area of future research:

> ***"...Our data must be interpreted in the context of the study design. First, although we used PSM and demonstrated excellent covariate balance, there is potential for residual confounding.[29] In particular, we did not explore the effect of outpatient specialist visits apart from GI/Hepatology clinic visits; this may be an area of inquiry in future studies as specialists such as cardiologists and nephrologists may plausibly impact operative risk in a highly comorbid cohort of patients..."***

3. Definition of the term "emergent" in describing surgery would be helpful, as an almost equivalent number of these patients were still able to undergo 60 day pre-operative clearance as elective cases.

Thank you for this important comment. All ASA classifications were determined by pre-operative anesthesiology assessment. This includes a designation of emergent versus non-elective. For instance, ASA 4E would be an emergent surgery, whereas ASA 4 would be non-emergent. In general, guidance is for an "emergent" surgery to be designated in instances where treatment delay would lead to a significant threat to patient life or body part. To address your comment, we have clarified this in the methods section.

4. Further elaboration on causes of post-operative mortality in this study cohort would be helpful and where those reductions were seen among those undergoing pre-operative risk stratification visits. In particular, infection has been established as a major cause of post-operative ACLF and mortality (Chang et al, 2023); what extent was initiation of pre-operative SBP prophylaxis correlated with mortality improvement in this study?

Thank you very much for this question. We agree that exploring mechanisms of post-operative mortality is important. Unfortunately we do not have detailed data regarding cause of death in this dataset to explore this in detail. To address your comment, however, we now identify this as an important area of inquiry for future studies in the discussion section.

5. It was interesting to see that PCP visits alone carried similar mortality benefit to liver subspecialty visits (approximately 30% relative reduction), as cirrhosis related risk factors are less likely to be addressed during these visits. Commenting on how this benefit compares to prior literature exploring routine pre-operative medical clearance in non-cirrhotic, high ASA (3&4) patients would be worthwhile.

Thank you for raising this issue. We agree that this is an interesting finding. The Veterans' patient population carries a higher burden of metabolic, cardiovascular, and mental health-related comorbidities versus the general population. In this cohort, therefore, the role of the PCP in mitigating post-operative risk may be substantial, both through management of non-hepatic comorbidities as well as through coordination with other specialties. Though speculative, this may help to explain the observed protective effects with PCP visits. To address your important point, we have now expanded on this idea in the discussion section:

> ***"...This suggests that each provider may be optimizing different aspects of patient health, including cirrhosis-related and non-cirrhosis-related factors, that may impact operative risk. This may be especially salient in the Veterans' population, which generally carries a higher burden of metabolic, cardiovascular, substance use, and mental health-related comorbidities as compared to the general population. In this context, PCP management of non-hepatic comorbidities and coordination with other specialists may be critically important to mitigate postoperative risk, separate from the impact of GI/Hep providers on cirrhosis-related care..."***

6. The difference between Figure 2A and 2B is somewhat unclear and could be more clearly defined in the figure legend

Thank you for highlighting this issue. In the revised manuscript we have added a caption to Figure 2 in order to explain the differences between these panels more clearly. Both analyses demonstrate differences in post-operative mortality as stratified by pre-operative outpatient visit categorization in the propensity matched cohort, however panel B accounts for the competing risk or post-operative liver transplantation.

7. Table 1 suggests that this cohort was an overall lower risk patient population (by CPT, T bili, INR, plt). Subpopulation analysis of CPT B&C patients would be interesting if adequately powered to do so.

This is an excellent point. We agree that this warrants exploration. In the revised manuscript, we have added a subgroup analysis limited to CTP B/C patients. Though the sample size is limited for this analysis, we did identify an intensified protective association between PCP + GI/Hep

preoperative visits and postoperative mortality (SHR 0.19, 95% CI 0.006-0.62, p=0.006). This highlights that preoperative visits are especially critical in patients with more advanced liver disease. Though speculative, potential benefit with respect to medication adjustments is likely to be concentrated in these patients with CTP B/C cirrhosis. To address your important critique, we have updated the methods, results, and discussion with the above findings, and have added Supplemental Table 3 which contains model results.

8. Vocal Penn scoring sub-stratifies surgical risk of abdominal procedure by whether it is an open, laparoscopic, or abdominal wall surgery. It would be helpful if the authors elaborate as to why they did not do so in this study.

Thank you very much for pointing out this oversight. For the purposes of VOCAL-Penn Score calculation, we did have data granularity to subclassify open major abdominal versus laparoscopic major abdominal, and the calculated predicted probabilities presented in the initial manuscript were correct. To address this issue, however, we have now updated Table 1 and Supplemental Table 2 to include separate categorizations of abdominal wall, major abdominal – open, and major abdominal – laparoscopic.

<u>Reviewer #2 Comments:</u>

1. Being in care prior to operation, might just speak to the fact that patient had more compliance with medications, more labs that were recently checked, etc. How do you differentiate between that effect and specific PCP and GI/hepatology? This has been eluded to in discussion, I suggest make it more clear.

Thank you kindly for your thoughtful review of our manuscript, and for raising this important question. We agree that patients who are more compliant with medications/visits/labs, etc. are likely to have improved operative outcomes. However, we view this issue (a "healthy user" bias) to be a mediator of outcomes rather than a potential confounder to be adjusted. A major discussion point is that patients who complete outpatient visits with associated management appear to have reduced postoperative risk. Thus, the primary exposure itself (outpatient visits) is a marker of patient engagement. We have expanded the discussion in the revised manuscript to mention this issue specifically.

2.Also, how about those patients who just are not referred for surgery after such visit. i.e. the patients who make it to surgery after GI visit are presumably highly selected, so is it the high level of selection that results in better mortality or is it truly an association with GI visit and mortality?

Thank you for your important comment. We agree that this is a major limitation, and one that is generally common to retrospective studies of patients with cirrhosis undergoing surgery. Though it is difficult to speculate as to the association between preoperative visits and postoperative mortality in a broader cohort of patients with more advanced liver disease, in the revised manuscript we provide a subgroup analysis of patients with CTP B/C patients and note that there may in fact be a greater effect of preoperative outpatient visits on postoperative outcomes in these patients (see also our response to Reviewer #1, Query #7). To address your critique we now incorporate the above analysis into the methods, results, and discussion. We also highlight the cohort selection-related limitation that you have raised.

3. In the intro, I would avoid stating that impaired anticoagulation results in more bleeding, as we know the net effect in many of these patients is actually being prothrombotic and not increased risk of bleeding.

Thank you for this comment. We agree and have removed this statement.

4. Please provide a list of what was considered minor surgery or low risk procedure in your supplemental data since there is no consensus on this.

Thank you for this comment. We agree that there is no consensus on major versus minor surgery classification. The categorizations used in this study were adapted from the VOCAL-Penn Score derivation study (we now clarify this in the methods), and focus on major surgeries of interest. We cannot provide an exhaustive list of minor surgeries, however in brief these included primarily low-risk procedures that enter into the VASQIP database, such as: dental surgeries, adenectomies, cystoscopies, arthroscopies, skin biopsies and lesion removal, incision and drainage procedures, synovectomies, cataract surgery, central venous catheter insertion, hand surgeries including carpal tunnel or trigger finger surgery. To better articulate the types of surgeries that were included in the cohort, we have added a column to Supplemental Table 1 that provides several examples of major surgeries for each surgery category.

5. Now that MELD 3.0 is being widely used authors may want to discuss how it compares even if the outcomes are reported in MELD or MELD-Na

Thank you very much for this important comment. We appreciate that MELD 3.0 is becoming more widely used in broad literature addressing patients with liver disease. However, given that MELD 3.0 was primarily developed to improve estimation of waitlist mortality and address associated inequities on the basis of sex, it is not clear that applying MELD 3.0 in a non-transplant surgical context will provide much value. Moreover, historic non-transplant surgical literature for patients with cirrhosis has focused on usage of MELD or MELD-Na. For these reasons we chose to use MELD-Na in this stud. Finally, our propensity matched cohort is extremely well balanced in terms of MELD-Na, sex, and albumin (the latter two components which are incorporated into MELD 3.0). Thus we would not expect to see any major changes to results if we were to utilize MELD 3.0 as opposed to MELD-Na in this study.

6. Albumin is not include in your lab data, was this used to calculated child pugh score? If so, please include in your lab table. Same with INR/PT. Also, it is important to include granular data on number of patients with slight vs moderate ascites and number of patients with grade 1-2 vs grade 3-4 HE.

Thank you for highlighting this important issue. We do have data on albumin for this cohort, which we erroneously omitted from Table 1 in the initial submission (INR was included in Tables in the initial submission but may have been missed). Additionally, we do have granular data on ascites classification and hepatic encephalopathy classification that were used to compute the Child-Turcotte-Pugh score, as you have noted. This methodology is from previously published work in this cohort (PMID: 26188137). To address your important point, we have added albumin, ascites classification, and hepatic encephalopathy classification to Table 1 and Supplemental Table 2. There was adequate balance between these variables in the propensity matched cohort.

7. Can you define "no preoperative visit"? does this mean the patient was not seen by any provider? Or those two particular providers (PCP or GI/hepatology)? Since most patients were child pugh A, and

presumably not on medications for HE or ascites, what do you contribute the reduction in mortality after having that pre-op visit to?

Thank you for raising these questions. We agree that this is important to clarify and explore in more detail. In this study, "no preoperative visit" refers to an absence of PCP or GI/Hep outpatient visit, but does not preclude the possibility of outpatient visits with other specialties. As noted in our response to your first two queries, we now address this limitation/caveat in the discussion section and highlight that exploring the role of other specialties may be an important area of future research. Regarding your important observation that the majority of the cohort had CTP A cirrhosis, in the revised manuscript we now incorporate a subgroup analysis among CTP B/C patients with cirrhosis that demonstrates an intensified protective effect of PCP + GI/Hep preoperative visits on postoperative mortality. This analysis, as well as an additional exploratory analysis demonstrating that management changes (medication initiation, dose changes, paracentesis) were concentrated in CTP B/C patients, suggests that much of the observed reduction in mortality may be mediated by management changes in patients with more advanced cirrhosis. Please see also our responses to Reviewer #1, Query #7 and Reviewer #3, Query #1.

8. In discussing exploration of what might have contributed to post-op reduction in mortality, I do not believe we can speculate use of antibiotic for PPx. Conversely, in a study by Badal et al, this was associated with increased antibiotic resistance and it's not a widely accepted indication amongst hepatologists.

Thank you very much for this comment. The study by Badal, et al. offered important findings and results that call into question the routine use of empiric SBP prophylaxis in patients without a prior diagnosis of SBP. We did not intend to imply that patients should be initiated on routine antibiotic prophylaxis in the absence of an established clinical indication, such as prior SBP or low-protein ascites with concomitant hepatic or renal dysfunction. Furthermore, we acknowledge that the analyses regarding medication changes and paracentesis are exploratory and have flagged them as such in the methods and results. To address your important point, we have modified the discussion to (1) temper the language to make clear that these results are exploratory and (2) clarify that antibiotic prophylaxis should be used in patients with appropriate indications (i.e., prior SBP or low-protein ascites).

9. Also, while exploring the contribution of these visits, I am not sure how authors can draw conclusion that medication adjustment had an effect on reduced mortality, as we do not know how many of these visits were done to specifically address risk of surgery vs routine follow up. Recommendations might changes depending on patients plan to undergo surgery or routine management.

Thank you for your raising this important point. As per our response to the prior query, we highlight that the analyses of medication adjustment are exploratory in nature and intended to be hypothesis generating as to potential mechanisms that may underly the observed reduction in mortality in patients with preoperative visits. We are hopeful that these results will help to focus future research efforts. To address your comment, we have tempered the language in the discussion surrounding medication management and preoperative paracentesis, including in the conclusion paragraph.

Reviewer #3 Comments:

1. Given almost 90% were child A, which would be considered compensated cirrhosis, presumably none of the interventions described by authors (adjustment or initiation of diuretics, or hepatic encephalopathy medication, or SBP ppx medication) would be applicable for these patients. The main intervention hepatologist provide for child A compensated patients are HCC screening, and use of NSBB in a sub-set with clinically significant portal HTN, both of which are unlikely to affect post-operative mortality. Therefore recommend performing a sensitivity analysis separating child A (compensated) and child B/C (decompensated) patients.

Thank you very much for your critical review of our manuscript, and for this excellent comment. A similar suggestion was also made by Reviewers #1 (see Query #7) and Reviewer #2 (see Query #7). To address this issue, in the revised manuscript we now present a subgroup analysis limited to patients with CTP B/C cirrhosis. We observed an intensified protective effect in patients with both PCP and GI/Hep preoperative outpatient visits. This is generally consistent with the hypothesis that you have articulated—namely that medication adjustments/paracentesis in patients with more advanced liver disease may be a concentrated driver of the observed reduction in mortality. In response to your next query, we indeed found that patients with CTP B/C cirrhosis were more likely to undergo preoperative management changes versus CTP A patients. We have updated the methods, results, and discussion to incorporate this analysis, in addition to a new Supplemental Table.

2. can authors provide what percentage had any intervention done? It is unclear whether there are overlap between the percentages (are patients who get diuretic dose adjustment the same or overlapping with the ones getting encephalopathy treatment modification?)

Thank you for these questions. We agree these data points would be helpful to better understand the exploratory analyses. In the revised manuscript we now provide the proportion of patients who had any management changes (medication initiation, dose change, paracentesis), stratified by preoperative outpatient visit category (added to Table 3). We also demonstrate that management changes are more concentrated in patients with CTP B/C cirrhosis, which is again consistent with the points you raised in your prior query.

3. One major bias, is the fact that patients who have a hepatology or PCP visit prior to surgery are more likely to be the same patients that are more engaged in care, follow up with their providers, and take their medications as prescribed. Therefore they are more likely to have a better outcome regardless of the PCP or GI/Hep clinic visit. Recommend using a covariate to account for engagement in care (such as number of PCP or GI/Hep visits in the 1-2 year prior)

Thank you very much for raising this important issue, which was also mentioned by Reviewer #2 (see Query #1). We agree that a "healthy user" bias is important to consider, and this was something that we carefully evaluated prior to the initial manuscript submission. However, with respect to this particular study question, we do not view healthy usership to represent a bias, but rather a mediator of post-operative outcomes. A major discussion point is that patients with cirrhosis who are engaged with and complete outpatient visits are likely to have lower postoperative mortality. Thus, while we agree that accounting for engagement in care is important for many retrospective studies, in this particular case we intentionally do not adjust for this as the primary exposure itself is reflective of patient engagement. To address your important point, we now expand on this issue in the contextual factors section of the discussion.