PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comorbidity and multimorbidity in cirrhotic patients hospitalised in an internal medicine ward: a monocentric, cross-sectional study
AUTHORS	Lenti, Marco; Ballesio, Alessia; Croce, Gabriele; Brera, Alice Silvia; Padovini, Lucia; Bertolino, Giampiera; Di Sabatino, Antonio; Klersy, Catherine; Corazza, Gino Roberto

VERSION 1 – REVIEW

REVIEWER	Xu, Jian Shenzhen Center for Chronic Disease Control
REVIEW RETURNED	09-Dec-2023

GENERAL COMMENTS	1.Please briefly introduce the San MAtteo Complexity (SMAC) study design. 2.Please give different definitions and diagnostic methods of cirrhosis and cite references. 3.Supplement the sample size calculation formula. 4.Please give the definition of comorbid or multimorbidity and the diseases included. 5.Significant selection bias exists in hospital-based studies. How to control selection bias. 6.How confounders are collected and defined(page 5, line 42-50). 7.It is recommended that the study populations in Tables 1 through 3 be consistent

REVIEWER	Verma, Manisha Albert Einstein Medical Center
REVIEW RETURNED	08-Jan-2024

GENERAL COMMENTS	The findings of the study are not generalizable and the methods are inadequate to respond to the question.

REVIEWER	Heidet, Matthieu Assistance Publique - Hôpitaux de Paris, SAMU 94
REVIEW RETURNED	15-Jan-2024

GENERAL COMMENTS	Thank you for giving me the opportunity to review your article entitled "Determinants of clinical complexity in hospitalised cirrhotic patients". Through a secondary analysis of the SMAC monocentric, prospective cohort study of patients hospitalized in an internal medicine ward in Italy, this article aimed at 1) describing clinical complexity of cirrhotic patients, and 2) comparing the rates of co- and/or multi-morbidity in this subpopulation.

	The article reads well, and aims at better define, describe and understand differences in clinical complexity and multiple chronic conditions of cirrhotic patients. Nevertheless, several concerns arise after my review, which I believe may enhance the global clarity and robustness of the present work. MAJOR - The objectives of the present study are a bit blurry. Primary and secondary objectives are not well aligned between the abstract (co- and multi-morbidity), the strenghts and limitations shortlist (co- and multi-morbidity), the introduction (CC/MCC) or methods sections (CC, (co- and multi-morbidity) and the conclusion (first study to focus on the distinction of (co- and multi-morbidity)). I suggest you align all of the above for this makes the article less understandable. - The difference between comorbidty and multimorbidity appears hard to grasp, and does not sound consistent to me between the introduction and the methods section. Please clarify. - Although you state that a strength of the present study is to show that patients with alcohol-related cirrhosis are younger than the others, this result has already been shown previously in much larger studies (https://doi.org/10.1186/s12876-020-01239-6, which you cite in ref#11 by Vaz et al)). MINOR * ABSTRACT - Objectives : The only objective reported here is, in fact, the secondary one of the present study. You state in the methods section that the main objective is to "describie clinical complexity of cirrhotic patients". Please correct. Also, I do not quite understand the difference between comorbidity and multimorbidity. Can you be more precise, fro example by stating that comorbidity is at baseline (cirrhosis, chronic liver viral infections, diabetes, etc.) and that multimorbidity is at the acute phase (oedemato-ascitic decompensation, ketoacidosis, sepsis, etc ? - Design : Please briefly state which statistical methods were used to calculate associations with co- and multimorbidity. - Setting /participants : please detail the period of inclusion - Conclusion : The current version of the conclusion does not respond to the objective stated earlier ("We sought to determine the rate and differences between co-multimorbidity depending on the aetiology of cirrhosis"). Also, pathways of care should not appear in the abstract, but rather in the discussion section. INTRODUCTION - The CC and MCC acronyms are very close and tend to be confusing. I suggest you do not use them as such and systematically expand them throughout the main text. METHODS - Please consider dividing this section into subsections seimilar to those used in the abstract (setting, population and participants, objectives, data, variables, statistical analyses etc.), for it is a bit thick to read as is.

	- The sentence "Patients with a prognosis <48 hours and denial of informed consent were the only exclusion criteria" (p.6, L 22) is odd. Please rephrase. - The sentence "Applying these criteria, 187 cirrhotic patients (median age 78 years, IQR 66-84; 88 females) were identified" need to be moved to the results section. - I do not quite well understand why "cirrhosis decompensation, gastrointestinal bleeding, hepatic encephalopathy, ascites) have been categorised as being comorbid, while patients with association with other conditions have been categorised as having multimorbidity." - Please clarify what the sentence "There were no uneducated participants in this study" means - Did you conduct some automated methods for the selection of candidate variables, along with your clinically-driven choice, in order to complete their selection (i.e. stepwises)? I would suggest you proceed to such slection methods to come up with a complete model (clinical considerations are critical but may be subject to practicioneer and/or center-related selection bias) RESULTS - Why would you not exclude the 15 patients prior to comparing the populations' characteristics? - P.9, L24 : "As expected" belongs to the discussion part. L.31, "statistically" is mispelled, but can be deleted (if significant, it is statistical). - The entence "Regarding the rates of comorbidity and multimorbidity, we found a statically significant difference among the three groups (p=0.015), being comorbidity more prevalent in patients with alcohol aetiology and multimorbidity more prevalent in viral and NAFLD cirrhosis." (P.9 L.34) is unclear. Please rephrase. - Likewise, the sentence "Finally, in a multivariable model looking at factors affecting the risk of having multimorbidity (Table 3), we found that a CIRS comorbidity index >3 (OR 2.81, p=0.024) was significantly correlated, while the admission related to cirrhosis (OR 0.19, p= 0.002) was significantly and inversely correlated with this outcome." is tricky. Please consider fragmenting it, using consistent directions of associations (and not "inversely correlated to this outcome"). DISCUSSION - As an opening subsection, I would recommend you start by the "We Herein found [...] and hospitalized. The current opening paragraph is hard to follow, and discusses concepts. TABLES AND FIGURES - Multiple variables/wordin used in the tables do not appear in the main text (Edmonton, Barthel, SBT, schooling) and/or not exact (LOS = length of stay, not "long"). Table 3: I think "reference" is more adapted to ORs than "base". Please add more consistency by defining these variables/scores in the method section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

We thank the Reviewer for the thoughtful comments. We have tried to address all the points raised as detailed below.

1.Please briefly introduce the San MAtteo Complexity (SMAC) study design.
As suggested, we have now briefly introduced the SMAC study design.

2.Please give different definitions and diagnostic methods of cirrhosis and cite references.
As suggested, we have now given the definitions and diagnostic methods of cirrhosis along with the due references.

3.Supplement the sample size calculation formula.
We did not formally calculate the sample size for this sub-study, as all patients from the SMAC registry were included. However, given the overall sample of 1433 patients and 172 cirrhotic patients, we were able to fit a multivariable model with up to 17 predictors without overfitting. This has now been added in the statistical methods.

4.Please give the definition of comorbid or multimorbidity and the diseases included.
These definitions have already been reported in the Methods section; we have applied the internationally recognised definitions for these entities. Any known condition/disease was included when categorising patients.

5.Significant selection bias exists in hospital-based studies. How to control selection bias.
We thank the Reviewer for raising this point. We are aware that such a kind of study could be affected by selection biases, and this has now been acknowledged in the discussion. Indeed, the results of our study can only be generalized to a similar setting. Potential biases were here mitigated by a robust methodology, i.e., by applying a consecutive and unselected enrolment.

6.How confounders are collected and defined (page 5, line 42-50).
All confounders were defined and collected according to the original SMAC study protocol. We have now added some more information on the SMAC study in the Methods section, also according to a previous point.

7.It is recommended that the study populations in Tables 1 through 3 be consistent
As also suggested by another Reviewer, now we have only included 172 cirrhotic patients, and the results have been reported in all Tables.

Reviewer #2

The findings of the study are not generalizable and the methods are inadequate to respond to the question.

Indeed, the scope of this paper was not that of reporting a wide range of presentations of cirrhosis in different settings, but rather reflecting the real-life practice of an internal medicine setting. This has now been acknowledged as a limitation in the end of the discussion. Our primary aim, as already specified in the text, was to “look at possible determinants of CC in cirrhotic patients, compared to the

whole SMAC cohort, as well as the overall rates of co- or multimorbidity". We do feel that the statistical plan used, along with the several variables included, are in line with the aim of the research. We have now better clarified many points, as per other Reviewers' comments, and hopefully the methods are now clear enough to understand how our research question was addressed and dealt with.

Reviewer #3

Dear authors,

Thank you for giving me the opportunity to review your article entitled "Determinants of clinical complexity in hospitalised cirrhotic patients".

Through a secondary analysis of the SMAC monocentric, prospective cohort study of patients hospitalized in an internal medicine ward in Italy, this article aimed at 1) describing clinical complexity of cirrhotic patients, and 2) comparing the rates of co- and/or multi-morbidity in this subpopulation.

The article reads well, and aims at better define, describe and understand differences in clinical complexity and multiple chronic conditions of cirrhotic patients. Nevertheless, several concerns arise after my review, which I believe may enhance the global clarity and robustness of the present work.

We thank the Reviewer for the thoughtful and positive comments on our manuscript. We have tried to address all the points raised as detailed below.

MAJOR
- The objectives of the present study are a bit blurry. Primary and secondary objectives are not well aligned between the abstract (co- and multi-morbidity), the strengths and limitations shortlist (co- and multi-morbidity), the introduction (CC/MCC) or methods sections (CC, (co- and multi-morbidity) and the conclusion (first study to focus on the distinction of (co- and multi-morbidity)). I suggest you align all of the above for this makes the article less understandable.
We thank the Reviewer for pointing this out. We agree that there was some confusion with the use of the terms throughout the text. Hence, we have now amended the text so to use a consistent and clear language, with clear objectives. The title of the paper was also amended, so to reflect the main results of our paper.

- The difference between comorbidty and multimorbidity appears hard to grasp, and does not sound consistent to me between the introduction and the methods section. Please clarify.
As suggested, and according to the previous point, we have better clarified all these concepts throughout the text. Specifically, we have now anticipated the definitions of co- and multimorbidity in the introduction. Additionally, in order to make this clear, we have also added an example in the Methods section. We do agree that in real-life not all clinical scenarios are easily distinguishable, but yet an internationally recognized terminology has been adopted as per MeSH definitions. Hopefully, the amended version of the paper should be clear enough to all readers.

- Although you state that a strength of the present study is to show that patients with alcohol-related cirrhosis are younger than the others, this result has already been shown previously in much larger studies (https://doi.org/10.1186/s12876-020-01239-6, which you cite in ref#11 by Vaz et al)).
While this datum may appear as not novel, it should be noticed that the study by Vaz et al. was performed in a totally different setting. Actually, Vaz et al. report data from a population-based study, and not from a hospital, internal medicine setting. Under this point of view, our data are novel and very helpful in this specific setting, in which, in most cases, patients are older than 70 years and multimorbid. This difference has now been reported in the revised manuscript.

MINOR
* ABSTRACT
- Objectives: The only objective reported here is, in fact, the secondary one of the present study. You state in the methods section that the main objective is to "describie clinical complexity of cirrhotic patients". Please correct. Also, I do not quite understand the difference between comorbidity and multimorbidity. Can you be more precise, fro example by stating that comorbidity is at baseline (cirrhosis, chronic liver viral infections, diabetes, etc.) and that multimorbidity is at the acute phase (oedemato-ascitic decompensation, ketoacidosis, sepsis, etc ?
As per your previous comment, we have amended the Abstract and text so to be consistent with the objective of the research. The concepts of co- and multimorbidity have also been better defined so to avoid confusion in the text. In the Abstract, we kept the original descriptions.

- Design : Please briefly state which statistical methods were used to calculate associations with co- and multimorbidity.
We have amended the design as suggested.

- Setting /participants : please detail the period of inclusion
This has now been added.

- Conclusion: The current version of the conclusion does not respond to the objective stated earlier ("We sought to determine the rate and differences between co-multimorbidity depending on the aetiology
of cirrhosis"). Also, pathways of care should not appear in the abstract, but rather in the discussion section.
We have amended the conclusion as suggested.

INTRODUCTION
- The CC and MCC acronyms are very close and tend to be confusing. I suggest you do not use them as such and systematically expand them throughout the main text.
As suggested, we have now spelled out all the acronyms.

METHODS
- Please consider dividing this section into subsections similar to those used in the abstract (setting, population and participants, objectives, data, variables, statistical analyses etc.), for it is a bit thick to read as is.
As suggested, we have now amended the text.

- The sentence "Patients with a prognosis <48 hours and denial of informed consent were the only exclusion criteria" (p.6, L 22) is odd. Please rephrase.
As suggested, we have now rephrased the sentence.

- The sentence "Applying these criteria, 187 cirrhotic patients (median age 78 years, IQR 66-84; 88 females) were identified" need to be moved to the results section.
As suggested, we have now amended and moved this sentence to the Results section.

- I do not quite well understand why "cirrhosis decompensation, gastrointestinal bleeding, hepatic encephalopathy, ascites) have been categorised as being comorbid, while patients with association with other conditions have been categorised as having multimorbidity."
Also following the comments raised in previous points, and after some other amendments, this should now be clear. Since comorbidity implies the presence of an index disease, all cirrhosis complications are a consequence of the index disease.

- Please clarify what the sentence "There were no uneducated participants in this study" means
For clarity, the sentence has now been removed as of little importance in this context.

- Did you conduct some automated methods for the selection of candidate variables, along with your clinically-driven choice, in order to complete their selection (i.e. stepwise)? I would suggest you proceed to such selection methods to come up with a complete model (clinical considerations are critical but may be subject to practicioner and/or center-related selection bias)
We have selected all the clinical variables that were collected in the larger, SMAC study, and included them in the present study. Since the explorative nature of the study, we do feel that a clinically-driven choice is appropriate here.

RESULTS
- Why would you not exclude the 15 patients prior to comparing the populations' characteristics?
Also according to other Reviewers' comments, we have now removed these 15 patients in all analyses.

- P.9, L24 : "As expected" belongs to the discussion part. L.31, "statistically" is misspelled, but can be deleted (if significant, it is statistical).
The text has now been revised.

- The sentence "Regarding the rates of comorbidity and multimorbidity, we found a statically significant difference among the three groups (p=0.015), being comorbidity more prevalent in patients with alcohol aetiology and multimorbidity more prevalent in viral and NAFLD cirrhosis." (P.9 L.34) is unclear. Please rephrase.
We have now rephrased the sentence.

- Likewise, the sentence "Finally, in a multivariable model looking at factors affecting the risk of having multimorbidity (Table 3), we found that a CIRS comorbidity index >3 (OR 2.81, p=0.024) was significantly correlated, while the admission related to cirrhosis (OR 0.19, p= 0.002) was significantly and inversely correlated with this outcome." is tricky. Please consider fragmenting it, using consistent directions of associations (and not "inversely correlated to this outcome").
We have now rephrased the sentence so to make it clear.

DISCUSSION
- As an opening subsection, I would recommend you start by the "We Herein found [...] and hospitalized. The current opening paragraph is hard to follow, and discusses concepts.
We have now modified the discussion as suggested.

TABLES AND FIGURES

- Multiple variables/wording used in the tables do not appear in the main text (Edmonton, Barthel, SBT, schooling) and/or not exact (LOS = length of stay, not "long"). Table 3: I think "reference" is more adapted to ORs than "base". Please add more consistency by defining these variables/scores in the method section.
All the variables used have now been better explained in the Methods section, along with the references; we have also corrected the Table legend and Table 3.

VERSION 2 – REVIEW

REVIEWER	Heidet, Matthieu Assistance Publique - Hôpitaux de Paris, SAMU 94
REVIEW RETURNED	04-Mar-2024

GENERAL COMMENTS	Thank you for this thorough and satisfying revision. I still have minor comments, though: METHODS - Can you please give provide a table detailing results of univariable analyses? This would help highlight the differences (or consistencies) between your clinically-driven choice of variables and a method-driven strategy for the fitting of the multivariable model. - Can you please detail how you reached to the conclusion that "we were able to fit a multivariable model with up to 17 predictors without overfitting"? How did you define overfitting? RESULTS (also for ABSTRACT) - You can avoid repeating "patients" when you give effectives and percentages, just use n=X, Y%. TABLES - Please change Emonton > 5 to "Edmonton frailty score > 5"

VERSION 2 – AUTHOR RESPONSE

Reviewer #3

Q: Thank you for this thorough and satisfying revision.
I still have minor comments, though:

A: We thank the Reviewer for the positive comments on our study. We have tried to address all the points raised as detailed below.

METHODS
Q: - Can you please give provide a table detailing results of univariable analyses? This would help highlight the differences (or consistencies) between your clinically-driven choice of variables and a method-driven strategy for the fitting of the multivariable model.

A: As suggested, we have now added for descriptive purposes, in a Supplementary Table, the univariable analysis of the clinically based candidate variables, since this is how the study was designed, as per clinical research question.

Q: - Can you please detail how you reached to the conclusion that "we were able to fit a multivariable model with up to 17 predictors without overfitting"? How did you define overfitting?

A: We apologise, but there was a mistake in the first revision. Indeed, the multivariable model was built on 172 cirrhotic patients, as already specified. We have now reworded the sentence in the statistical methods and added a calibration plot as Supplementary Figure 1.

RESULTS (also for ABSTRACT)
Q: - You can avoid repeating "patients" when you give effectives and percentages, just use n=X, Y%.

A: We have amended the text as suggested.

TABLES
Q: - Please change Emonton > 5 to "Edmonton frailty score > 5"

A: We have amended the text as suggested (Edmonton Frail Scale >5).

NOTE FROM THE EDITORAL OFFICE:
- You have cited reference #20 right after reference #18 which makes your citations incorrect. Please review again your main document and ensure that all references will be cited and will appear in numerical order.

A: We have checked all references, and these are correctly identified. Particularly, after reference #18, we cited references #19-22. Hence, all reference numbers are correct.

VERSION 3 – REVIEW

REVIEWER	Heidet, Matthieu Assistance Publique - Hôpitaux de Paris, SAMU 94
REVIEW RETURNED	22-Mar-2024

GENERAL COMMENTS	Thank you for these inputs, which are now fully satisfying to me. All the best,