Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Thank you very much for giving me the opportunity to read your manuscript. The hypothesis that the lockdown measures significantly impact on mental health and medical adherence of patients with CLD is important. The authors demonstrate that lockdown meaasures have a significant impact especially on their patients suffering from chronic liver disease. I am not sure whether the first part of the questionnaire where all the questions start with "are you aware of" leads to a reliable dataset or whether the mode of questionning is too suggestive. The standardized questionnaire of the second part is demonstrated in subscores, the formal analysis with paired t-test including repetitive testing without formal correction might lead to an overestimation of the effects.

Specific comments to Authors: Reply to Reviewer #1

We thank Reviewer 1 for the accurate evaluation of our paper. We have not only tried to appropriately answer questions but also to get the chance to improve the paper by integrating the interesting comments provided.

1. **Title.**

Does the title reflect the main subject/hypothesis of the manuscript? The title does not reflect that this study has been an observational study of the outpatients belonging to a single centre; perhaps the authors could add this information

Reply to Reviewer 1, Title point: We aknolwledge the suggestion of Reviewer 1 and changed the title accordingly as follows: Covid-19 emergency: changes in quality of life perception in patients with chronic liver disease. An Italian single-centre study.

2. Abstract.

Does the abstract summarize and reflect the work described in the manuscript? Yes, however, it would be great to know the exact time frame between first and second questionnaire (mean +/- SD). Perhaps the total scores of CLDQ-1 could be mentioned as well.

Reply to Reviewer 1, Abstract point: We thank Reviewer 1 for the observation that allowed us to improve the clarity of our paper. As stated in the text, given the difficulties encountered in our country as a result of the Covid Pandemic, we decided to actually question the patients only once by phone. During the telephone contact, to evaluate possible changes in the items addressed as a result of the lockdown period, the questionnaire was administered to the patients with the specific request to recall their quality-of-life perceptions at two different time points: t0, which examined these perceptions as referred to a period located two weeks before the date of ministerial lockdown decree, and t1, again addressing the same perceptions two weeks before the questionnaire completion. Thus, the patients had to recall their memories regarding those two periods of time, and were not contacted at two different time points. Ministerial lock down decree was officially applied starting from March 8th, 2020.

However, to improve clarity, we reworded the text as follows: "With the aim of evaluating possible changes in the quality of life items addressed, the questionnaire was administered to patients at the time of telephone contact with the specific request to recall their quality-of-life perceptions during two different time points. In detail, patients were asked to recall these perceptions first during time 0 (t0), a period comprising the two weeks preceding the date of ministerial lockdown decree (from 23rd February to 7th March 2020); then, in the course of the same phone call, they were asked to recall the same items as experienced throughout Time 1 (t1), the second predetermined time frame encompassing the two weeks (from 6th April to 19th April) preceding our telephone contact and questionnaire administration." We thank the Reviewer for the suggestion, we thus adopted total CLDQ-1 scores to present more clearly the results. However, for the sake of brevity, following the limits indicated by

editorial guidelines regarding the length of abstract, these have been provided as table in the text. A short sentence has been however added indicating that all six total CLDQ-1 scores were significantly worsened at t1 as compared to t0, both in the abstract and in the text.

3. Key words.

Do the key words reflect the focus of the manuscript? Perhaps the authors want to add "chronic Liver disease questionnaire" or "CLDQ-1", up to my mind it would be more specific than "autoimmune diseases or Surveys and Questionnaires"

Reply to Referee 1, Key words point: We thank Referee 1 for the suggestion, added the keywords indicated and deleted "survey and questionnaires"

4 .Background.

Does the manuscript adequately describe the background, present status and significance of the study? Perhaps the authors could provide some details (publications) concerning the change of health related quality of life during/before and after the COVID-pandemic and in how far patients with chronic diseases are more severely affected.

Reply to referee 1, Background point: We thank Referee 1 and, also according to the other reviewers indications, we implemented the references regarding the effects of the pandemic in other settings and chronic medical conditions. . The issue of quality of life among patients with chronic diseases during the Covid-19 pandemic has been the subject of clinical studies in different countries and clinical settings. During the pandemic and because of it, the presence of a chronic health problem has generally been shown to represent per se a risk factor for a worsening in the quality of life. In a study from Singapore, analysing QoL among patients with cardiovascular disease, a significant worsening of mental health related issues was described [5]. In another study from Poland, conducted among stage III and IV oncology patients undergoing chemotherapy, a questionnaire was administered including questions about quality of life during the Covid-19 pandemic: the study showed significant reduction in cognitive ($P < .0001$) and

social (P < .0001) functioning, as well as worsening of symptoms such as fatigue, insomnia and appetite [6]. In the study by Falcone et al. patients followed during the Covid-19 pandemic with thyroid cancer followed in a single endocrine cancer centre in Italy received two questionnaires to evaluate changes in quality of life. Some patients were contacted by phone and answered questions during a single call. Others, instead, had access to the questionnaires by links provided by mail. The research team produced ex novo the first questionnaire, which was developed ad hoc to explore and measure the emotional impact of the rapid spread of the Covid-19 pandemic given the absence in the literature of a similar instrument, while the second questionnaire was a validated Italian translation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). In this paper HRQoL appeared to be affected by the Covid-19 pandemic among this cohort of patients, regardless of their disease severity or current health-care needs [7]. Nevertheless, diverging results have been described among patients with IBD, both by Azzam N. *et al* and Fahad D. *et al*, in two different studies from Saudi Arabia. In the latter, as explored and analysed by means of a questionnaire submitted through various online communication channels including email, organizational portals, and social media platforms (WhatsApp, Twitter, and Facebook), HRQoL appeared to be unaffected by the Covid-19 pandemic [8-9]. In this paper, evaluating HRQoL among patients with IBD pre- and post-Covid-19 pandemic using the IBD-disk questionnaire in a Saudi Arabia tertiary care IBD centre, HRQoL appeared to be unaffected by the Covid-19 pandemic among this cohort of patients. These results suggest that different diseases, patients samples, and investigative methods adopted might account for the diverging results observed in these latter IBD studies.

5 Methods.

Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail?

a) How the first part of the questionnaire has been developed? Could it be that the question “Are you aware of..” might be suggestive to answer with “yes”? I would suggest to further discuss this issue, at least in the discussion section.

Reply to section a of question 5, Methods point: as reported in the material and methods and as suggested by the Food and Agriculture Organization of the United Nations, regarding the development of questionnaires this section was pre-tested and validated in a group of 25 inpatients, 15 (60.0%) men, mean age 64 years, affected by CLD and admitted to our hospital ward during March 2020, to verify its full comprehensibility. The results obtained in this test group were not included in the final analysis. We agree with Reviewer 1 regarding the potential suggestion effect of the question as it was formulated; however, considering the peculiar, and at times awkward, modality of contact (telephone call), which demands for simple and clear questions and answers formats, we decided to opt for this potentially criticisable but straightforward and explicit format. As suggested in the recent publication by the Food and Agriculture Organization of the United Nations, regarding the development of questionnaires to be used as instruments to investigate the impact of Covid-19 pandemic, even if in different settings, the questionnaire was designed to be easily conducted in the same manner each time [11]. We have thus formulated closed-ended questions to make answering easier. We developed simple and clear questions in order to avoid misunderstandings, and asked the simplest questions initially and the most difficult at the end, so that the interviewees could feel more comfortable. The response to each question was scored as either positive (yes) or negative (no).

Fortunately, direct white coat effect was avoided by the indirect telephone contact.

To address this correct observation provided by Reviewer 1, we reworded the text in the materials and methods section as follows for better comprehension: This section was pre-tested and validated on a smaller-scale target group of 25 inpatients, 15 (60.0%) men, mean age 64 years, affected by CLD and admitted to our hospital ward during March 2020, to verify its full comprehensibility and practical applicability as a tool to be administered over the phone.

We were aware of potential suggestion effect of this part of the questionnaire as it was formulated; however. considering the peculiar and at times awkward modality

of contact (telephone call) for which it was developed, which demands for short, simple and clear questions and answers format, grouped by category, we decided to opt for this potentially criticisable but straightforward and explicit format. The results obtained in this test group were not included in the final analysis.

A short sentence on the limits of our study was also added in the discussion section. We acknowledge that the small number of patients enrolled and the potential suggestion effect of our questionnaire in the format we have adopted might represent a limitation of our study. Nevertheless, the novelty constituted by a global viral pandemic find researchers with limited dedicated instruments to study the event, thus potential limitations are an expected element of the studies addressing quality of life.

b) Do you know comparable publications where this kind of questionnaire yielded to different results?

Reply to section b of question 5, Methods point: As indicated in background section, we have enclosed data regarding similar studies during Covid-19 pandemic in different disease conditions. To answer this question we mentioned the study by Falcone et al (please see reply to Referee 1, background point).

c) Why have the authors decided not to provide the total scoring of CLDQ-1 and how did they adjust for repetitive testing (Bonferroni), when assessing all the subscores separately? Maybe multivariate regression considering time as a variable might be an approach?

Reply to section c of question 5, Methods point:

We thank the Reviewer 1 for the comment. We did not consider correction for repetitive testing primarily because our aim was to assess multiple areas relative to quality of life perception with the use of a questionnaire intended to be a single tool, among the patients of our study group taken as a whole, during two presumed time frames, not a single hypothesis with multiple tests confronting different groups. In addition our hypothesis

was that quality of life had in fact worsened among our patients according to our everyday experience. It was indeed this clinical evidence, gathered during the assistance of our patients that lead us to perform this preliminary study. We thus wanted to highlight that, during the pandemic, quality of life was globally made worse at multiple levels within our group of patients with chronic and autoimmune liver disorders since we believe relevant to bring this aspect of care to the attention of the medical community. We also believe that bringing this issue to the attention of the healthcare community might pose the basis to develop novel strategies aimed at overcoming the difficulties posed by a global emergency.
Nevertheless, considering the small data set, following the comments of Reviewer 1, in order to improve clarity and transparency, and to provide data analysis in a more homogeneous form by reducing the number of test used, we have analyzed and reported all data by Wilcoxon non-parametric test (no changes in the results was observed as compared to the previous analysis) and, integrating the suggestion of Reviewer 1, we also provided cumulative total CLDQ-1 scores. See new tables as numbered four and five in the text. As stated in the abstract section, patients were asked to recall their perceptions as experienced during two time frames, thus according to their memories, at the only telephone call performed for each of them, so we did not consider time as a variable.

d) Might it be possible to provide a figure visualizing the whole timeline including first and second time point of the questionnaire? Is it correct that the questionnaire prior to the implementation of the lockdown-strategy the questionnaire has been answered face-to-face while at the second time point it has been done via telemedicine? Is it possible to discuss potential bias of the results depending on the manner how questions are posed, such as the "White-coat effect"?

Reply to section d of question 5, Methods point: As described in the reply to section c of question 5, Methods, and in the reply to abstract section, each patients was contacted only once by phone, and in that occasion the questionnaire was administered during this single phone call. We asked patients to recall their memories focussing on different items regarding quality of life perceptions during the two predefined time frames provided by

the interviewer. Thus, since no actual timeline variable is present, no figure will be added. Comments to format of question adopted have been provided in reply to section a of question 5, Methods point.

6. Results.

Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field?

a) The mean score of all reported domains (1,5,17) have been much better compared to the validation study of Rucci which you also cited, do you have an explanation for this?
b) Do you know the reasons for death in your deceased persons?
c) Is the ratio appropriate for this evaluated time frame?

Reply to section a of question 6, Results point: Our study evaluated patients with compensated liver cirrhosis without liver cancer, and autoimmune liver disease managed in our outpatient liver disease clinic. The majority of our patients with cirrhosis had a Child Pugh score of A (91%), and no one have a Child >7 (decompensated cirrhosis). In our population, less than half of the patients, (22, 45%) had HCV related cirrhosis, but they had already been cured from the infection with the new DAAs. Aim of the validation study by Rucci and coworkers was instead to report on the validity, reliability and sensitivity of the Italian version (Chronic Liver Disease Questionnaire-I) only among subjects with active HCV infection, who were then assigned to treatment with either interferon alone or in combination with ribavirin. In addition, the number of patients with compensated cirrhosis is not provided and no patient with concomitant HCV-autoimmune liver disease is apparently present. Given these relevant difference we did not compare the two groups and CLDQ total scores.

Reply to section b of question 6, Results point: At the time of inclusion phase, three of the patients that we had plan to include in the present study were dead and were thus excluded from the study. However, none of these three patients had died because of Covid related disease or complication.

Reply to section c of question 6, Results point: The point of period has been addressed in the reply to section c and d of question 5, Methods, and reply to Abstract section.

We believe that our experience adds novel data regarding the effects produced by the covid 19 epidemic on the perception of quality of life among patients with compensated cirrhosis and autoimmune liver disease. This paper could provide comparative information with other diseases states, consideration on adherence to treatment in autoimmune liver disorders and suggesting possible actions to support patients in times in which forced social distancing might interfere in the patient physician relationship. See also reply to sections b and c of question 7: discussion point.

7. Discussion.

Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently?

a) Yes, however, there are several aspects which could be inspiring. The authors write that their patients "correctly used personal protective equipment ….", I suggest to formulate it with more caution, because the correct use has been self-reported for example: the patients reported to correctly apply… You rise concerns concerning the fact that your patients considered changing their medication autonomously, could you further discuss this issue? How high is the percentage without COVID in your population? Several studies suggest that roughly 50% of chronic diseased

adhere to their prescribed medication schemes for example: Sabaté E, ed. Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization; 2003 2. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006;296(21):2563-2571

Reply to section a of question 7; Discussion point: We thank Reviewer 1 for the observations and for the interesting points raised. We agree on the point regarding self-reporting and reworded the sentence as follows: "The patients reported to correctly apply personal protective equipment (PPE), respect social distancing, and to frequently wash their hands, in compliance with the governmental recommendations".

Reply to sections b and c of question 7; Discussion point: Our study showed that in most cases patients did not feel the need to contact either their general practitioner or their liver disease specialist regarding the management of their liver diseases.

Only less than 1/3 of our patients with ALD (28%) had thought of modifying their treatment on their own. So most patients acted according to the indications provided by major immunology and liver disease scientific societies [18 ,3] which suggest maintaining treatments, fearing reactivation more than immunosuppression, especially in a historical period in which exacerbations had to be absolutely avoided in order to limit access to hospital facilities [2].

It is however to be underlined that, regarding overall adherence to treatment among patients with ALD, studies indicate that these patients usually display an overall adherence of 80% or more to prescribed medications (19,20). Nevertheless, these studies also show how altered/depressed mood might interfere with adherence to medical treatments. Sockalingam S. *et al* noted that in patients with ALD, overall treatment adherence was more than 80%, and that subjects with greater adherence were the less anxious and depressed. Accordingly, a recent review indicates that the co-presence of anxiety or depression, regardless of the stage of liver disease, significantly reduces quality of life and may be associated with non-adherence to prescribed therapy

regimens among patents with ALD. [21]. Thus, early recognition of "more fragile" patients might increase adherence to treatments, and in the context of a policy aimed at maintaining and boosting physician-patient relationship, telemedicine contact in times of social distancing might help reaching out and support uncertain patients in making the correct decisions [22]. Their specialists should reassure patients during these difficult social health emergencies to maintain a solid and realistic vision of their disease in order to avoid developing altered perceptions of its potential consequences, and dangerous drifts such as those regarding chronic medical treatments. It can be thus speculated that providing continuous contact with the patients, even with a limited telephone approach, would help them maintain a better quality of life and correctly follow medical prescriptions.

We added part of this text in the discussion, and suggested that telemedicine might support uncertain patients in making the correct decisions.

8 Illustrations and tables.

Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends?

a) I recommend an additional figure demonstrating the time line
   As per the above specified reasons (abstract and material and methods reply on timeline), this figure is not indicated.
b) In my version the figure legends are not completely displayed for example the numbers are not explained. We are sorry for the inconvenient. Appropriate and correct legend for figure 1 was enclosed in the version submitted.

9 Biostatistics.

Does the manuscript meet the requirements of biostatistics? There seems to be repetitive testing of various subscores without adaptation of the level of significance and no

statement concerning this issue in the discussion. Total scores have not been compared but several subscores independently

Reply to Biostatistic point: as reported in Reply to section c of question 5, Methods point, we have tried follow the comments of Reviewer 1, in order to improve clarity and transparency, and to provide data analysis in a more homogeneous form by reducing the number of test used, we have analyzed and reported all data by Wilcoxon non-parametric test. We have also commented why we have chosen not to use adjustments for repetitive testing in our current study. We followed the interesting input of Reviewer 1 comments and provided cumulative total CLDQ-1 scores. (see below)

10 Units.

Does the manuscript meet the requirements of use of SI units? n.a**.**

11 References.

Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references?

We have red with interest the Kovalic metaanalysis wich reinforce the assumption that patients with CLD are more likely to have more severe or critical COVID-19 illness when compared to those without CLD, and moreover, those with CLD are more likely to have a higher mortality. As you suggest we will insert this study among the references cited, however highlighting as limit that the majorityof the strudies of the metanalysis were from China.

12 Quality of manuscript organization and presentation.

Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate?

It is clearly written and organized. It would be interesting to know more about the differences between the organization in Italy compared to other countries.

Reply to quality of manuscript organization and presentation: we thank the reviewer for the kind words. Also according to the comments of reviewer, we have proposed in alternative our vision on how to adapt services for patients with chronic liver diseases in case of pandemic, and we hope that Reviewer 1 considers these as a possible organizational proposals to concretely approach these dire situations both in our and other countries in the future.

13 Research methods and reporting.

Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? The biostatistics review certificate contains the informed consent form The Institutional Review Board Approval Form or Document contains the recommendations to protect against COVID19

Reply to Research methods and reporting point: the indication provided by the editorial board have been fully followed.

14 Ethics statements.

For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics?

In my account this is not available (see above).

Reply to ethics statements point: requirements indicated by the editorial board have been followed, and Ethics requirements fulfilled.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Interesting study on the impact of the COVID19 situation in the hardly hit area on the care for patients with chronic liver disease. I read with interest the results which are important in understanding of how the unprecedented situation has affected patients' lives and the quality of care. Such reports are needed for the regulators to understand the need to be prepared for the pandemic situation. I have no concerns or objections, the study on a relatively small number of patients is well written, the message is clear. The findings could probably be generalized to ohter areas or countries, and perhaps other specialties or diseases (is there data on that?). What is missing, is the brief but clear suggestions of authors how to manage the situation, what are the necessary steps to be taken rapidly, when such a lockdown would take place in the future. In other words, authors opinion on how, with the same personal resources, the outpatient clinic should transform itself at the moment of lockdown. Which services should be maintained and which should be transfromed. Does their institution have a plan now what should be done, should there be one?

The Signed Informed Consent form that we upload was the informed consent that all patients that we visit in our outpatients service have to sign before the visit. With this consent they allow us to access to their personal data and to their medical informations.

Reply to Referee 2, question 1:

We cited other papers about this topic, such as a work written by Nahla A. about the HRQoL in patients with IBD pre- and post-Covid-19 pandemic using the IBD-disk

questionnaire in a tertiary care center in Saudi Arabia. In this paper no disability and HRQoL appears to be unaffected by the Covid-19 pandemic among their cohort of patients. Another study in Singapore analyzing QoL in patient whit cardiovascular disease, and a significant worsening of the mental health of these patients was observed.

Finally in Italy, Costantini at al, validated the Italian version of Covid-19 Peritraumatic Distress Index and measured the prevalence of peritraumatic distress in this phase 1 Covid-19 in general population. Nevertheless, as far as we know, our paper is currently the only one addressing this topic among patients with chronic compensated liver diseases including autoimmune forms.

Reply to Referee 2, question 2:

Our experience is limited to patients with compensated liver cirrhosis and patients with autoimmune liver disease, both of which managed on our outpatient's service. What we most noted was the importance of maintaining a contact with patients, guaranteeing them a continuity of cares. The spread of telemedicine with video call, telephone, e-mail, fax made possible to maintain a contact with patients without exposing them to the infectious risks of the face-to face visit. This new approach to visit, as recommended by the Italian Society of Hepatology (AISF), has to be institutionalized by the hospital: the visit have must have an ad hoc code, dedicated booking agendas and must be reported as a visit performed in telemedicine. This method can replace a face-to-face visit in many hepatological conditions in which, thanks to a condition of substantial clinical stability, it is not necessary to carry out a physical examination of the patient but only to collect, even indirectly, parameters clinical-laboratory easily communicated by the patient himself.

For patients with a more severe disease, and with a higher risk of HCC , a face-to face visit and the ultrasound screening remains the most appropriate methods, and a reorganization of these activity, with the introduction of adequate security measures, such as social distancing, a pre- triage, an adequate sanitation of the environments between a visit and other, is necessary to guarantee a secure service for that patients.

Finally, another aspect that has to be empathized, is the importance to create a closer communication with the general physician and with other specialist that work in smaller centers.

In conclusion what we learned from this lockdown was the ability to reorganize our work routine to new needs, implementing new techniques and methods of assistance.
At the moment some of measures indicated were adopted by our Institution. Our psychologists introduced a telephone support for patients with oncological malignities.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1 Title. The reflects the main subject of the manuscript. 2 Abstract. The abstract summarizes and reflects the work described in the manuscript. 3 Key words. The key words reflect the focus of the manuscript 4 Background. The manuscript adequately describes the background, present status and significance of the study. 5 Methods. The manuscript describes methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail. 6 Results. The research objectives were achieved by the experiments used in this study. 7 Discussion. The manuscript interprets the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. It is important to know the impact of this pandemic in all specific population. 8 Illustrations and tables. the tables were sufficient, good quality and appropriately illustrative of the paper contents. 9 Biostatistics. The manuscript met the requirements of biostatistics. 10 References. There are few references. It would be good to know a little more references about this subject. 11 Research methods and reporting. Authors prepared their manuscripts according to STROBE Statement. 12 Ethics statements. The manuscript met the requirements of ethics.