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Title: Do Peripartum and Postmenopausal Women with Primary Liver Cancer Have a Worse Prognosis? A Nationwide Cohort in Taiwan

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Dear Reviewer and Editors,

Thank you for the careful review and comments to help improve the manuscript.

We have read thoroughly and taken all comments into consideration.

Please find our point to point [replies](#) to the reviewers (marked in [blue](#)) and revised text accordingly (all [changes](#) are marked in [red](#)).

We are always grateful for your support.

With our best regards,

Sincerely,

Hsueh-Chou Lai

Reviewer #1's comment: I read with interest the study focused on the differences in survival in patients with liver cancer. Authors have chosen to compare the rate between peripartum occurrence and matched controls. At the same time, to compare prognosis according to the menopause. There are original findings of the study and the manuscript is well written and presented. The findings are important since there were only few studies addressing women with liver cancer. The only issue that I see in this study, is the definition of postmenopausal women. Authors chose to define it by age, but the problem is that age is also a strong predictor of overall mortality. The group of premenopausal women were 30 years younger than the postmenopausal group, so the statement authors make that postmenopausal women with liver cancer have worse survival only because they are postmenopausal cannot be considered as correct. Likewise, they state that they matched the group with controls the same way as in the perinatal group, but this is impossible since the postmenopausal group was defined only by age. It is also impossible to adjust the comparison for age. Having the national database it would be interesting to compare both premenopausal and postmenopausal women with propensity scored men (younger than 50, and older than 50), providing a clear and practically important (sex related) difference on how female reproductive status effect the prognosis of liver cancer.

Reply to the reviewer:

Thank you for the constructive comments. In response to the issues raised, please refer to the following explanation.

1. The definition of postmenopausal women:

As mentioned in *study populations* under **MATERIALS AND METHODS**, we defined women aged 50 and beyond as postmenopausal period based on a recent cohort analysis that indicated the mean age at menopause is 50.2 years in Taiwan. While a precise diagnosis of menopause should include clinical symptoms and hormonal tests such as FSH and AMH, we could only define menopause by age since the above data is not available from the database we have used in our study. Moreover, it is impracticable to screen out whether menopause or not via ICM codes because the information of related ICM codes is incomplete in the database.

Text revised in p.6: To further realize the correlation between menopause and PLC prognosis, we defined women aged 50 and beyond as postmenopausal period. While natural menopause may occur from 45 to 55 of age^[22], a recent cohort analysis including 36,931 postmenopausal women indicated that the mean age at menopause is 50.2 years in Taiwan^[23].

2. Applying propensity score matching in the postmenopausal group:

Thank you for pointing out this issue. Indeed, it may be impossible to adjust the covariates perfectly via the propensity score matching as we defined the postmenopausal status by age. However, our results still indicated that postmenopausal women with primary liver cancer have an overall worse prognosis.

We have also added this to the limitations in **DISCUSSION**.

Text revised in p.11: Nevertheless, these results should be interpreted with caution because of several limitations in this study. First, detailed information related to the risk of PLC is not available. ... Third, **defining menopause by age alone may not be comprehensive enough since it is hard to make an optimal covariate adjustment.**

3. Data comparing both premenopausal and postmenopausal women with propensity scored men:

Thank you for providing us a great suggestion on our future research topics. We are also planning to use the database established by our institution and another lately-released nationwide database with more detailed information for further study soon.

Science editor's comment: 1 Scientific quality: The manuscript describes a Retrospective Cohort Study of the Prognosis of women with primary liver cancer. The topic is within the scope of the WJH. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The manuscript is well written and presented, but this is impossible since the postmenopausal group was defined only by age. Authors should clarify this questions. The questions raised by the reviewers should be answered; (3) Format: There are 6 tables and 2 figures ; (4) References: A total of 30 references are cited, including 6 references published in the last 3 years; (5) Self-cited references: There are 10 self-cited references. 2 Language evaluation: Classification: Grade A. A language editing certificate issued by Enago was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJH. 5 Issues raised: (1) Please provide the official certificate issued by the English language editing company; (2) The title is too long, and it should be no more than 18 words; (3) The 'Author contributions' passage describes the specific contribution(s) made by each author. The authors' names will be listed in the following format: full family (sur)name followed by abbreviated first and middles names; for example, Bryan L Copple should be revised as Copple BL; (4) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text; (9) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision. 6 Recommendation: Conditional acceptance.

Reply to the editor:

Thank you for the comments with detailed instructions.

1. **Please provide the official certificate issued by the English language editing company.**

The English language editing was completed and the company could only provide us the receipt. The receipt is submitted for your reference.

2. **The title is too long, and it should be no more than 18 words.**

The title is shortened to “Do Peripartum and Postmenopausal Women with Primary Liver Cancer Have a Worse Prognosis? A Nationwide Cohort in Taiwan”.

3. **The ‘Author contributions’ passage describes the specific contribution(s) made by each author.**

The ‘Author contributions’ passage has been added in the 2nd page of the manuscript as follows: Tseng GW did the study conception and design, and initial draft of the manuscript; Lin MC did the data analysis and interpretation, and initial draft of the manuscript; Lai SW, C Peng CY, Chuang PH, Su WP, Kao JT participated in the study conception; Lai HC did the data analysis and interpretation, manuscript drafting and revision. Guarantor of the article: Fung-Chang Sung PhD, MPH. All authors have read and approved the final manuscript.

4. **The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.**

According to your request, the figures are submitted as a separate PowerPoint file. The tables are submitted as a separate word file as well.

5. **The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.**

Thank you for the reminder. The ‘**ARTICLE HIGHLIGHTS**’ section has been added in the 11th to 13th pages of the manuscript as follows:

ARTICLE HIGHLIGHTS

Research background

Primary liver cancer (PLC), the sixth most common cancer, accounts for the fourth leading cause of cancer-related death worldwide. Given the continuous rise of the global burden, there are increasing concerns about PLC outcomes in different populations.

Research motivation

For a long time, most studies about PLC put their focus on men due to higher incidence and riskier morbidities compared to women. Even with growing evidence on the protective effects of female sex hormones in animal research, few clinical cohorts pay attention to women with PLCs. Therefore, we are interested in the issue of how female reproductive status is related to the prognosis of PLCs.

Research objectives

This study aimed to assess whether peripartum and postmenopausal women with PLC have lower overall survival rates in a large cohort of subjects in Taiwan.

Research methods

This is a retrospective cohort of the PLC prognosis among peripartum, non-peripartum, premenopausal, and postmenopausal women using the Taiwan National Health Insurance Research Database from 2000-2012. There were 200 eligible subjects enrolled in the study of peripartum PLC, whereas 13,440 subjects enrolled in the research of menopausal PLC. 4:1 Propensity score matching was applied to adjust the covariates.

Research results

While the survival rate was overall lower in patients with peripartum PLC, there was no significant difference in the risk of death and the survival rate at different follow-up durations among patients with/without peripartum PLC. In the menopausal PLC cohort, significantly lower risk of death (aHR = 0.64, 95% CI = 0.61-0.68, $p < .001$) and higher survival rate when followed for 0.5 (72.44% vs. 64.16%), 1 (60.57% vs. 51.66%), 3 (42.92% vs. 31.28%), and 5 year(s) were seen in patients diagnosed with PLC younger than 50 years old (premenopausal) compared with patients diagnosed with PLC at or older than 50 years (postmenopausal).

Research conclusions

According to our dataset, it is concluded that younger age and female hormonal factors may reduce the occurrence and deterioration of PLCs. Females with paripartum PLC have no difference in survival rates compared with those patients without peripartum. Menopausal females with PLC have worse survival rates compared with those patients without menopause.

Research perspectives

To further clarify the association between sexual hormone and PLC outcome, future

studies with more detailed information and better-controlled confounders are required.

6. The “Case Presentation” section was not written according to the Guidelines for Manuscript Preparation. Please re-write the “Case Presentation” section, and add the “FINAL DIAGNOSIS”, “TREATMENT”, and “OUTCOME AND FOLLOW-UP” sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

There is no “Case Presentation” section in the guidelines for manuscript preparation of retrospective cohort study. Please let us know if this is not a typo.

Company editor-in-chief’s comment: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.

Reply to the editor:

Thank you for the comment and the decision of conditional acceptance. The revised manuscript and the reply to the reviewer are submitted.