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Dear Editors and Reviewers,

Thank you for your comments on our research. Your guidance and comments are very helpful. We have tried to revise our manuscript according to the reviewers' suggestions. We would like you to reconsider our revised manuscript for publication in the World Journal of Clinical Oncology. Our revised sections are described in detail as follows. The revised sections of the manuscript are highlighted.

Reviewer #1:

1. The inclusion and exclusion criteria of patients should be detailed.

Author response: The inclusion and exclusion criteria are already described in the manuscript (Page 6, lines 160-162).

2. If possible, a validation set should be used for the conclusion.

Author response: We agree and have revised the Abstract.

This is the conclusion of our study: "Preoperative CA125 levels above 20 U/ml or HE4 levels above 113 pmol/L are associated with an increased risk of having high-risk features and presented as prognostic factors in clinical stage 1 postmenopausal endometrial cancer patients".

3. A differential diagnosis of endometrial cancer from colorectal cancer or ovarian cancer should be designed when applying the CA125 or HE4.

Author response: We agree and have revised the Methods section (page 6).

It is correct that CA125 and HE4 can be elevated in other malignancies, such as ovarian cancer and colorectal cancer. However, this retrospective study was focused on endometrial cancer patients, and synchronous ovarian or colorectal cancers were excluded.

4. The authors mentioned "Normal reference value of CA125 was 0-35 U/ml and HE4 was 100-150 pmol/L."; while the cutoff values of CA125 and HE4 were respectively 20 U/ml and 13 pmol/L. How to avoid the false-positive?

Author response:

Although the normal reference values of CA125 and HE4 were 0-35 U/ml and 100-150 pmol/L, we did not use this level for distinguishing endometrial cancer patients with and without high-risk features.

From the ROC curve, we used the cut-off values that had the best sensitivity and specificity, which were 20 U/ml and 113 pmol/L for CA125 and HE4, respectively. These tumor markers are used as screening tests; therefore, they still have false positives and false negatives.

Reviewer #2:

1. The title of the study should reflect its main result

Author response: We agree and have revised the title.

The title has been changed to “Preoperative CA125 and HE4 levels for the prediction of high-risk features in clinical stage 1 postmenopausal endometrial cancer patients” according to the main results.

2. Abstract 1) Results- “The mean age was 57.4 years; 69.5% of them were menopause.” This sentence needs to be rewritten.

Author response: We agree and have revised the Abstract.

This sentence was rewritten as “The mean age of the patients was 57.4 years, and 69.5% of them were postmenopausal.”

3. Results- “Median CA125 level was 22.1 U/ml and HE4 was 104.7 pmol/L.” This sentence needs to be rewritten.

Author response: Agree and revised the Abstract.

This sentence was rewritten as “The median CA125 and HE4 levels in all patients were 22.1 U/ml and 104.7 pmol/L, respectively.”

4. Results- “CA125 and HE4 levels were significantly elevated in those with large tumor size, deep myometrial invasion, lymphovascular space invasion (LVSI), extrauterine metastasis, and advance stage.” Compared to which group?

Author response:

CA125 and HE4 levels were significantly elevated in patients with high-risk features, such as large tumor sizes, deep myometrial invasion, LVSI, extrauterine metastasis and advanced stage, compared to those without these high-risk features.

5. Introduction 1) “However, the cut-off value of HE4 was reported and varied in different studies.” The studies were not cited.

Author response: We agree and have revised the Introduction (page 6, line 148).

The references were added (reference no. 10-16).

4. The methodology could be divided into sections and there is no mention of ethical aspects of the research.

Author response: We agree and have revised the manuscript (Method, page 6).

We have rewritten the manuscript according to the STROBE statement checklist, and ethical aspects have been added.

5. Results; the tables and figures could go through a formatting process.

Author response: We agree and have made these revisions.

Reviewer #3:

1. The title should be revised as: 'Preoperative CA125 and HE4 level for prediction of high-risk features in clinical stage 1 postmenopausal endometrial cancer patients.'

Author response: We agree and have revised the Title.

2. Page 4, Line 100: The authors have cited an outdated GLOBOCAN data. Please cite the new one published in 2018: Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.

Author response: We agree and have revised the Introduction (page 5 and reference No. 1).

3. The following references should be cited and discussed. 1. Dong C, et al. Value of HE4 Combined with Cancer Antigen 125 in the Diagnosis of Endometrial Cancer. Pak J Med Sci. 2017 Jul-Aug;33(4):1013-1017. 2. Knific T, et al. Novel algorithm including CA-125, HE4 and body mass index in the diagnosis of endometrial cancer. Gynecol Oncol. 2017 Oct;147(1):126-132. 3. Stiekema A, et al. Serum HE4 is correlated to prognostic factors and survival in patients with endometrial cancer. Virchows Arch. 2017 Jun;470(6):655-664. 4. Importance of Preoperative Knowledge of the Biomarker HE4 in Early-stage Endometrial Cancer Regarding Surgical Management. 5. Presl J, et al. Importance of Preoperative Knowledge of the Biomarker HE4 in Early-stage Endometrial Cancer Regarding Surgical Management. Anticancer Res. 2017 May;37(5):2697-2702. 6. Wang Y, et al. Predictive value of serum HE4 and CA125 concentrations for lymphatic metastasis of endometrial cancer. Int J Gynaecol Obstet. 2017 Jan;136(1):58-63.

Author response: We agree and have revised the Introduction and Discussion (Reference No. 8, 9, 15, 16, 27).

These references have been added and cited in the revised manuscript.

Reviewer #4:

The manuscript requires major revision with correction of grammatical errors, note that there are many fragmented statements. Attached manuscript with some suggestions.

Author response: We agree and have made revisions.

This manuscript was revised according to the reviewer's suggestions, and it was sent to correct all grammatical errors by a native English speaker.

Best regards,

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