Peer Review File
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Reviewer A

Comment 1: *Your aim is unclear. You use a diseased population of women with cervical cancer and then you look backward in time to see what their test results were. This is not a valid epidemiologic study design.*

Reply 1: Thank you for your comment. Our research is a real-world study as we observed in clinical practice that some patients were diagnosed with cervical cancer solely through LEEP without following the three-step diagnostic protocol for cervical cancer. We retrospectively collected clinical data from patients diagnosed with cervical cancer through LEEP, assessing doctors' adherence to the standard diagnostic protocol in real-world settings and evaluating whether there was any misuse of LEEP.

This study is not a typical epidemiological research but rather focuses on evaluating issues in clinical practice. By examining past screening results, we aim to identify challenges that may have existed in physicians' implementation of standard screening strategies for cervical cancer. This information can be valuable for future improvements in screening strategies and enhancing the accuracy of early diagnosis of cervical cancer.

Certainly, we are aware of the limitations of this study design, and we explicitly acknowledge these limitations in the Discussion section. In future research, we will consider adopting more rigorous epidemiological designs to further validate our findings. Thank you for your attention and suggestions.

Changes in the text: This comment was not changed in the original manuscript.

Comment 2: *It is unclear how the LEEP procedure fits in with the diagnosis of cervical cancer. Did you exclude all cervical cancers that were so big that they were found by visual inspection? Did you exclude all cervical cancers found at colposcopic biopsy? Did you exclude all cervical cancers whose women presented with post coital bleeding?*

Reply 2: Thank you for raising these important points. Our study did not exclude the population you mentioned, as one of our objectives is to investigate potential overuse of LEEP in clinical practice. In real-world scenarios, even patients who have already presented with vaginal bleeding, visible lesions, or biopsy-confirmed cervical cancer have undergone LEEP. By collecting clinical data from patients diagnosed with cervical cancer through LEEP, we aim to gain a more accurate understanding of how medical professionals in the region implement standardized cervical cancer screening procedures, including any instances of overuse.

We appreciate your insight, and in future research, we will consider expanding our criteria to provide a more comprehensive understanding of the diagnostic landscape. Thank you for your thoughtful questions and suggestions.

Changes in the text: This comment was not changed in the original manuscript.

Comment 3: *You found 191 cancers. What is the cancer incidence in your province? What is your total population? Is this greater than the 50/100,000 women seen in Africa?*

Reply 3: Thank you for your inquiry. The focus of our study was on evaluating the implementation of standard cervical cancer screening strategies rather than providing a comprehensive assessment of cancer incidence in the province or comparing it to other regions. Therefore, we did not calculate the cancer incidence in our province or provide information about the total population in our study. Our study aimed to address specific issues related to cervical cancer diagnosis and screening practices in the context of the LEEP procedure. However, we acknowledge the importance of considering regional variations in cancer incidence for a more comprehensive understanding.

For a broader perspective on cervical cancer incidence in the province or comparisons with other regions, we recommend referring to dedicated epidemiological studies or cancer registries that specifically address such questions. We appreciate your interest in the broader context of cancer incidence and will take this into consideration for future research. Thank you for bringing this to our attention.

Changes in the text: This comment was not changed in the original manuscript.

Comment 4: How can you evaluate screening methods when not all women received all screens?

Reply 4: Thank you for highlighting this concern. We acknowledge the importance of evaluating

screening methods comprehensively, and we understand that not all women received all screens in our study. The limitations in data completeness are a crucial aspect to consider when interpreting our findings.

In our retrospective study, we aimed to assess the actual implementation of standard cervical cancer screening strategies in clinical practice. However, due to various reasons, such as patient compliance, access to healthcare, and other factors, not all women underwent all recommended screening tests. While this limitation impacts the ability to provide a complete assessment of screening methods, our study aimed to reflect the real-world challenges and practices faced by healthcare professionals in western China. In future research, we will consider strategies to address data completeness issues, possibly through prospective study designs or enhanced efforts to ensure comprehensive screening coverage.

We appreciate your valuable input and will take this into account for refining our research approach in future studies.

Changes in the text: This comment was not changed in the original manuscript.

Reviewer B

Comment 1: *The sentences on line 48-49 (Cervical cancer is the third most common cancer among women in the world, and its incidence is the highest among female genital malignancies) and 51-53 (At present, cervical cancer is one of the few gynecological malignancies that can be effectively prevented or even eliminated through early screening and HPV vaccination) require references*.

Reply 1: Thank you for bringing this to our attention. We appreciate your diligence in ensuring the accuracy and credibility of our statements. We have placed the relevant references in the appropriate place [1, 2]

Changes in the text: Page 2 line 49-51 and page 3 line 53-55.

Comment 2: *The sentence on line 63-65 (In this study, the clinicopathological data of 191 patients diagnosed as cervical cancer after 63 loop electrosurgical excision procedure (LEEP) in our hospital were collected, and the 64 results of cervical cancer screening were firstly analyzed) should*

present in result of manuscript, not at introduction.

Reply 2: Thank you for your careful review and feedback. We appreciate your suggestion regarding the placement of specific study details. We understand that the sentence on lines 63-65, providing information about the study design and data collection, would be more appropriately placed in the Results section rather than the Introduction.

Changes in the text: Page 3 line 64-68.

Comment 3: *What are the primary and secondary objectives of this study, and how was the sample size calculated based on the primary objective? Please provide more details on the statistical analysis.*

a. Evaluate the prevalence of standard cervical screening program.

b. Identify potential risk factors associated with missed diagnoses of cervical cancer within the standard screening program.

c. The difference risk factors in squamous and non-squamous carcinoma.

Reply 3： Thank you for your careful review and feedback. Our primary objective is to investigate the risk factors for patients ultimately diagnosed with cervical cancer through LEEP surgery after standard screening, which also represents the high-risk factors for missed diagnosis after standard screening. Our secondary objective is to assess whether there is overuse of LEEP surgery and evaluate the actual mastery of standard cervical cancer screening among medical personnel in the context of LEEP diagnosis for cervical cancer. Since there is currently no relevant literature reference for cervical cancer diagnosis after LEEP surgery, it is difficult to determine an appropriate effect size, and there are numerous challenges in collecting such cases. Therefore, we have endeavored to collect as many cases as possible during our research, and the current sample size is the largest possible under the existing conditions.

Changes in the text: This comment was not changed in the original manuscript.

Comment 4: *Materials and methods*

1. The basic clinical characteristics mentioned on lines 77-78 must be explicitly defined as both demographic data and risk factors you intend to evaluate. Avoid ending the sentence with "etc."

Reply 4： Thank you for your insightful feedback on our manuscript. We appreciate your attention

to detail. We have updated all the details.

Changes in the text: The clinicopathological data included basic clinical characteristics: age, age of first sexual life, menopause, history of pregnancy, The number of abortion, delivery mode, clinical symptoms, histology. Page 3 line 76-78.

Comment 5: *2. The number of 191 patients on line 82 should present in result section, not in this current section.*

Reply 5： Thank you for your valuable feedback. We appreciate your guidance on improving the organization of our manuscript. We will relocate the information about the number of patients to the Results section, as suggested.

Changes in the text: Combined with cervical cancer screening criteria, the standard screening rate, risk factors for missed diagnosis and clinicopathological characteristics were analyzed and compared. Page 4 line 80-82.

Comment 6: *3. What is the standard or non-standard screening program for cervical cancer screening in your country? Please define the details of the program.*

Reply 6： Thank you for your inquiry regarding the standard or non-standard cervical cancer screening program in our country. We appreciate your interest in obtaining more details about the screening protocol. To address your query, we will include a brief description of the cervical cancer screening program implemented in our region.

Changes in the text: Standard cervical cancer screening includes cytology, HPV testing, colposcopy and biopsy, while non-standard cervical cancer screening does not include all of them. the standard or non-standard screening program for cervical cancer screening were performed before LEEP. **This comment was not changed in the original** manuscript.

Comment 7: *Statistical analysis*

1. The detail of the basic descriptive statistic should define, such as percent, SD, mean….

Reply 7： Thank you for your feedback regarding the need for more detailed descriptive statistics in the Statistical Analysis section. We appreciate your suggestion, and we will enhance the presentation of basic descriptive statistics by including specific measures such as percentages,

standard deviations (SD), and means.

Changes in the text: Descriptive statistics, including percentages (%) for categorical variables and measures such as mean and standard deviation (SD) for continuous variables, were utilized to summarize the basic clinicopathological characteristics of the study population. The Chi-square test was employed for Categorical variables. Page 4 line 85-88.

Comment 8: *2. Dose Non-parametric test on line 88 is Mann-Whitney U test?*

Reply 8: Thank you for your inquiry regarding the non-parametric test mentioned on line 88. We appreciate your attention to detail. In response to your question, we confirm that the non-parametric test referred to in this context is the Mann-Whitney U test.

Changes in the text: The Mann-Whitney U test was used for univariate analysis when the sample number did not conform to normal distribution. Page 4 line 89-90.

Comment 9: *3. X2-test was used for multivariate analysis on line 90 is inappropriate. This is multivariable logistic regression.*

Reply 9: Thank you for bringing this to our attention. We appreciate your careful review of our manuscript. We acknowledge the error in the description of the statistical analysis on line 90, and we will correct this information accordingly and delete the wrong description.

Changes in the text: we delete "X^2 test was used for multivariate analysis". Page 4 line 90.

Comment 10: *4. Uni/multivariate is incorrect, it is uni/multivariable*.

Reply 10: Thank you for pointing out the terminology error in our manuscript. We appreciate your diligence in reviewing our work. We will make the necessary correction to accurately reflect the statistical analysis terminology.

Changes in the text: Page 4 line 91.

Comment 11: *5. How many powers or beta of this study? (80% of power?)*

Reply 11: Thank you for your question regarding the statistical power of our study. We appreciate your interest in this important aspect of the research.

Changes in the text: All the above statistical analyses used α=0.05 as the test level, all analyses

had a power > 80%. with P < 0.05 implying statistical significance. Page 4 line 92-93.

Comment 12: *6. How to calculate sample size of this study? What is an appropriate sample size?*

Reply 12： Thank you for your question regarding the calculation of the sample size for our study. We appreciate your interest in understanding the methodology behind our sample size determination. Because of the many difficulties in collecting cases, we have tried to collect as many cases as possible while conducting the study, and the current sample size is the maximum sample size under the existing conditions.:

Changes in the text: This comment was not changed in the original manuscript.

Result

Comment 1: *1. Should present the results with mean±SD for normal distributed data, median (IQR) for non-distributed data and n(%) for discrete data.*

Reply 1: Thank you for your question regarding the presentation of data of our study. We appreciate your interest in this important aspect of the research.

Changes in the text: Page 18-24.

Comment 2: *2. According to Bethesda system, ASCUS-H is ASC-H.*

Reply 2: Thank you for your comment regarding the Bethesda system. We appreciate your clarification, and we will ensure that our manuscript accurately reflects this information.

Changes in the text: 4 cases of ASCUS and 2 cases of ASC-H. (page 5, line 116)

Comment 3: *3. The 40 cases underwent a standard screening program. How many cases (%) were misdiagnosed?*

Reply 3: Thank you for your question regarding the misdiagnosis rate in the group of 40 cases that underwent a standard screening program. We appreciate your interest in obtaining this information. Can I understand that the problem you are talking about is located on line 129-130. We calculated the missed diagnosed rate (%) and added this information to the appropriate place in the manuscript.

Changes in the text: Page 5， line 128-131.

Comment 4: *Table 2, The hospital level should be presented in Table 1.*

Reply 4: Thank you for your suggestion. We appreciate your attention to detail. We will make the necessary adjustment to ensure that the hospital level is presented in Table 1, as per your recommendation.

Changes in the text: Table 1 and Table 2, page 16-19.

Comment 5: *Table 3, Show only the number and percentage of the standard and non-standard screening groups, defining them in each age group. Present other details as a table in the supplementary appendix.*

Reply 5: Thank you for your valuable suggestion. We appreciate your guidance on improving the presentation of data in Table 3. We will modify the table to include only the number and percentage of the standard and non-standard screening groups, defining them in each age group. Other details will be presented in a supplementary appendix.

Changes in the text: Table 3 (page 21) and supplementary appendix table 1(page 23-24).

Comment 6: *Table 4, The standard screening group only consisted of 40 cases. Please explain why you used N=80 in the univariable and multivariable analysis. Review and re-analyze the data correctly. Instead of the chi-square value, present the crude odds ratio with its 95% confidence interval (CI).*

Reply 6: Thank you for your comment and clarification. We appreciate your attention to the details of our study. We would like to clarify that for Table 4, we utilized the Chi-square test to compare differences, and not univariable and multivariable analysis. Therefore, the N=80 does not represent the number of cases in the standard screening group but rather the total number of cases in the study. Crude odds ratios and their 95% confidence intervals (CIs) are also not available

Changes in the text: This comment was not changed in the original manuscript.

Comment 7: *Table 5*

- Use "multivariable logistic regression analysis" instead of "instant multifactor analysis."

- Omit the regression coefficient, standard error, and Wald test results, as they are not clinically meaningful.

- Exp(B) is the adjusted odds ratio in multivariable analysis and the value should present only 2-3 decimal point with 95%CI such as 2.01(0.12-3.12): adjusted OR(95%CI)

Reply 7: Thank you for your valuable comments on Table 5. We appreciate your guidance, and we will make the necessary adjustments to improve the presentation of the results.

1.instant multifactor analysis" will be replaced with "multivariable logistic regression analysis" for clarity.

2.The regression coefficient, standard error, and Wald test results will be omitted from the table, as they are not clinically meaningful.

3.The adjusted odds ratio (Exp(B)) will be presented with only 2-3 decimal points along with the 95% confidence interval, as suggested. For example: 2.01 (0.12-3.12): adjusted OR (95% CI).

Changes in the text: Table 5(page 22)

Comment 8: *Table 6*

- Move this table to the supplementary appendix.

- Use odds ratios instead of chi-square values.

Reply 8: Thank you for your feedback on Table 6. We appreciate your suggestions, and we will make the necessary adjustments to address your concerns.

1.Table 6 will be moved to the supplementary appendix as per your recommendation.

2. Our main objective was to illustrate the differences between their groups, so the use of the chi-square values in the table.

Changes in the text: Table 6 amend to **appendix table 2 (page 24)**

Comment 9: *Discussion and Abstract*

- While the discussion section is generally good, revise it after addressing the issues mentioned above.

- Emphasize the study's primary objective more than the secondary objective. Ensure the discussion aligns with the findings.

Reply 9: Thank you for your valuable feedback on the Discussion and Abstract sections. We appreciate your guidance and will revise the text accordingly to address the issues raised.

Changes in the text: Page6, line 142-146.

Comment 10: *Other recommend*

This study includes many tables with detailed information. To improve readability, please revise the text to include only the key findings, particularly the primary objective's results. You can explain less important information in a separate paragraph and move the detailed tables to a supplementary appendix, (if you would like to present).

Reply 10: Thank you for your thoughtful recommendation. We understand the importance of improving readability in the manuscript. To address this concern, we will revise the text to focus on key findings, particularly those related to the primary objective. Less critical information will be summarized in a separate paragraph, and detailed tables will be moved to a supplementary appendix. Modifications have been highlighted with yellow markers in the Revised Manuscript.

Changes in the text: Page6, line 142-146；Supplementary appendix table 1(page 23-24) and table 2 (page 24).

1. Singh, D., et al., *Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative.* Lancet Glob Health, 2023. **11**(2): p. e197-e206.
2. Zhang, S., et al., *Cervical cancer: Epidemiology, risk factors and screening.* Chin J Cancer Res, 2020. **32**(6): p. 720-728.