

## PEER REVIEW HISTORY

*Gynecology and Obstetrics Clinical Medicine* publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| <b>TITLE (PROVISIONAL)</b> | Genitourinary syndrome of menopause among breast cancer survivors : An untold story |
| <b>AUTHORS</b>             | Saraluck, Apisith<br>Phenwan, Tharin<br>Peerawong, Thanarpan                        |

## VERSION 1 - REVIEW

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| <b>REVIEWER NAME</b>                 | <i>Krychman, Michael L.</i> |
| <b>REVIEWER AFFILIATION</b>          |                             |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest     |
| <b>AI DISCLOSURE</b>                 | none                        |
| <b>DATE REVIEW RETURNED</b>          | 01-Oct-2024                 |

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| <b>GENERAL COMMENTS</b> | <p>Article Review<br/>Gynecology and Obstetrics Clinical Medicine</p> <ul style="list-style-type: none"> <li>- Maybe best to change physicians/doctors to health care professionals since mid-level providers are often involved in the care of BC patients</li> <li>- Why was a self reported questionnaire used and not a standardized validated instrument.</li> <li>- Define patient population and their demographics better</li> <li>- Family? How was this defined?</li> <li>- Explain Thai cultural embarrassment.</li> <li>- What this study adds: we already know that in general sexuality and medical situations, patients will not voluntarily disclose symptoms and active conversations from the provider to the patient will yield better results for symptom disclosure – this was</li> <li>- Please be consistent. Oestrogen versus estrogen</li> <li>- When discussing treatments – you should separate non-hormonal- vaginal moisturizers/ lubricants, local hormonal therapy and then experimental/ non approved- these should be presented based on level of evidence and approval status.</li> <li>- What were the medication of exclusion?</li> <li>- Were the data stratified based on medication use either AI or tamoxifen use</li> <li>- Expand a bit more on the rationale about culture and its influencing reporting or not reporting GSM symptoms.</li> </ul> |
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|  | <ul style="list-style-type: none"> <li>- Please use the menopause society, IMS or other guidelines for treatment considerations—the notion that “ the absence of consensus evidence based guidelines for the safe and effective treatment of GSM is prevalent in the literature in this population. They have many guidelines and are well accepted.</li> <li>- Please discuss strengths of the paper</li> <li>- Please discuss shortcomings of the research</li> </ul> |
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| <b>REVIEWER NAME</b>                 | <b><i>Kiesel, Ludwig</i></b> |
| <b>REVIEWER AFFILIATION</b>          |                              |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest      |
| <b>AI DISCLOSURE</b>                 | none                         |
| <b>DATE REVIEW RETURNED</b>          | 18-Jan-2025                  |

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| <b>GENERAL COMMENTS</b> | <p>This manuscript investigate women who are survivors of breast cancer reporting genito-urinary symptoms which is a relevant clinical concern. The study explores their attitude towards disclosing these symptoms and is the first of its kind.</p> <p>The investigation is well defined and provides clear statements of their findings.</p> |
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#### VERSION 1 – AUTHOR RESPONSE

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| Comment                                                                                                                                        | reply                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Reviewer: 1                                                                                                                                    | We would like to sincerely thank the reviewer for the thoughtful and constructive feedback. We have carefully addressed each point raised, as outlined below                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| - Maybe best to change physicians/doctors to health care professionals since mid-level providers are often involved in the care of BC patients | Thank you for this suggestion. We agree and have revised the manuscript by replacing the terms “physicians” and “doctors” with “healthcare professionals” throughout the text.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| - Why was a self-reported questionnaire used and not a standardized validated instrument.                                                      | <p>We thank the reviewer for this insightful comment. The rationale for using a self-reported questionnaire in this study was based on the following reasons:</p> <ol style="list-style-type: none"> <li>1. One of the primary objectives of this study was to explore the issue of disclosure of GSM symptoms, which is an underreported and culturally sensitive topic, particularly in the Thai/Asian context (as the main rationale of our study). There is currently no standardized or validated questionnaire specifically designed to assess disclosure behavior or attitudes toward GSM symptoms. Therefore, we used questions from a previously published study conducted among Thai postmenopausal women (Reference 15) that explored similar disclosure issues.</li> <li>2. We intentionally used a self-reported, paper-based questionnaire format to allow participants to report sensitive symptoms and disclosure behavior confidentially, without direct interviewer interaction. We believe this approach reduced participants' feelings of embarrassment, cultural hesitation, or fear of judgment, thus encouraging more honest and open responses.</li> <li>3. While validated questionnaires for GSM exist, they have not been adapted or validated for the specific context of Thai BCSs, especially concerning disclosure attitudes. Therefore, using a self-reported survey referencing a locally used questionnaire helped ensure linguistic and cultural appropriateness.</li> </ol> |
| Define patient population and their demographics better                                                                                        | <p>Thank you for this helpful comment.</p> <p>We have revised the <b>Participants (Methods, Result)</b> and <b>Table 1</b> sections to provide clearer definitions of the study population, including sociodemographic and clinical characteristics. Education level to improve interpretability. Menopausal status, marital status, and treatment history were also detailed. We believe this revision improves the clarity and transparency of our cohort description.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| Family? How was this defined?                                                                                                                                                                                                                                 | Thank you for pointing this out. In our study, the term “family” was defined as non-partner immediate family members, including parents, children, and siblings. Spouses or sexual partners were not included in this category. We have now clarified this definition in the <b>Methods section</b> and the <b>Figure 2 legend</b> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Explain Thai cultural embarrassment.                                                                                                                                                                                                                          | We appreciate this important observation. We have now stated first part in introduction and expanded the Discussion section to explain that in Thai culture, topics related to sexual health, menopause, and intimate symptoms are considered sensitive and often associated with embarrassment or shame, leading to reluctance in disclosure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| What this study adds: we already know that in general sexuality and medical situations, patients will not voluntarily disclose symptoms and active conversations from the provider to the patient will yield better results for symptom disclosure – this was | <p>Thank you very much for your insightful comment. We fully agree that previous studies, particularly from developed Western healthcare settings, have shown that patients often do not voluntarily disclose sensitive symptoms, and that provider-initiated conversations improve disclosure rates.</p> <p>From your comment, we have revised the “What is already known on this topic” section to include this foundational knowledge:</p> <p><i>“Patients may hesitate to disclose symptoms unless prompted by healthcare providers, especially when topics are intimate or sensitive.”</i></p> <p>At the same time, we respectfully note that our study adds culturally specific evidence from Thai breast cancer survivors, a population underrepresented in GSM literature. While the general principle of disclosure behavior may be known, our findings demonstrate a uniquely high rate of non-disclosure driven by embarrassment, and further highlight that two-thirds of symptomatic women expected the <b>physician to initiate</b> the conversation reflecting strong cultural influences on communication.</p> <p>Additionally, we incorporated your suggested phrasing,</p> <p><i>“Active provider-initiated conversations yield better symptom disclosure,”</i></p> <p>into the “How this study might affect research, practice or policy” section, to clearly align with your feedback.</p> <p>We hope these revisions clarify the specific contribution of our study and appreciate your thoughtful guidance in improving its clarity and positioning.</p> |

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| Please be consistent. Oestrogen versus estrogen                                                                                                                                                                                        | Thank you for noticing this inconsistency. We have now standardized the spelling to “estrogen” throughout the manuscript in accordance with journal preferences.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| When discussing treatments – you should separate non-hormonal- vaginal moisturizers/ lubricants, local hormonal therapy and then experimental/ non approved- these should be presented based on level of evidence and approval status. | <p>Thank you for this helpful and constructive suggestion. In response, we have revised the treatment discussion in the <b>Discussion</b> section to clearly separate GSM management options into three categories non-hormonal therapies, local hormonal therapies, and experimental or non-approved therapies.</p> <p>The revised paragraph reflects these distinctions and includes commentary on each option’s level of evidence and regulatory status. We appreciate your feedback, which helped strengthen the clarity and clinical relevance of our treatment discussion.</p>                                                                                                                                                                               |
| What were the medication of exclusion?                                                                                                                                                                                                 | Thank you for this important comment. We have now clarified the medication exclusion criteria in the <b>Methods – Participants</b> section. Participants were excluded if they were currently using any local vaginal estrogen (e.g., estriol or estradiol), systemic hormone therapy, ospemifene, vaginal DHEA, or other investigational or hormone-modulating treatments for GSM. In addition, we excluded participants who reported using herbal supplements known or marketed to have estrogen-like properties (e.g., <i>Pueraria mirifica</i> , soy isoflavones), as these may also influence GSM symptoms or disclosure behavior. This revision was made to reduce potential confounding and improve the interpretability of symptom patterns in our cohort. |
| Were the data stratified based on medication use either AI or tamoxifen use                                                                                                                                                            | <p>Thank you for this insightful comment. In our study, anti-estrogen therapy use was recorded as a binary variable (received vs. not received), and specific differentiation between tamoxifen and aromatase inhibitors (AIs) was not systematically collected.</p> <p>We have now clarified and acknowledged it as a limitation in the <b>Discussion</b>.</p>                                                                                                                                                                                                                                                                                                                                                                                                    |
| Expand a bit more on the rationale about culture and its influencing reporting or not reporting GSM symptoms.                                                                                                                          | Thank you for highlighting this. We have expanded the rationale in the <b>Introduction</b> section to further elaborate on how Thai cultural norms, social beliefs, and embarrassment may influence the underreporting of GSM symptoms among breast cancer survivors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Please use the menopause society, IMS or other guidelines for treatment considerations—the notion that “ the absence of consensus evidence based guidelines for the safe and effective treatment of GSM is prevalent in the            | We have revised the relevant section of the manuscript to more accurately reflect this nuance. The updated text now acknowledges the existence and strength of current guidelines, while clarifying that the challenge lies in tailoring these recommendations to breast cancer survivors based on treatment history, risk profile, and cultural factors. We appreciate your                                                                                                                                                                                                                                                                                                                                                                                       |

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| literature in this population. They have many guidelines and are well accepted.                                                                                                                                                                                                                                                                 | feedback in helping us improve the accuracy and clarity of this discussion.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Please discuss strengths of the paper                                                                                                                                                                                                                                                                                                           | <p>Thank you for your valuable feedback. We have revised the final paragraph of the Discussion section to explicitly highlight the strengths of our study. These include the novelty of the research, being the first to explore the full spectrum of GSM symptoms. We also emphasize the cultural context, which provides unique insight into disclosure behavior in a setting where such discussions are often considered sensitive or taboo. In addition, we note the strength of using anonymous self-reported questionnaires, which encouraged more open expression of “untold” experiences that may be missed in face-to-face interviews. This culturally specific data is clinically relevant for guiding future communication strategies and individualized survivorship care.</p> <p>We hope that these additions address your comment and help clarify the value of our study.</p>                                                                                                            |
| Please discuss shortcomings of the research                                                                                                                                                                                                                                                                                                     | <p>Thank you for this helpful suggestion. In response, we have expanded the <b>Limitations</b> section of the Discussion.</p> <p>we acknowledge that the cross-sectional design limits causal inference and that the sample size, while adequate for descriptive and bivariate analyses, was not sufficient for robust multivariate modeling. We also clarified that anti-estrogen therapy was recorded only as a binary variable (yes/no), and not stratified into tamoxifen and aromatase inhibitors (AIs), despite their differing mechanisms and clinical impacts on GSM symptoms. Lastly, we discuss the potential limitation in generalizability due to the study’s Thai population, while also emphasizing that this enhances its relevance for developing culturally tailored survivorship care strategies in Asian contexts.</p> <p>We believe this expanded discussion more transparently addresses the study's limitations and provides important context for interpreting our findings.</p> |
| Reviewer: 2                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p>This manuscript investigate women who are survivors of breast cancer reporting genito-urinary symptoms which is a relevant clinical concern. The study explores their attitude towards disclosing these symptoms and is the first of its kind.</p> <p>The investigation is well defined and provides clear statements of their findings.</p> | <p>We sincerely thank the reviewer for your positive feedback and recognition of the relevance and clarity of our study. We appreciate your encouraging comments and are glad that the design and findings were found to be well defined and meaningful. This support reinforces the importance of addressing GSM in breast cancer survivorship care.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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| Associate Editor                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p>1.Patient Cohort Homogeneity Concerns:</p> <p>Please clarify whether the selected breast cancer patients exhibited uniformity in tumor staging, histological grading, and treatment protocols. Heterogeneity in these parameters may confound the interpretation of study outcomes.</p> | <p>We thank the Associate Editor for this valuable comment. We acknowledge that the study participants exhibited variability in tumor stage, histological grading, and treatment protocols, which may contribute to clinical heterogeneity. However, we believe that the cohort also demonstrated an acceptable level of clinical homogeneity relevant to our study objectives. Specifically, we applied an inclusion criterion requiring that all participants had completed their primary breast cancer treatment including surgery, chemotherapy, and/or radiation therapy at least three months prior to recruitment. This approach was intended to ensure that participants were in the <b>survivorship phase</b>, as defined by the National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer Survivorship Care, and to minimize the potential influence of acute treatment-related effects on genitourinary symptoms and disclosure behavior. We have clarified this criterion in the <b>Methods → Participants</b> section and acknowledged its relevance in the Discussion.</p>                                                                                                                                                                                                         |
| <p>Were there standardized criteria to ensure consistency in disease progression monitoring?</p>                                                                                                                                                                                           | <p>As this was a cross-sectional study focusing on GSM symptoms and disclosure behavior, our objective was not to evaluate oncological outcomes. Therefore, standardized criteria for disease progression monitoring were not applied. Participants were recruited during routine follow-up care after completion of active treatment, and baseline tumor stage and treatment protocols were recorded. We have now acknowledged the absence of standardized disease progression monitoring as a limitation in the Discussion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>2.Questionnaire Validity Issues:</p> <p>The use of a self-reported questionnaire introduces potential subjectivity bias.</p>                                                                                                                                                            | <p>We thank the reviewer for this insightful comment. The rationale for using a self-reported questionnaire in this study was based on the following reasons:</p> <ol style="list-style-type: none"> <li>1. One of the primary objectives of this study was to explore the issue of disclosure of GSM symptoms, which is an underreported and culturally sensitive topic, particularly in the Thai/Asian context (as the main rationale of our study). There is currently no standardized or validated questionnaire specifically designed to assess disclosure behavior or attitudes toward GSM symptoms. Therefore, we used questions from a previously published study conducted among Thai postmenopausal women (Reference 15) that explored similar disclosure issues.</li> <li>2. We intentionally used a self-reported, paper-based questionnaire format to allow participants to report sensitive symptoms and disclosure behavior confidentially, without direct interviewer interaction. We believe this approach reduced participants' feelings of embarrassment, cultural hesitation, or fear of judgment, thus encouraging more honest and open responses.</li> <li>3. While validated questionnaires for GSM exist, they have not been adapted or validated for the specific context of</li> </ol> |

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|                                                                                                                                                                                                                           | Thai BCSs, especially concerning disclosure attitudes. Therefore, using a self-reported survey referencing a locally used questionnaire helped ensure linguistic and cultural appropriateness.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 3.Baseline Data Completeness:                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| The baseline characteristics of patients (e.g., BMI, education level, income status) are critical confounding variables in oncology studies. Were these factors systematically recorded and adjusted for in the analysis? | <p>Thank you for this insightful comment. In our study, key baseline characteristics including age, BMI, marital status, and education level were systematically recorded and are presented in Table 1. We have reviewed and clarified the reporting of these variables for greater accuracy. Among these, education level was found to be significantly associated with GSM symptom disclosure and was further analyzed using binary logistic regression. However, due to the limited number of disclosure events (n = 30), we did not conduct multivariate regression in order to avoid model overfitting. This decision has now been clarified in both the <b>Statistical Analysis</b> and <b>Limitations</b> sections of the manuscript.</p> <p>We also acknowledge that income status, while potentially an important socioeconomic confounder, was not collected in this study. This limitation has been addressed in the revised <b>Limitations</b> section, with a recommendation for its inclusion in future research.</p> |
| If not included, please discuss how the omission might impact the generalizability of findings, particularly in relation to socioeconomic influences on treatment adherence or outcomes.                                  | Thank you for raising this important point. We have now added this consideration to the <b>Limitations</b> section and highlighted the importance of incorporating income and broader socioeconomic factors in future studies to improve the depth and applicability of results.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

## VERSION 2 – REVIEW

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| REVIEWER NAME                 | <b>BERESHY, RANEEM</b>                 |
| REVIEWER AFFILIATION          | Yarmouk University Faculty of Medicine |
| REVIEWER CONFLICT OF INTEREST | No Conflict of Interest                |
| AI DISCLOSURE                 | none                                   |
| DATE REVIEW RETURNED          | 27-Apr-2025                            |

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| GENERAL COMMENTS | Dear authors of the article titled: |
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|  | <p>"Genitourinary syndrome of menopause among breast cancer survivors : An untold story "</p> <p>The manuscript highlight consequences on women from psychosocial aspect in terms of Genitourinary syndrome of menopause "GSM", although fewer comments outlined below, would you consider them kindly :</p> <p>-Highlight by which way the hormonal changes after surgical management for breast cancer present .</p> <p>-The body mass index reflecting the fat stores in our body may play vital role through peripheral aromatization process were hormones synthesis happen in women especially postmenopause; which may impact to which degree the genitourinary may manifest.</p> <p>-Consider terms such as secondary amenorrhea, premature ovarian failure through the context of your manuscript .</p> <p>-Highlight the scale used to determine the severity index of GSM.</p> <p>-Reflect the idea from including postmenopausal women whom naturally got menopause; if we study the impact of breast cancer therapies on women by which its induce menopause .</p> |
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| <b>REVIEWER NAME</b>                 | <b><i>Giannini, Andrea</i></b> |
| <b>REVIEWER AFFILIATION</b>          | University of Rome La Sapienza |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest        |
| <b>AI DISCLOSURE</b>                 | none                           |
| <b>DATE REVIEW RETURNED</b>          | 30-Apr-2025                    |

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| <b>GENERAL COMMENTS</b> | <p>I read with great interest the Manuscript titled "Genitourinary syndrome of menopause among breast cancer survivors : An untold story ". In my opinion, this topic analyzed is interesting enough to attract readers' attention.</p> <p>Although the manuscript can be considered already of good quality, I would suggest following recommendations:</p> <p>- I suggest a round of language revision, in order to correct few typos and improve readability.</p> <p>- The authors could extend and improved the discussion by evaluating and citing current evidence about possible therapeutic strategy to improve quality of life and symptoms of syndrome of menopause. I would be glad if the authors discuss this important point, referring to: PMID 32252962 and 36037664.</p> <p>Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest to the readers and, in my opinion, it deserves priority to be published after minor revisions.</p> |
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## VERSION 2 – AUTHOR RESPONSE

| Comment                                                                                                                                                                                                                                                           | reply                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| <p>Reviewer3:</p> <p>The manuscript highlight consequences on women from psychosocial aspect in terms of Genitourinary syndrome of menopause “GSM”, although fewer comments outlined below, would you consider them kindly :</p>                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p>-Highlight by which way the hormonal changes after surgical management for breast cancer present .</p>                                                                                                                                                         | <p>We appreciate the reviewer’s thoughtful comment. However, we would like to clarify that our study focused specifically on breast cancer survivors who experienced a hypoestrogenic state due to systemic treatments such as chemotherapy and radiation therapy, as clearly stated in the <b>inclusion criteria</b> section of the manuscript. Surgical treatment, such as mastectomy, does not directly cause hormonal changes and was not considered a contributing factor to hypoestrogenism in this context.</p> <p>The surgical data presented in Table 1 were included solely to describe the baseline clinical characteristics of the participants and to provide a comprehensive overview of their cancer treatment history, not to imply a hormonal consequence of surgery.</p> |
| <p>-The body mass index reflecting the fat stores in our body may play vital role through peripheral aromatization process were hormones synthesis happen in women especially postmenopause; which may impact to which degree the genitourinary may manifest.</p> | <p>Thank you for this insightful observation. We agree that BMI may influence the severity of GSM symptoms through peripheral aromatization, which contributes to circulating estrogen levels in postmenopausal women. While this mechanism is biologically plausible, our analysis did not find a statistically significant association between BMI and symptom disclosure or severity in this cohort. However, we have now added a brief discussion of this point in the manuscript to acknowledge its potential relevance and recommend further investigation in future studies.</p>                                                                                                                                                                                                    |
| <p>-Consider terms such as secondary amenorrhea, premature ovarian failure through the context of your manuscript .</p>                                                                                                                                           | <p>Thank you for this valuable suggestion. We agree that the terms <i>secondary amenorrhea</i> and <i>premature ovarian failure (or insufficiency)</i> are important and clinically appropriate for describing the menstrual and hormonal disturbances that may occur in breast cancer survivors due to systemic treatments. In response, we have revised the manuscript to incorporate these terms where contextually appropriate, especially in relation to treatment-induced hypoestrogenism and early menopause among our study population.</p>                                                                                                                                                                                                                                        |

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| <p>-Highlight the scale used to determine the severity index of GSM.</p>                                                                                                                                                                                                                                                                                                      | <p>Thank you for this important point. We acknowledge the need to clarify the basis for determining the severity of GSM symptoms. In our study, the severity index was derived from participants' self-reported responses to the Thai GSM questionnaire, which was adapted from a previously validated survey used in Thai postmenopausal women (reference 15). Participants rated each symptom on an ordinal scale ranging from "None," "Mild," "Moderate," "Severe," to "Worst." This scale was used to quantify the symptom burden and categorize severity accordingly, as presented in Table 2. We have now clarified this point in the <b>Methods</b> section of the manuscript.</p>                                                                                                                                                                                                                                     |
| <p>-Reflect the idea from including postmenopausal women whom naturally got menopause; if we study the impact of breast cancer therapies on women by which its induce menopause .</p>                                                                                                                                                                                         | <p>Thank you for this insightful comment. We acknowledge that including both naturally menopausal women and those with treatment-induced menopause may introduce heterogeneity. However, our study primarily aimed to explore the prevalence and disclosure of GSM symptoms among breast cancer survivors as a whole, rather than to directly compare GSM severity between natural and iatrogenic menopause.</p> <p>To address potential confounding, we clearly described menopausal status (natural vs. treatment-induced) and presented it in the demographic data (Table 1). In the analysis, we also compared disclosure patterns between these two groups, although the association was not statistically significant.</p> <p>Nonetheless, we agree this is a critical point and have now included a note in the <b>Discussion</b> to reflect this limitation and recommend stratified analysis in future research.</p> |
| <p>Reveiwer4</p> <p>I read with great interest the Manuscript titled "Genitourinary syndrome of menopause among breast cancer survivors : An untold story ". In my opinion, this topic analyzed is interesting enough to attract readers' attention.</p> <p>Although the manuscript can be considered already of good quality, I would suggest following recommendations:</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p>- I suggest a round of language revision, in order to correct few typos and improve readability.</p>                                                                                                                                                                                                                                                                       | <p>We appreciate the reviewer's suggestion. In response, we have performed a comprehensive language revision using a professional</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | editing service (Editage) to correct typographical errors and enhance the overall clarity and readability of the manuscript.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| - The authors could extend and improved the discussion by evaluating and citing current evidence about possible therapeutic strategy to improve quality of life and symptoms of syndrome of menopause. I would be glad if the authors discuss this important point, referring to: PMID 32252962 and 36037664. Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest to the readers and, in my opinion, it deserves priority to be published after minor revisions. | Thank you for highlighting this important point. We agree that a discussion of current therapeutic strategies for managing GSM in breast cancer survivors is essential to improve the clinical relevance and applicability of our findings. In response, we have revised and expanded the Discussion section by incorporating current evidence and recommendations from recent publications, including the North American Menopause Society and ISSWSH consensus statement (PMID: 32252962) and a recent review highlighting both challenges and emerging strategies (PMID: 36037664). These references have now been cited appropriately to strengthen our discussion of treatment options and clinical implications. |

### VERSION 3 - REVIEW

|                                      |                                        |
|--------------------------------------|----------------------------------------|
| <b>REVIEWER NAME</b>                 | <b><i>BERESHY, RANEEM</i></b>          |
| <b>REVIEWER AFFILIATION</b>          | Yarmouk University Faculty of Medicine |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest                |
| <b>AI DISCLOSURE</b>                 | none                                   |
| <b>DATE REVIEW RETURNED</b>          | 07-May-2025                            |

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| <b>GENERAL COMMENTS</b> | All Comments have been Considered |
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| <b>REVIEWER NAME</b>                 | <b><i>Giannini, Andrea</i></b> |
| <b>REVIEWER AFFILIATION</b>          | University of Rome La Sapienza |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest        |
| <b>AI DISCLOSURE</b>                 | none                           |
| <b>DATE REVIEW RETURNED</b>          | 13-May-2025                    |

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| <b>GENERAL COMMENTS</b> | <p>I read with great interest the Manuscript titled "Genitourinary syndrome of menopause among breast cancer survivors : An untold story ". In my opinion, this topic analyzed is interesting enough to attract readers' attention.</p> <p>Although the manuscript can be considered already of good quality, I would suggest following recommendations:</p> <ul style="list-style-type: none"> <li>- I suggest a round of language revision, in order to correct few typos and improve readability.</li> <li>- It would be interesting to add few lines about current evidence about this topic and various possible therapeutic strategies for treatment of Genitourinary Syndrome of Menopause's symptoms and quality of life. I would be glad if the authors discuss this important point, referring to PMID: 28490209 and 32744453.</li> </ul> |
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|  | Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest to the readers and, in my opinion, it deserves the priority to be published after minor revisions. |
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### VERSION 3 – AUTHOR RESPONSE

Reviewer 3: All Comments have been Considered

Response: Thank you so much.

Reviewer4:

- I suggest a round of language revision, in order to correct few typos and improve readability.

Response: In response, we have performed a comprehensive language revision using a professional editing service (Editage) to correct typographical errors and enhance the overall clarity and readability of the manuscript.

- The authors could extend and improved the discussion by evaluating and citing current evidence about possible therapeutic strategy to improve quality of life and symptoms of syndrome of menopause. I would be glad if the authors discuss this important point, referring to: PMID 32252962 and 36037664.

Response:

We appreciate the reviewer's valuable suggestion to expand the discussion with relevant evidence on therapeutic strategies for genitourinary syndrome of menopause (GSM). We fully agree that improving the quality of life of breast cancer survivors (BCSs) with GSM is of critical importance, and our discussion has already addressed this topic with support from several major international guidelines and original studies, including references from the North American Menopause Society (NAMS), International Menopause Society (IMS), European Menopause and Andropause Society (EMAS), and recent systematic reviews (e.g., References 8, 9, 19, 23, 24, 25, and 39).

Regarding the two suggested references:

- PMID 28490209 reports on a small-scale study with only 46 participants, and while relevant, its sample size and publication year (2017) limit its generalizability and relevance as current high-level evidence.

- PMID 32744453 is a narrative review authored by the reviewer. While the review provides a comprehensive summary, our manuscript prioritizes referencing original data and consensus guidelines to maintain objectivity and comply with journal recommendations on referencing style and citation balance.

Additionally, we have currently reached the journal's limit of 40 references. We have therefore carefully prioritized citations based on guideline-level evidence and recent high-quality studies with broader applicability.

Nonetheless, we sincerely value the reviewer's contribution and have ensured that the discussion emphasizes a wide range of evidence-based therapeutic options and emerging strategies for GSM in BCSs.

#### VERSION 4 – REVIEW

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| REVIEWER NAME                 | Giannini, Andrea               |
| REVIEWER AFFILIATION          | University of Rome La Sapienza |
| REVIEWER CONFLICT OF INTEREST | No Conflict of Interest        |
| AI DISCLOSURE                 | none                           |
| DATE REVIEW RETURNED          | 26-May-2025                    |

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| GENERAL COMMENTS | The quality of the manuscript has improved thanks to the changes made. I think it could be of interest to the readers and, in my opinion, it deserves the priority to be published. |
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#### VERSION 4– AUTHOR RESPONSE

| Comment                                                                                                                                                                                                                                                                                                                                                             | Reply                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Associate Editor</b><br><br>Ensure that all data in the article is truthful, accurate, and reliable, and the literature citations are error-free (Reference format: three authors + et al.). Optimize the images. For example, in Figure 1, capitalize the first letter of each phrase on the horizontal axis. Please try to revise and return it within 3 days. | <ul style="list-style-type: none"><li>- All references have been reviewed and updated to follow the required format of “three authors + <i>et al.</i>” where applicable. The reference list now includes exactly 40 citations.</li><li>- Figure 1 has been revised to ensure capitalization of the first letter of each phrase on the horizontal axis as requested.</li><li>- We have reviewed all content to ensure that the data presented are truthful, accurate, and reliable, and that all citations are correct.</li></ul> |
| <b>Editor-in-Chief</b><br><br>The attachment is a recent literature, which also involves the management of menopausal symptoms in breast cancer survivors. Would it be possible to include this as a reference?                                                                                                                                                     | We have included the suggested recent literature (Partridge AH. <i>N Engl J Med.</i> 2025) discussing novel non-hormonal management for menopausal symptoms among breast cancer survivors. The reference has been incorporated into the discussion section and added to the reference list.                                                                                                                                                                                                                                      |

#### VERSION 5 - REVIEW

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| REVIEWER NAME                 | <b>Giannini, Andrea</b>        |
| REVIEWER AFFILIATION          | University of Rome La Sapienza |
| REVIEWER CONFLICT OF INTEREST | No Conflict of Interest        |
| AI DISCLOSURE                 | none                           |
| DATE REVIEW RETURNED          | 06-Jul-2025                    |

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| GENERAL COMMENTS | <p>I read with great interest the Manuscript titled "Genitourinary syndrome of menopause among breast cancer survivors : An untold story ". In my opinion, this topic analyzed is interesting enough to attract readers' attention.</p> <p>Although the manuscript can be considered already of good quality, I would suggest following recommendations:</p> <ul style="list-style-type: none"><li>- I suggest a round of language revision, in order to correct few typos and improve readability.</li><li>- The authors could extend and improved the discussion by evaluating and citing current evidence about possible therapeutic strategy to improve quality of life and symptoms of genitourinary syndrome of menopause. I would be glad if the authors discuss this important point, referring to: PMID 32252962 and 36037664.</li></ul> <p>Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest to the readers and, in my opinion, it deserves priority to be published after minor revisions.</p> |
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#### VERSION 5 – AUTHOR RESPONSE

1. The comments from Reviewer #4 appear identical to those received during Round 2, regarding language revision and discussion of therapeutic strategies (PMID: 32252962 and 36037664).

– These issues were fully addressed and included in our revised manuscript and rebuttal during Round 2.

– Moreover, in Round 4, Reviewer#4 clearly stated that the manuscript was of good quality and ready for publication after minor revisions.\*\* No new comments were provided in that round.

2. \*\*The current Associate Editor comment\*\* seems to be a repetition of the \*\*Editor-in-Chief's suggestion from Round 4\*\*, recommending citation of the recent NEJM article (PMID: 40454644).

– We have already cited and incorporated this article into the discussion and reference list as requested.

Based on this, we suspect that the current minor revision request may be a result of a \*\*systematic error that recycled comments from earlier rounds\*\*.

We kindly request clarification on whether our Round 4 submission (which included all requested revisions) is under the correct review and that the most recent version is being evaluated.

**VERSION 6 - REVIEW**

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| <b>REVIEWER NAME</b>                 | <b><i>Giannini, Andrea</i></b> |
| <b>REVIEWER AFFILIATION</b>          | University of Rome La Sapienza |
| <b>REVIEWER CONFLICT OF INTEREST</b> | No Conflict of Interest        |
| <b>AI DISCLOSURE</b>                 | none                           |
| <b>DATE REVIEW RETURNED</b>          | 14-Jul-2025                    |

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| <b>GENERAL COMMENTS</b> | The quality of the manuscript has improved thanks to the changes made. I think it could be of interest to the readers and, in my opinion, it deserves the priority to be published. |
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