

## Peer Review File

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### Reviewer A

**Comment 1:** A key point to consider in this work is the inclusion criteria. The authors included patients undergoing total thyroidectomy and partial surgery. Table 2 shows that they included 19 unilateral surgeries and patients with lymph node metastases. However, there is no data in the manuscript regarding the type of lymphadenectomy performed (central or lateral neck dissection?). This data is necessary for the analysis because it is known that central neck dissection increases the risk of devascularization and/or accidental removal of the parathyroid glands. It is known that patients undergoing lobectomy are not at risk of hypocalcemia. Therefore, it would be appropriate to repeat the analysis by removing patients undergoing partial surgery.

Reply 1: We sincerely thank the reviewer for suggestions. We have carefully read the references provided by the reviewers and benefited a lot. As mentioned in the article, central neck lymph node dissection was an independent risk factor for postoperative hypocalcemia and patients who undergo lobectomy are not at risk for hypocalcemia. In our research, all enrolled patients were treated with “unilateral thyroidectomy or bilateral thyroidectomy + central lymph node dissection ± lateral cervical lymph node dissection” according to the side of their cancer. That's why we didn't exclude patients with unilateral thyroidectomy. We have revised this part according to reviewer's suggestion. For details, see page 4, line 116-118.

Changes in the text: All enrolled patients underwent unilateral thyroidectomy or bilateral thyroidectomy + central lymph node dissection ± lateral cervical lymph node dissection. (see page 4, line 116-118 for details).

**Comment 2:** Line 84-85 “Serum calcium is at a critical value or low level” The authors should explain what they mean by critical value or low. They should give the definition of hypocalcemia and indicate the values for which they considered it appropriate to practice therapy with calcium or vitamin D.

Reply 2: The authors apologize for the confusing the reviewer. “Serum calcium is at a critical value or low level” means that serum calcium is lower than the lower limit of the reference value provided by the laboratory of our hospital. The reference value of serum calcium in the laboratory of our hospital is shown on page 5, line 136-137. In the manuscript, the context about the diagnostic criteria for SH was shown on page 5, line 129-133. In order to make the expression more clear, we have revised the relevant parts of the original manuscript, as detailed on page 5, line 129-137. The author is sorry for not mentioning SH management in the original text. In this study, once diagnosed with SH, oral calcium supplementation should be initiated promptly. If symptoms remain significant after oral calcium supplementation, or if severe symptoms (such as convulsions of limbs) are present from the outset, intravenous calcium gluconate supplementation should be administered. To give a clearer understanding, in the revised manuscript, we have added the management of SH (page 5, line 137-140).

Changes in the text: (4) Serum calcium is lower than the lower limit of the reference value provided by the laboratory of our hospital. ( see page 5, line132-133 for details).

Once diagnosed with SH, oral calcium supplementation should be initiated promptly. If symptoms remain significant after oral calcium supplementation, or if severe symptoms (such as convulsions of limbs) are present from the outset, intravenous calcium gluconate supplementation should be administered. ( see page 5, line137-140 for details).

**Comment 3:** Line 95 “serum calcium is 2.025 to 2.75 mmol/L”: the authors should explain whether in their department 2.75 mmol/l is considered a normal value of calcemia since for other department it may indicate hypercalcemia.

Reply 3: Thank you for your kind suggestion. As we all know, different detection methods for serum calcium may have different reference values. In our center, hypocalcemia was diagnosed by reference values rely on the clinical laboratory of Nanjing Drum Tower Hospital, The Affiliated Hosptial of Nanjing University Medical

School. We consider the serum calcium values within this reference range to be normal.

Changes in the text: iPTH and serum calcium were detected by the clinical laboratory of Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School. The normal iPTH level is 1.96 to 9.33 pmol/L and serum calcium ( without albumin adjustment) is 2.025 to 2.75 mmol/L.( see page 5, line 133-137 for details).

**Comment 4:** Lines 98-99 “During the operation, dissect thyroid surgical membrane and identify the parathyroid carefully”. Please check whether the verb is missing.

Reply 4: A careful proof-reading has been conducted for the revised manuscript to improve the language and grammar. We have tried our best to polish the language in the revised manuscript. For details, see page 5, line 120-121.

Changes in the text: During the operation, the surgeon should dissect thyroid surgical membrane and identify the parathyroid carefully.( see page 4, line 107-108 for details).

**Comment 5:** Lines 105-103: It is recommended that a “statistical analysis” chapter be created.

Reply : Thank you for your remainder. We have added the heading "Statistical Analysis", see page 5,line 141.

Changes in the text: *Statistical Analysis*.( see page 5,line 141 for details).

**Comment 6:** The authors analyze data from 137 patients of whom only 118 underwent total thyroidectomy. The main bias of this work is having included 19 lobectomies in the analysis. As is well known, unilateral surgery preserves the two contralateral parathyroid glands and limits the risk of postoperative hypocalcemia. For this reason, in high-volume centers for lobectomies alone, no postoperative follow-up is required.

Reply: Thank you for your kind suggestion. As mentioned in comment 1, all

patients enrolled in this study were treated with “ unilateral thyroidectomy or bilateral thyroidectomy +central lymph node dissection ± lateral cervical lymph node dissection”. We did not exclude patients with unilateral thyroidectomy because central neck lymph node dissection is an independent risk factor for SH. In our study, SH still occurred in some patients who underwent unilateral thyroidectomy (2/48, 4.17%). In future studies, we will make more detailed classification of cervical lymph node dissection in order to make study more rigorous.

Changes in the text: -

**Comment 7:** Lines 172-153 “This study showed that the incidence of SH after surgery in older patients with thyroid cancer is 35.04%”. The authors should indicate whether they considered only patients undergoing total thyroidectomy.

Reply: Thank you for pointing out problem. Previously, we mentioned the reasons for not excluding patients with unilateral thyroidectomy. Therefore, in the discussion section, we did not separate them for statistics. In order to make the data more clear, we have revised the original manuscript to increase the incidence of SH in patients with unilateral/bilateral resection, as detailed on page 8, line 233-235. We promise that in the following studies, we will adopt the suggestions of reviewers to make a more detailed classification of cervical lymph node dissection.

Changes in the text: this study showed that the incidence of SH after surgery in older patients with thyroid cancer is 35.04%, of which 4.17% were unilateral thyroidectomy and 95.83% were bilateral thyroidectomy. ( see page 8, line 233-235 for details).

### **Reviewer B**

**Comment 1:** Clarify what is uncertain about postoperative iPTH's predictive value and why focusing on older patients would answer an important research gap. Is there a previous study that determined postoperative iPTH's predictive value in various age groups?

Reply: The authors apologize for the confusing the reviewer. While postoperative

iPTH is widely used as a marker for predicting hypocalcemia in patients undergoing thyroid surgery, its predictive value may vary across different patient populations. Existing studies often generalize findings across all age groups. Older patients often have unique physiological and clinical characteristics, such as reduced renal function, altered calcium metabolism, or comorbidities, which may affect iPTH dynamics and its predictive utility. There are studies reported that patients over the 50 years have a 20-fold increased risk of developing postoperative hypocalcemia. Therefore, in our study, we focus on patients who over 60 years old, aiming to provide new ideas for the treatment of SH in older patients. For greater clarity, we have revised the manuscript, as detailed on see page 3, line 65-74 and page 3, line 84-85.

Changes in the text: However, existing studies often generalize findings across all age groups. ( see page 3, line 84-85 for details).

**Comment 2:** A brief explanation of age-related changes in calcium metabolism, parathyroid function, or recovery capacity that might make older patients uniquely vulnerable to SH should be included.

Reply: Thank you very much for the constructive points. In the revised manuscript, we have added this section of relevant content, as detailed on page 3, line 65-74 for details.

Changes in the text: Tolone et al. reported that patients over the 50 years have a 20-fold increased risk of developing postoperative hypocalcemia[5]. Data from previous studies in our center suggested a similar conclusion that SH often occurs in older patients. With aging, there is often a decline in intestinal calcium absorption due to reduced vitamin D synthesis and responsiveness, which can impair calcium homeostasis[6]. Age-related declines in renal function can also impair the activation of vitamin D, which is essential for PTH-mediated calcium regulation[7]. In short, older patients with thyroid cancer tend to have a higher burden of underlying diseases, a lower metabolic rate, diminished physiological recovery capacity, and an elevated risk of postoperative complications compared to younger patients. ( see page 3, line 65-74 for details).

**Comment 3:** The study's objective should be relevant to the article's subject. Since the title is "The predictive value of postoperative iPTH for symptomatic hypocalcemia in older patients with thyroid cancer", the main objective ought to be "to further explore the predictive value of postoperative iPTH on SH" instead of "to analyze the potential risk factors of SH after thyroid cancer surgery in older patients"

Reply: Thank you for your insightful suggestion. We have modified the manuscript according to the reviewer's comment, as detailed on the page 3, line 88- page 4, line 89.

Changes in the text: The purpose of this study is to analyze the potential risk factors of SH after thyroid cancer surgery in older patients, and to further explore the predictive value of postoperative iPTH on SH, so as to provide new ideas for clinical prevention and treatment of SH following thyroid cancer surgery in older patients (see page 3, line 87- page 4, line 90 for details).

**Comment 4:** The article did not mention whether a power calculation was performed to determine an adequate sample size.

Reply: We appreciate the reviewer's valuable comment regarding the power calculation for determining the sample size in our study. As this is a retrospective study, the sample size was determined based on the available data from medical records during the study period, rather than a pre-specified power calculation. Due to the strict admission criteria of this study, only a total of 137 patients were enrolled. However, we believe this sample size is sufficient to draw meaningful conclusions, considering the nature of the retrospective analysis. We acknowledge that power calculations are typically conducted in prospective studies to ensure adequate sample sizes for detecting statistically significant effects. In retrospective studies like ours, the sample size is often constrained by the available data. We hope to expand the sample size in future studies to further enhance the credibility of the findings.

Changes in the text: -

**Comment 5:** Key details such as how participants were screened and selected should be provided. Whether patients were consecutively included or selected based on specific characteristics is unclear, which could introduce selection bias.

Reply: We're sorry for confusing the reviewer. In our study, our main inclusion criteria were thyroid cancer patients over 60 years old who underwent thyroid surgery in our department, and the main exclusion criteria were patients with severe cardiovascular disease, abnormal kidney function, or other serious systemic disease, patients with a history of hypocalcemia, patients who are taking medication that may affect blood calcium and missing data. We sincerely thank the reviewer for raising this question, which made us aware that there may be problems with the description of the article. Thus we have revised the manuscript by making some adjustments to the word order and expression of this part according to reviewer's suggestion, as detailed on the page 4, line 108-113.

Changes in the text: Inclusion criteria included thyroid cancer patients with age  $\geq 60$  years, and the operation was performed by the Department of Thyroid Surgery, Drum Tower Hospital Affiliated to the School of Medicine of Nanjing University. Exclusion criteria included patients with severe cardiovascular disease, abnormal kidney function, or other serious systemic disease, patients with a history of hypocalcemia, patients who are taking medication that may affect serum calcium and missing data. ( see page 4, line 108-113 for details).

**Comment 6:** Other potential confounders such as comorbidities, surgeon expertise, and perioperative medications should also be considered.

Reply: Thank you for your insightful suggestion. First, we have excluded patients with severe cardiovascular disease, abnormal kidney function, or other serious systemic conditions from the exclusion criteria to reduce the interference of comorbidities with results. Second, all procedures were performed by surgeons with similar experience, and the surgical methods were standardized to minimize the impact of differences in physician levels. Finally, none of the enrolled patients used drugs that affected blood calcium before surgery. We are sorry that this was not

reflected in the original manuscript due to our mistake. We have added this part in the revised manuscript, see page 4, line 110-113 for details.

Changes in the text: Exclusion criteria included patients with severe cardiovascular disease, abnormal kidney function, or other serious systemic disease, patients with a history of hypocalcemia, patients who are taking medication that may affect serum calcium and missing data. ( see page 4, line 110-113 for details).

**Comment 7:** The authors excluded patients with missing data but did not describe the extent of missing data or provide sensitivity analyses to assess the potential impact of these exclusions on the results.

Reply: We thank the reviewers for valuable comments. Indeed, we did not describe in detail the extent of missing data in our study, nor did we conduct sensitivity analyses to assess the potential impact of excluding missing data on the results. This is one of the limitations of our study. According to the reviewer's suggestion, we have added the details of the missing data. In our study, a total of 4 patients were excluded due to missing data, accounting for 2.69% of the initial sample size. The missing data mainly involved the following variables: preoperative iPTH and preoperative serum calcium. This is because some patients underwent relevant examinations in other hospitals before surgery, resulting in the absence of this part of data in the medical records. So we eliminated them out. We have supplemented the description of missing data in the manuscript and added relevant content in the results section, see page 15, line 383 Figure 1 and page 6, line 154-161 for details.

Changes in the text: According to the inclusion and exclusion criteria mentioned above, among the 151 patients, 6 patients had severe cardiovascular disease, abnormal kidney function, or other serious systemic disease, 2 patients had a history of hypocalcemia, 2 patients were taking medication that may affect serum calcium, and 4 patients had incomplete data. These patients were excluded and a total of 137 older patients, ranging in age from 60 to 81 years old, with an average age of 65.35 years old (Table 1), were included in this study, of which 48 (35.04%) patients developed SH, and 89 (64.96%) patients were asymptomatic (Table 2). (see page 6, line



154-161).

Figure 1 (see page 15, line 383).

**Comment 8:** The first paragraph should give a brief summary of the overall findings before moving on to the next issue.

Reply: We thank the reviewer for their valuable suggestion. We have revised the Discussion section to provide a concise summary of the overall findings before delving into further analysis. The revised text can be found in the Discussion section on page 8, line 217-227.

Changes in the text: In our study, 48 (35.04%) developed SH, while 89 (64.96%) remained asymptomatic among the 137 included patients. Univariate logistic regression analysis identified significant differences between the SH and asymptomatic groups in terms of gender, preoperative iPTH, postoperative iPTH, postoperative serum calcium, and procedure of surgery. Multivariate logistic regression further demonstrated that both preoperative and postoperative iPTH levels were independent risk factors for predicting postoperative SH. Notably, postoperative iPTH showed high diagnostic efficacy with an AUC of 0.855 (95% CI: 0.794-0.917), while preoperative iPTH had lower predictive value (AUC = 0.570). These findings suggest that postoperative iPTH is a reliable marker for predicting SH in older thyroid cancer patients, whereas preoperative iPTH has limited utility in this context. (see page 8, line 217-227).

**Comment 9:** While statistical significance is noted, the clinical significance of the findings is not adequately discussed.

Reply : We sincerely appreciate the reviewer's valuable comment regarding the clinical significance of our findings. In response to this suggestion, we have expanded the Discussion section to include a detailed analysis of the clinical implications of our results, as detailed in page 9, line 249 - page11 , line 309 . We believe these additions have strengthened the manuscript by bridging the gap between statistical significance and clinical relevance. Thank you again for your insightful suggestion, which has

significantly enhanced the quality of our work.

Changes in the text: At present, the relationship between preoperative iPTH and SH is still controversial. This study found that preoperative iPTH is an independent predictor of SH in older thyroid cancer patients after surgery, and older patients with higher preoperative iPTH levels are more likely to develop SH. This finding is consistent with the results reported by Del et al.[19] and Maeda et al.[20]. Interestingly, Zuberi et al. showed that there was no statistical significance in preoperative iPTH level in the incidence of SH after thyroid surgery[21]. The authors hypothesize that several factors may contribute to this phenomenon. On one hand, older patients may exhibit elevated baseline iPTH levels compared to younger patients due to age-related factors such as vitamin D deficiency or declining renal function, which contribute to increased iPTH levels with age[7]. On the other hand, compared to younger patients, older patients have a diminished capacity to regulate endocrine homeostasis, leading to greater fluctuations of iPTH after thyroid surgery. The authors suggest that future studies should include additional indicators, such as vitamin D levels, to enable a more comprehensive assessment of parathyroid function. However, this study found that the AUC of preoperative iPTH in predicting postoperative SH in older patients with thyroid cancer was only 0.570 (95% CI: 0.466-0.675), its predictive value was lower compared with postoperative iPTH. There is still no definite conclusion on its predictive value for SH occurrence, which needs further study.

The results of the univariate logistic regression analysis indicated statistical differences between the SH group and the asymptomatic group in terms of gender. However, gender did not show statistical significance in the multivariate analysis, suggesting that it is not independent predictors of SH. Existing studies have shown a correlation between SH and gender after thyroid cancer surgery, but the results are not entirely consistent. Several studies have shown that female gender is one of the predictors of permanent postoperative hypocalcemia, which may be related to factors such as smaller parathyroid gland size in women, increased susceptibility to intraoperative damage, and the potential influence of estrogen levels on calcium

metabolism and parathyroid function[22, 23]. While Lalos A et al.[24] and Jan BS et al.[25] reported that no statistical difference was found between sex in predicting post-operative SH, which was consistent with our findings. Future research is needed to further clarify the relationship between gender and SH.

Although total thyroidectomy was associated with a significantly higher incidence of postoperative hypocalcemia compared to unilateral thyroidectomy in our study, multivariate analysis revealed that surgical procedure was not an independent predictor of SH. This finding contrasts with previous studies that identified total thyroidectomy as an independent risk factor[26]. The discrepancy may be attributed to advancements in surgical techniques, such as intraoperative nerve monitoring and meticulous parathyroid gland identification, which may have mitigated the impact of total thyroidectomy on parathyroid function. These findings highlight the importance of individualized postoperative management strategies, particularly for patients undergoing total thyroidectomy, while underscoring the need for further research to elucidate the complex interplay between procedure of surgery and other risk factors.

In our study, univariate analysis revealed that postoperative serum calcium levels were significantly lower in the SH group compared to the asymptomatic group. It is well known that decreased postoperative serum calcium levels are one of the manifestations of SH. However, further multivariate analysis showed that postoperative serum calcium levels were not an independent predictor of SH in older thyroid cancer patients. The authors speculate that this phenomenon may be related to the following reasons. First, the study population consisted exclusively of older patients aged over 60 years, which differs from previous studies in terms of age-related baseline characteristics. Second, postoperative serum calcium levels are a dynamically changing indicator. The actual timing of surgery completion varied among patients, while postoperative serum calcium levels in this study were uniformly measured from blood samples collected at 6:00 AM on the first postoperative day. This may explain why postoperative serum calcium did not emerge as an independent predictive factor in our analysis. Despite these findings, postoperative calcium monitoring remains clinically significant for the early detection

of hypocalcemia. Future studies should explore the dynamic changes in calcium levels and their interactions with other risk factors to better predict and manage postoperative SH. (see page 9, line 249 - page 11, line 309 for details).

**Comment 10:** How the study differs from prior research, particularly its focus on older patients, should be highlighted and any conflicting findings in the literature should also be discussed.

Reply : We sincerely appreciate the reviewer's valuable comment. Our study focuses on older patients (aged  $\geq 60$  years), which distinguishes it from prior research that primarily investigated a general population or younger cohorts. According to the reviewer's comments, we have revised the original manuscript, as detailed in page 7, line 207- page 8, line 216.

Changes in the text: Our study focuses specifically on older patients (aged  $\geq 60$  years), which distinguishes it from prior research that primarily investigated a general population or younger cohorts. Older patients often exhibit unique physiological characteristics, such as reduced renal function, vitamin D deficiency, and diminished endocrine homeostasis, which may influence postoperative outcomes, including SH[6, 7]. By concentrating on this demographic, our study provides insights into predicting SH in a population that is both understudied and at higher risk for complications, aiming to provide ideas for the prevention and treatment of SH in older patients with thyroid cancer, so as to reduce hospitalization costs, shorten hospitalization time and improve the postoperative life quality of patients. (see page 7, line 207- page 8, line 216 for details).

**Comment 11:** Line 209 Page 7 Spelling correction; First should be first.

Reply: We're sorry for the spelling mistake due to our oversight. We have checked and corrected the manuscript, see page 11, line 324 for details.

Changes in the text: First of all, strengthen preoperative management, routine monitoring of preoperative iPTH and preoperative calcium. ( see page 11, line 324-325 for details).

**Comment 12:** How these limitations might have impacted the findings should be discussed. The role of confounding variables and their potential influence on the observed associations should be mentioned.

Reply : Thank you for your constructive suggestion. We have revised the discussion of the study's limitations. Please refer to page 12, line 331-339 for the specific changes. We believe these revisions have strengthened the manuscript and provided a more comprehensive perspective on the implications of our findings. Thank you again for your constructive suggestions, which have significantly improved the quality of our work.

Changes in the text: There are some limitations in this study. First, it was a retrospective study, which may have introduced selection bias. Second, it was a single-center study with a small data sample, and the results may not be general to other settings. Third, certain relevant factors, such as perioperative vitamin D, were not included in the analysis. The authors sincerely hope that prospective studies can be conducted in the near future by designing well-structured research protocols, which will provide more clinically relevant guidance. Additionally, we aim to collaborate with multiple centers in future research, increase the sample size, and incorporate additional indicators, such as vitamin D levels, to enhance the rigor and depth of the study. ( see page 12, line 331-339 for details).

**Comment 13:** After the limitations are discussed, the final paragraph should include recommendations for further research.

Reply : We sincerely appreciate the reviewer's valuable feedback regarding the discussion of limitations and the inclusion of recommendations for further research. In response to this suggestion, we have revised the manuscript to explicitly address the limitations of our study and to provide clear recommendations for future research, see page 12, line 331-339 for details.

Changes in the text: There are some limitations in this study. First, it was a retrospective study, which may have introduced selection bias. Second, it was a single-center study with a small data sample, and the results may not be general to

other settings. Third, certain relevant factors, such as perioperative vitamin D, were not included in the analysis. The authors sincerely hope that prospective studies can be conducted in the near future by designing well-structured research protocols, which will provide more clinically relevant guidance. Additionally, we aim to collaborate with multiple centers in future research, increase the sample size, and incorporate additional indicators, such as vitamin D levels, to enhance the rigor and depth of the study. ( see page 12, line 331-339 for details).

### **Reviewer C**

**Comment 1:** in the title please define iPTH.

Reply 1: We sincerely thank the reviewer for careful reading. As suggested by the reviewer, we have corrected manuscript (see page 1, line 1-2).

Changes in the text: The predictive value of postoperative intact parathyroid hormone for symptomatic hypocalcemia in older patients with thyroid cancer. ( see page 1, line 1-2 for details)

**Comment 2:** in the introduction section, line 46 hypocalcemia is classified as either temporary or permanent: please define.

Reply 2: Thank you for your insightful suggestion. As suggested by the reviewer, we have added the definition of temporary/permanent hypocalcemia in the manuscript, as detailed on page 2, line 56- page 3, line 60.

Changes in the text: .Depending on the duration of postoperative hypocalcemia, SH can be classified as temporary hypocalcemia and permanent hypocalcemia. Temporary hypocalcemia is defined both by the American Thyroid Association and the European Society of Endocrinology as postoperative hypocalcemia lasting less than 6 months, and permanent hypocalcemia as lasting more than 6 months[2, 3]. ( see page 2, line 56- page 3, line 60 for details)

**Comment 3:** line 53: which studies are being referred to?

Reply : We thank the reviewer for pointing out the need for clarification

regarding the referenced studies. In response to this comment, we have added two relevant references to support our discussion. These references are: Pepe, J., et al., Diagnosis and management of hypocalcemia. *Endocrine*, 2020. 69(3): p. 485-495. and Gafni, R.I. and M.T. Collins, Hypoparathyroidism. *N Engl J Med*, 2019. 380(18): p. 1738-1747. These references have been added to the manuscript on page 20 , line 492-493, to provide a more comprehensive context for research. We believe these additions address the reviewer's concern and enhance the overall quality of the manuscript.

Changes in the text: Muscle stiffness, laryngeal spasms and asphyxia caused by strong muscle contraction may occur, resulting in impaired quality of life and even life-threatening conditions for patients after surgery[2, 8, 9]. (see page 3, line 76-78 for details).

[8].Pepe, J., et al., Diagnosis and management of hypocalcemia. *Endocrine*, 2020. 69(3): p. 485-495. (see page 20, line 492 for details).

[9].Gafni, R.I. and M.T. Collins, Hypoparathyroidism. *N Engl J Med*, 2019. 380(18): p. 1738-1747. (see page 20, line 493 for details).

**Comment 4:** why do you mean for "critical value"

Reply: The authors apologize for the confusing the reviewer. “Serum calcium is at a critical value or low level” means that serum calcium is lower than the lower limit of the reference value provided by the laboratory of our hospital. The reference value of serum calcium in the laboratory of our hospital is shown on page 5, line 136-137. In order to make the expression more clear, we have revised the relevant parts of the original manuscript, as detailed on page 5, line 132-133.

Changes in the text: (4) Serum calcium is lower than the lower limit of the reference value provided by the laboratory of our hospital. ( see page 5, line 132-133 for details).

**Comment 5:** In your analysis calcemia is reported as albumin-adjusted?

Reply: We thank the reviewer for raising this important point. In our study, we

reported serum calcium levels without albumin adjustment. That's because our study population had normal albumin levels, and thus the impact of albumin on total calcium was minimal. For clarity, we have added to the manuscript that serum calcium levels have not been corrected for albumin as detailed on page 5, line 136. However, we acknowledge that albumin-adjusted calcium may provide a more accurate reflection of physiologically active calcium levels, especially in patients with abnormal albumin levels. In future studies, we will consider incorporating albumin-adjusted calcium measurements to further refine our analysis.

Changes in the text: The normal iPTH level is 1.96 to 9.33 pmol/L and serum calcium ( without albumin adjustment) is 2.025 to 2.75 mmol/L. ( see page 5, line 135-137 for details).

**Comment 6:** Is preoperative vitamin-d serum levels evaluated?

Reply: Thank you for your insightful suggestion. Current studies have found that patients with low preoperative vitamin D serum levels are more likely to develop postoperative hypocalcemia. Some researchers have suggested that preoperative assessment of vitamin D levels could serve as a risk prediction tool. However, this study was retrospective, and preoperative vitamin D serum levels were not routinely assessed at our center. We acknowledge that this is one of the limitations of this study. Based on your suggestion, we will address this topic in the discussion section ( see page 11, line 310- 319 for details) and consider evaluating vitamin D levels in future studies to further enrich our findings.

Changes in the text: Vitamin D plays a critical role in calcium metabolism and parathyroid function, and its deficiency has been linked to an increased risk of postoperative SH[27, 28]. However, in our retrospective study, we did not have the data for preoperative vitamin D levels, which limits our ability to fully assess its impact on SH. This gap is primarily due to the fact that preoperative vitamin D testing is not routinely performed in clinical practice, particularly among older patients. Despite this limitation, our analysis of other key indicators provides valuable insights into the prediction of SH. We believe that future research should incorporate



preoperative vitamin D levels to better understand its role in postoperative hypocalcemia and to develop more comprehensive predictive models. ( see page 11, line 310- 319 for details).

**Comment 7:** Do you find any differences in SH development between total thyroidectomy and lobectomy? (line 121)

Reply: We thank the reviewer for valuable comments. The results of this study showed that 118 patients underwent total thyroidectomy and 19 underwent unilateral thyroidectomy. Among the 118 patients who underwent total thyroidectomy, 46 patients developed SH (28.98%). However, SH occurred in only 2 of 19 patients who underwent unilateral thyroidectomy (10.53%). We have added a detailed description of the results of this study on page 6, line 167-170. In addition, we have provided a detailed explanation in the univariate analysis section of the original paper: univariate logistic regression analysis showed a statistically significant difference in procedure of surgery between the SH group and the asymptomatic group, as detailed on page 6, line 175- page 7, line 184. Finally, we will include relevant content in the discussion section to make the article more comprehensive and rigorous, as detailed on page 10, line 281-291.

Changes in the text: Among the 118 patients who underwent total thyroidectomy, 46 patients developed SH (28.98%). However, SH occurred in only 2 of 19 patients who underwent unilateral thyroidectomy (10.53%). ( see page 6, line 167-170 for details) .

Although total thyroidectomy was associated with a significantly higher incidence of postoperative hypocalcemia compared to unilateral thyroidectomy in our study, multivariate analysis revealed that surgical procedure was not an independent predictor of SH. This finding contrasts with previous studies that identified total thyroidectomy as an independent risk factor[26]. The discrepancy may be attributed to advancements in surgical techniques, such as intraoperative nerve monitoring and meticulous parathyroid gland identification, which may have mitigated the impact of total thyroidectomy on parathyroid function. These findings highlight the importance

of individualized postoperative management strategies, particularly for patients undergoing total thyroidectomy, while underscoring the need for further research to elucidate the complex interplay between procedure of surgery and other risk factors. ( see page 10, line 281-291 for details) .

**Comment 8:** line 132: Could the preoperative differences in preoperative iPTH be related to preoperative subclinical hypoparathyroidism?

Reply: Thank you for your question. Our study found that older thyroid cancer patients with higher preoperative iPTH levels are more likely to develop SH after surgery. Compared to previous studies, our findings are consistent with theirs. Subclinical hypoparathyroidism is typically characterized by normal blood calcium levels but reduced iPTH levels, whereas in our study, preoperative iPTH levels in SH group were elevated, which does not align with the features of subclinical hypoparathyroidism. Elevated iPTH may be associated with primary or secondary hyperparathyroidism rather than hypoparathyroidism. In older patients, increased iPTH levels may be due to vitamin D deficiency or declining renal function. In response to the reviewer's suggestion, we have added additional content to make this section more compelling. Please refer to page 9, line 249-267 for details.

Changes in the text: This study found that preoperative iPTH is an independent predictor of SH in older thyroid cancer patients after surgery, and older patients with higher preoperative iPTH levels are more likely to develop SH. This finding is consistent with the results reported by Del et al.[19] and Maeda et al.[20]. Interestingly, Zuberi et al. showed that there was no statistical significance in preoperative iPTH level in the incidence of SH after thyroid surgery[21]. The authors hypothesize that several factors may contribute to this phenomenon. On one hand, older patients may exhibit elevated baseline iPTH levels compared to younger patients due to age-related factors such as vitamin D deficiency or declining renal function, which contribute to increased iPTH levels with age[7]. On the other hand, compared to younger patients, older patients have a diminished capacity to regulate endocrine homeostasis, leading to greater fluctuations of iPTH after thyroid surgery.

The authors suggest that future studies should include additional indicators, such as vitamin D levels, to enable a more comprehensive assessment of parathyroid function. ( see page 9, line 250-263 for details) .

**Comment 9:** Please define the calcium supplementation therapy in your Center.

Reply: Thank you very much for your valuable advice. We apologize for not elaborating on this point in the original manuscript. Based on your suggestion, we have added this section, as detailed on page 5, line137-140, and hope that this modification makes the manuscript more complete.

Changes in the text: Once diagnosed with SH, oral calcium supplementation should be initiated promptly. If symptoms remain significant after oral calcium supplementation, or if severe symptoms (such as convulsions of limbs) are present from the outset, intravenous calcium gluconate supplementation should be administered. ( see page 5, line137-140 for details).

**Comment 10:** line 222 correct "an general"

Reply: Thank you very much for your kind suggestion. We're sorry that there was a misnomer due to our oversight. We have made modifications according to the reviewer's comments, as detailed on page 12, line 333.

Changes in the text: Second, it was a single-center study with a small data sample, and the results may not be general to other settings. ( see page 12, line 332-333 for details).