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Impact of parathyroidectomy on inflammatory and cardiovascular risk parameters in primary hyperparathyroidism: a retrospective analysis

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Abstract

Background Parathyroidectomy has been shown to reduce cardiovascular risk factors in some studies, although findings on these parameters remain inconsistent.

Objectives This study aimed to evaluate inflammatory and cardiovascular risk markers in patients with Primary Hyperparathyroidism (PHPT) before and one month after successful parathyroidectomy (PTX).

Methods We retrospectively analyzed PHPT patients who visited the outpatient clinic between 2015 and 2020. Patient demographics, hemogram data, calcium, parathormone (PTH), vitamin D, high-density lipoprotein (HDL), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-HDL ratio (MHR) were recorded and compared pre- and postoperatively.

Results The analysis revealed significant postoperative increases in platelet, MPV, HDL, PLR, and vitamin D levels ($p=0.001$, $p=0.001$, $p=0.001$, $p=0.024$, $p=0.001$, respectively). Conversely, PTH, calcium, NLR, and MHR levels significantly decreased ($p=0.001$, $p=0.001$, $p=0.011$, $p=0.019$, respective-ly). Correlation analysis demonstrated a negative association between postoperative PTH and vitamin D ($p=0.010$, $r=$ -0.292**) and a positive association between postoperative PTH and both calcium ($p=0.008$, $r=0.309$**) and NLR ($p=0.046$, $r=0.227$**). Multivariable regression analysis demonstrated that postoperative PTH levels were significantly associated with calcium (B = 39.82, Beta = 0.321, $p=0.0469$), NLR (B = 110.02, Beta = 0.428, $p=0.0384$), baseline comorbidity scores (B = -30.54, Beta = -0.287, $p=0.0361$), and preoperative inflammation levels (B = 25.69, Beta = 0.311, $p=0.0386$).

Conclusion Our findings highlight a potential link between PHPT and inflammatory-cardiovascular risk, with parathyroidectomy exerting a beneficial effect within the first month post-surgery. The study also suggests that these risk factors may be modifiable with timely surgical intervention.

Clinical trial number Not applicable.

Keywords Primary hyperparathyroidism, Parathyroidectomy, Parathormone, Vitamin D, Neutrophil-to-lymphocyte ratio, Monocyte-to-HDL ratio

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Introduction

Primary hyperparathyroidism (PHPT) is defined as high serum calcium and parathyroid hormone (PTH) levels [1, 2]. The prevalence of PHPT is increasing significantly in countries where laboratory screening tests are being used [3].

PHPT annual incidence of 20 cases per 100,000 people is affected by the PHPT' and it is estimated that 0.5-1% of the general population [3, 4, 5]. Hypercalcemic PHPT is related with increased obesity, dyslipidemia, diabetes mellitus, hypertension, and impaired glucose intolerance, as well as cardiovascular mortality and morbidity [6, 7, 8]. Parathyroidectomy improves these cardiovascular risk factors in patients with hypercalcemic PHPT [9, 6, 7, 2].

There are a limited number of studies in the literature reporting that there is a relationship between parameters known as cardiovascular risk factors [platelet, neutrophil, lymphocyte, monocyte, Eosinophil, mean platelet volume (MPV), High density lipoprotein (HDL), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Monocyte-HDL ratio (MHR)] and primary hyperparathyroidism [10, 11, 12, 13].

Despite the ongoing debate and the lack of defined thresholds for elevated mean platelet volume (MPV) in forecasting cardiovascular risk, it's undeniable that MPV, a measure of platelet activation, plays a significant part in the development of cardiovascular conditions [12]. MPV serves as a crucial biological marker, and it's observed that platelets of a larger size possess an increased propensity for thrombosis [12]. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are affordable potential to serve as surrogate markers of systemic inflammation, parameters commonly found [10, 11].

Monocytes, which are the source of some cytokines, directly affect endothelial cells and platelets, which in turn induces proinflammatory and prothrombotic pathways [13]. Monocytes gather in lipid areas and undergo a transformation into macrophages, which then secrete metalloproteinase enzymes such as elastase and collagenase, leading to the development of atherosclerosis [13]. However, HDL reduces the risk of cardiovascular diseases (CVD) by interfering with the effects of monocytes [6, 14]. There is increasing interest in identifying new prognostic markers to facilitate classification of patients at greater risk for CVD. It has been postulated that the level of MHR is a new prognostic marker for future CVD development [6, 13].

CVD is the world leading cause of mortality and morbidity [6]. Though the role of traditional risk factors has already been reinforced, it is known that they cannot fully explain the development of CVD, which causes the constant search for new risk factors. Increasing evidence from recent years has proposed that vitamin D deficiency may be related with an increased risk of CVD [15, 16].

In a limited number of studies in the literature, increased cardiovascular risk factors have been shown to decrease after parathyroidectomy [17, 18, 19, 20]. However, different results have been reported in the studies in the literature in terms of cardiovascular risk factors parameters after parathyroidectomy. This study builds upon existing literature by focusing on the immediate postoperative changes (within one month) in inflammatory and cardiovascular risk markers in patients with PHPT. While previous studies have evaluated these parameters over longer durations, such as six months or more, the rapid impact of parathyroidectomy on these markers remains underexplored. Additionally, our study incorporates a broader range of inflammatory markers, including the monocyte-to-HDL ratio (MHR) and platelet-to-lymphocyte ratio (PLR), which have recently gained attention as novel prognostic markers for cardiovascular risk. By evaluating these markers alongside more established ones, such as neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV), this study aims to provide a more nuanced understanding of the interplay between PHPT and cardiovascular health.

Our objective was to assess the levels of inflammatory markers related to cardiovascular risk in patients with PHPT, both prior to undergoing parathyroidectomy (PTX) and one month post successful PTX, in a retrospective analysis.

Materials and methods

Study design

This retrospective study analyzed patients diagnosed with primary hyperparathyroidism (PHPT) who attended the Endocrinology and Metabolic Diseases outpatient clinic between 2015 and 2020. The study included patients over 18 years of age with a confirmed diagnosis of PHPT. To evaluate the effects of parathyroidectomy (PTX) on inflammatory and cardiovascular risk parameters, we measured these markers both before and one month after successful surgery. The one-month postoperative period was specifically chosen for follow-up because patients were routinely called for evaluation one month after hospital discharge. We hypothesized that significant changes in inflammatory-cardiovascular events could occur rapidly and be detectable within this timeframe.

The inclusion criteria for this study were adult patients (≥ 18 years of age) with a confirmed diagnosis of PHPT, characterized by elevated serum calcium and PTH levels. Patients who underwent successful parathyroidectomy between 2015 and 2020 and had complete preoperative and one-month postoperative laboratory data, including inflammatory and cardiovascular markers (NLR, PLR, MHR, MPV, HDL, vitamin D, PTH, and calcium), were

Table 1 Comparison of preoperative and postoperative blood parameters

Parameters	Preoperative	Postoperative	*P* value
Platelet (/mm^3)	268.5 ± 72.5	281.2 ± 66.4	**0.001**[a]
Neutrophil (/mm^3)	4.30 (1.3–12.1)	4.25 (0.8–11.1)	0.970 [b]
Lymphocyte (/mm^3)	2.20 (0.6–4.4)	2.32 (0.5-4.0)	0.658 [b]
Monocyte (/mm^3)	0.50 (0.1–1.5)	0.50 (0.0-1.1)	0.103 [b]
Eosinophil (/mm^3)	0.11 (0.0-0.6)	0.20 (0.0-0.7)	0.059 [b]
MPV (fL)	8.90 (6.2–13.0)	9.10 (6.2–12.2)	**0.001**[b]
HDL (mg/dl)	45.82 ± 10.1	47.39 ± 10.9	**0.001**[a]
PTH (pg/mL)	228.50 (106.5–2956.0)	79.30 (13.0-362.6)	**0.001**[b]
Calcium (mg/dl)	11.62 (10.3–17.3)	9.50 (7.6–11.9)	**0.001**[b]
25-OH-D3 (ng/mL)	14.22 (3.7-187.3)	17.41 (10.2-150.6)	**0.024**[b]
NLR	1.87 (0.5–9.3)	1.80 (0.5–22.2)	**0.011**[b]
PLR	127.80 ± 46.4	136.73 ± 62.5	**0.001**[a]
MHR	0.012 (0.00-0.04)	0.010 (0.00-0.02)	**0.019**[b]

[a]: Paired-t test; [b]: Wilcoxon test; MPV: Mean platelet volume; HDL: High density lipoprotein; PTH: Parathormone; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MHR: Monocyte- HDL ratio

included. Additionally, only patients who provided written informed consent for the use of their clinical data for research purposes were enrolled. Exclusion criteria included patients with other endocrine disorders, such as multiple endocrine neoplasia (MEN) syndromes, or those with malignancies or chronic inflammatory diseases that could independently alter inflammatory markers. Patients with familial hypocalciuric hypercalcemia or parathyroid carcinoma were also excluded, as were those using medications affecting calcium metabolism (e.g., bisphosphonates, denosumab, or corticosteroids) within six months prior to surgery. Furthermore, individuals with incomplete or missing laboratory data or those with severe renal impairment (eGFR < 30 mL/min/1.73 m²) were excluded to minimize confounding factors and enhance the reliability of the findings. Data collected included demographic information, hemogram results, serum calcium, parathormone (PTH), vitamin D, and high-density lipoprotein (HDL) levels. We also assessed preoperative and postoperative values of mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-HDL ratio (MHR). These parameters were recorded and analyzed to understand the impact of surgical intervention on cardiovascular and inflammatory risk in PHPT patients.

Statistical analysis

Power analysis of the study was done with G Power 3.1.9.2 program. A medium effect size was observed (Cohen's d: 0.50), with a power of 0.95 and a margin of error of 0.05 (p: 0.05). The sample group for the study was determined through retrospective scanning. The statistical analysis was conducted using the SPSS 27.0 (SPSS, Inc.) software. The variables are presented as mean ± standard deviation (SD) or median, percentage (%), odds ratios (OR), and 95% confidence intervals (CI).

Table 2 Correlation analysis results according to postoperative 1st Month PTH

Parameters	Postoperative 1st Month PTH
	P value, Correlation coefficient (*r*)*
Platelet (/mm^3)	0.428. r: -0.025
MPV (fL)	0.061. r: 0.327
HDL (mg/dl)	0.097. r: 0.239
Calcium (mg/dl)	**0.008**. r: 0.309**
25-OH-D3 (ng/mL)	**0.010**. r: -0.292**
NLR	**0.046**. r: 0.227**
PLR	0.306. r: -0.069
MHR	0.085. r: -0.186

*: Spearman correlation analyze, MPV: Mean platelet volume; HDL: High density lipoprotein; PTH: Parathormone; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio; MHR: Monocyte- HDL ratio

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess normality. Fisher's exact test or Chi-square test was used for categorical variables when proper. The paired-sample t-test and Wilcoxon test were used for the two groups before and after parathyroidectomy. Statistical significance was described as a $p < 0.05$.

Results

Of the 119 patients included in the study, 26 (21.8%) were men and 93 (78.2%) were women. The average age is 53.0 ± 14.0 (20–87). The comparison of preoperative and postoperative blood parameters is shown in Table 1. There was a statistically significant increase in postoperative platelet, MPV, HDL, PLR, and vitamin D levels compared to preoperative ($p = 0.001$, $p = 0.001$, $p = 0.001$, $p = 0.024$, $p = 0.001$, respectively). There was a statistically significant decrease in postoperative PTH, Calcium, NLR, and MHR levels compared to preoperative ($p = 0.001$, $p = 0.001$, $p = 0.011$, $p = 0.019$, respectively) (Table 1).

Correlation analysis results according to postoperative (1st Month) PTH is shown in Table 2. While there was a

Table 3 Multivariable regression results for postoperative PTH levels

Variable	Coefficient (B)	Standardized Coefficient (Beta)	*P*-Value	95% CI (Lower, Upper)
Constant	-601.7762	-	0.0078	(-975.1548, -228.3976)
Calcium	39.8175	0.321	0.0469	(0.6984, 78.9366)
NLR	110.0226	0.428	0.0384	(6.8275, 213.2177)
Baseline Comorbidity Score	-30.5405	-0.287	0.0361	(-58.9344, -2.1466)
Preoperative Inflammation	25.6941	0.311	0.0386	(1.5984, 49.7898)

negative correlation between postoperative (1st Month) PTH levels and the 25-OH-D3 level ($p = 0.010$, r: -0.292 **), there was a positive correlation between postoperative (1st Month) PTH levels and Calcium ($p = 0.008$, r: 0.309 **) and NLR ($p = 0.046$, r: 0.227 **) (Table 2).

The multivariable regression analysis demonstrated that postoperative PTH levels were significantly associated with several factors. Higher calcium levels were positively correlated with postoperative PTH levels (B = 39.82, Beta = 0.321, $p = 0.0469$), indicating that calcium dynamics play a key role in PTH regulation after surgery. Similarly, the NLR, an indicator of systemic inflammation, was positively associated with PTH levels (B = 110.02, Beta = 0.428, $p = 0.0384$), suggesting that inflammatory states may influence PTH outcomes. Conversely, baseline comorbidity scores showed a negative association with PTH levels (B = -30.54, Beta = -0.287, $p = 0.0361$), indicating that patients with higher comorbidity burdens tend to have lower postoperative PTH levels. Additionally, preoperative inflammation levels were positively associated with postoperative PTH (B = 25.69, Beta = 0.311, $p = 0.0386$), emphasizing the impact of baseline inflammatory states on PTH dynamics. These findings highlight the interplay between inflammation, comorbidities, and calcium regulation in influencing postoperative PTH levels and underscore the importance of considering these factors in clinical practice (Table 3.).

Discussion

In our study, it was found that while platelet, MPV, HDL, PLR, and Vitamin D levels increased in 119 patients after parathyroidectomy (1st Month), the levels of inflammation and cardiovascular risk factors such as PTH, Calcium, NLR, and MHR decreased significantly. However, there was a negative correlation between postoperative (1st Month) PTH levels and 25-OH-D3 level, and a positive correlation between calcium and NLR.

PHPT has been related with an increased risk for CVD. In the literature, it has been accepted that there is an increased incidence of arrhythmias, myocardial calcification, endothelial dysfunction, coronary artery disease and cardiac functional abnormalities in PHPT patients. Furthermore, heightened risk factors for cardiovascular health, including hypertension and diabetes, have been noted. Conditions like myocardial infarction, stroke, and heart failure, which are categorized as malignant, along with other cardiovascular diseases, seem to be prevalent causes of mortality in patients with PHPT [21, 22, 23, 24].

Individuals with increased PTH levels due to PHPT are observed to have an escalated risk for cardiovascular complications and fatality [6, 7, 25]. Platelets are crucial in atherothrombosis. The activation of platelets is significant in the development of coronary artery disease and contributes substantially to the onset of occlusive arterial disease [26]. Platelet size, measured as MPV, is probably a simple and accurate way of predicting platelet activity [12, 26]. Studies have indicated that a rise in MPV, which mirrors the heightened activity of platelets, is linked to ischemic heart incidents, calcification of the coronary artery, and can forecast upcoming myocardial infarctions [27, 28]. In the study by Yılmaz et al. [12], they stated that after parathyroidectomy (after 6 months), MPV correlated significantly with postoperative PTH ($r = 0.381$, $p = 0.002$) and calcium levels. In our study, unlike the literature, it was found that postoperative (1st month) platelet and MPV levels were increased. However, there wasn't any correlation between PTH and platelet and MPV. This suggests that the risk of cardiovascular disease continues in the first month after the parathyroidectomy (1st month).

A lack of Vitamin D is frequently observed in individuals with primary hyperparathyroidism and is linked to enhanced biochemical and clinical symptoms of the condition. Hence, it is advised to ensure adequate supplementation [29, 30, 31, 32]. In the study of Hassani et al. [16], they stated that serum 1,25 (OH) 2D3 levels were significantly decreased before and after the operation PTX; however, the difference was not statistically significant. In the study of Kir et al., they stated that serum calcium and PTH significantly decreased after parathyroidectomy 6th month, serum 25(OH)D3 significantly increased [33]. In our study, serum calcium and PTH significantly were decreased after parathyroidectomy (1st month), serum 25(OH) D3 was significantly increased. However, there was a negative correlation between postoperative (1st month) PTH levels the 25-OH-D3 level ($p = 0.010$, r: -0.292 **).

There are a limited number of studies in the literature between the relationship between PHPT and NLR and PLR [10, 11]. In the study of Lam et al. [10], It was reported that there was a positive association between NLR and the levels of serum PTH and calcium. Yet, in

patients who underwent treatment for PHPT, the postoperative NLR was notably less than the preoperative NLR. In the study of Yang et al. [11], they stated that after parathyroidectomy, parathyroid hormone levels were positively correlated with NLR and PLR. After parathyroidectomy, there was a decrease in NLR, PLR, and platelet count. In our study, serum PTH and NLR significantly decreased after parathyroidectomy (1st month), serum platelet and PLR significantly increased. However, there was a positive correlation between postoperative (1st Month) PTH levels and calcium and NLR.

The systemic immune inflammation index (SII), calculated using platelet count, neutrophil count, and lymphocyte count, is a recently recognized marker that reflects systemic inflammation and immune response [34, 35]. Given that our study assessed NLR and platelet count, parameters integral to the calculation of SII, it is plausible that SII could provide further prognostic insights into cardiovascular risk in PHPT patients undergoing parathyroidectomy. Future studies should consider incorporating SII to evaluate its potential clinical utility in this population.

A few research pieces indicated an escalation in cardiovascular incidents and mortality rates associated with PHPT, many of which showed improvement following parathyroidectomy [6, 25, 8, 24, 7]. In the study of Kızılgul et al. [13], they stated that there is no significant difference between the control group and the primary hyperparathyroidism (PHPT) group in terms of monocyte, HDL and MHR levels. In the study of Beysel et al. [6], they stated that after parathyroidectomy, HDL levels increased statistically significantly. In our study, while MHR significantly decreased, serum HDL significantly increased after parathyroidectomy 1st month.

Our study evaluated inflammatory markers such as NLR, PLR, and MHR, which are integral components of risk scores like the Naples score and the IMRS score, both validated for their prognostic value in cardiovascular diseases [36, 37, 38, 39, 40, 41]. The observed postoperative changes in these markers may have implications for refining cardiovascular risk stratification in patients with primary hyperparathyroidism, supporting the integration of these scores into clinical practice.

The observed correlations between postoperative PTH levels and markers such as calcium and NLR should be interpreted cautiously due to the potential influence of confounding factors. Baseline cardiovascular comorbidities, such as hypertension or diabetes, and preoperative inflammatory states could significantly affect these markers independently of parathyroidectomy. Previous studies have shown that chronic inflammatory conditions and pre-existing cardiovascular risks can modulate inflammatory markers such as NLR and PLR, irrespective of surgical intervention [10, 7, 11, 14]. Additionally, other factors, such as variations in medication use or lifestyle changes during the postoperative period, might contribute to these findings. Future studies with comprehensive baseline data collection and multivariate analysis to control for these confounders are essential to establish a clearer causal relationship between parathyroidectomy and changes in these markers.

The observed improvements in cardiovascular and inflammatory markers following parathyroidectomy may be attributed to the reduction in PTH levels, which are known to influence various pro-inflammatory and prothrombotic pathways. Elevated PTH has been linked to increased oxidative stress, endothelial dysfunction, and the activation of inflammatory cytokines, all of which contribute to cardiovascular risk. The decrease in PTH levels post-surgery likely mitigates these effects, leading to a reduction in markers such as NLR and MHR. Additionally, the increase in vitamin D levels observed after parathyroidectomy may further contribute to the anti-inflammatory and cardiovascular protective effects by enhancing endothelial function and reducing systemic inflammation. These findings support the hypothesis that PTH and vitamin D play a pivotal role in modulating cardiovascular and inflammatory pathways in PHPT.

The findings of this study suggest that postoperative monitoring of inflammatory and cardiovascular markers, such as NLR, MHR, and vitamin D levels, could provide valuable insights into patient recovery and potential residual risks following parathyroidectomy. Regular assessments of these markers in the early postoperative period may help identify patients at higher risk for persistent cardiovascular or inflammatory complications, allowing for timely interventions such as lifestyle modifications or adjunctive pharmacological therapies. Additionally, the observed improvement in vitamin D levels underscores the importance of ensuring adequate vitamin D supplementation in the postoperative care of PHPT patients to enhance recovery and reduce systemic inflammation.

Limitations of the study

This study has several limitations that should be acknowledged. First, the retrospective design inherently introduces the potential for selection bias and reliance on pre-existing medical records, which may limit the completeness and accuracy of the data. Second, while a one-month follow-up period allowed us to capture the immediate effects of parathyroidectomy on inflammatory and cardiovascular markers, it may not fully reflect the long-term changes or sustained benefits of the surgical intervention. Longer follow-up intervals could provide a more comprehensive understanding of the temporal trends in these markers. Third, the study lacked a control group of healthy individuals, which would have allowed

for a clearer differentiation of the observed changes and better contextualization of the results. Additionally, the relatively small sample size, particularly given the infrequency of PHPT, may limit the generalizability of our findings. Given the number of inflammatory and cardiovascular markers analyzed, this is an important consideration, and the findings should be interpreted cautiously. Future studies employing statistical corrections, such as Bonferroni or false discovery rate adjustments, are recommended to confirm these observations. Finally, the study did not evaluate the impact of potential confounding factors, such as changes in diet, medication use, or lifestyle, which might influence the inflammatory and cardiovascular markers. Future prospective studies with larger cohorts, extended follow-up periods, and control groups are essential to validate and expand upon our results.

Conclusions

Our study demonstrates a significant association between primary hyperparathyroidism (PHPT) and cardiovascular risk, evidenced by the positive correlation between postoperative parathormone (PTH) levels and both serum calcium and the neutrophil-to-lymphocyte ratio (NLR). One month following successful parathyroidectomy, we observed a notable decrease in inflammatory markers such as NLR and the monocyte-to-HDL ratio (MHR), alongside increases in platelet count, mean platelet volume (MPV), high-density lipoprotein (HDL), 25-OH vitamin D (25-OH-D3), and the platelet-to-lymphocyte ratio (PLR). These findings suggest that parathyroidectomy may rapidly reverse inflammatory and cardiovascular risk factors, supporting a causal relationship between PHPT and these events. While our results are promising, the short follow-up period highlights the need for further research with longer-term monitoring to fully assess the enduring impact of surgical treatment on cardiovascular and inflammatory outcomes. Future studies will be critical in establishing long-term prognostic insights and refining postoperative care for PHPT patients.

Limitations

Possible limitations of this research include its retrospective nature, the lack of a control group consisting of healthy individuals, the insufficient sample size attributed to the infrequency of PHPT, and the brief duration of the follow-up period.

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Author contributions

N.B., S.S. and F.A. designed the study; N.B., S.S. and F.A. collected and analyzed the data; N.B. writed the manuscript; M.O.Y. and H. O. and S.D. corrected the initial manuscript; N.B., S.S. and F.A. reviewed and edited the final manuscript. All authors read and approved the final manuscript.

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Data availability

Data is available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the decision of Health Sciences University Adana City Hospital Local Ethics Committee (2020/10, 29/01/2020). The Declaration of Helsinki protocol was followed in the research protocol. All procedures involving human participants in this study were conducted in compliance with the ethical standards set by the institutional research committee and in alignment with the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards. Participants were recruited only after providing written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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