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Serum Calcium as a Preoperative Surrogate of Tumour Burden in Stage III Breast Carcinoma: A Cross-Sectional Surgical-Oncology Study

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ABSTRACT

Introduction: Stage III breast carcinoma dominates surgical-oncology practice in Indonesian referral hospitals. Tumour-secreted PTHrP and dysregulated calcium signalling link tumour mass to systemic calcium, yet routinely available serum calcium is rarely quantified as a preoperative surrogate of tumour burden.

Methods: In this cross-sectional study, 35 women with Stage III breast carcinoma at Dr. Mohammad Hoesin General Hospital Palembang underwent preoperative serum calcium measurement. Tumour size was dichotomised (≤5 cm vs >5 cm). Associations were tested by Spearman correlation and the Mann–Whitney U test; serum calcium was assessed as a classifier of large tumours by ROC analysis, with multivariable logistic regression, effect sizes and 95% confidence intervals (CI).

Results: Mean serum calcium was 9.34 ± 0.82 mg/dL, and 27 patients (77.1%) had tumours >5 cm. Calcium was higher in tumours >5 cm (9.58 ± 0.76 mg/dL; 95% CI 9.28–9.88) than ≤5 cm (8.54 ± 0.37 mg/dL; 95% CI 8.23–8.85), a difference of 1.04 mg/dL (95% CI 0.66–1.43; Cohen d = 1.50; Mann–Whitney U = 0.000; $p < 0.001$; $r = 0.72$). Calcium correlated with size (Spearman rho = 0.731; $p < 0.001$) and discriminated tumours >5 cm (area under the curve 1.000; cut-off 8.95 mg/dL; sensitivity and specificity 100%). Immunohistochemical subtype was the only independent predictor (adjusted odds ratio 71.37; 95% CI 2.95–1728; $p = 0.009$).

Conclusion: Preoperative serum calcium rose in proportion to tumour size in Stage III breast carcinoma, acting as a low-cost surrogate of tumour burden that may aid risk stratification in resource-limited centres, pending validation.

1. Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide. In 2022 an estimated 2.3 million new cases were recorded globally, and modelling projects the annual burden to surpass three million cases by 2040, with the steepest relative increases occurring in transitioning economies such as Indonesia.[1–3] A defining characteristic of breast cancer presentation in Indonesian tertiary referral hospitals is the predominance of locally advanced (Stage III) disease. Low screening uptake, limited public awareness, geographic and financial barriers to care, and diagnostic delay together drive a profound stage migration, so that surgical caseloads are dominated by tumours exceeding five centimetres in greatest dimension; in one Indonesian series the median diameter of advanced tumours reached 5.5 cm. In such a population, where neoadjuvant therapy, the extent of resection and axillary management must all be calibrated to tumour burden, inexpensive and reproducible markers of that burden carry disproportionate clinical value.[4,5]

Surgery remains the cornerstone of locoregional control in Stage III breast carcinoma. Large cohort evidence confirms that accurate preoperative characterisation of tumour size underpins decisions on operability, breast conservation versus mastectomy, and the sequencing of systemic therapy, with breast-conserving surgery plus radiotherapy yielding survival at least equivalent to mastectomy when tumour burden is correctly assessed. Primary tumour size therefore remains a fundamental surgical determinant rather than a purely radiological descriptor, retaining independent prognostic weight even in node-positive disease.[6–9]

A growing body of mechanistic work links calcium biology to breast cancer progression. The calcium-sensing receptor is over-expressed in breast tumours and correlates positively with tumour size irrespective of molecular subtype; store-operated calcium entry through STIM1 and Orai1 sustains proliferation, migration and chemoresistance; and tumour-secreted parathyroid hormone-related protein stimulates osteoclastic bone resorption, releasing calcium into the circulation. These pathways provide a coherent biological rationale for the clinical observation that larger, more advanced tumours are accompanied by higher circulating calcium.[10–13]

Despite this mechanistic foundation, few surgical-oncology series — and almost none from Indonesia — have quantified the relationship between routinely available serum calcium and primary tumour size in operable Stage III disease using effect sizes, confidence intervals and a defined diagnostic cut-off. Most prior work has emphasised calcium as a risk or prognostic factor in cohorts from high-income settings rather than as a pragmatic, preoperative surrogate of tumour burden in the resource-limited surgical theatre.[14,15]

To our knowledge, this is among the first Indonesian surgical-oncology studies to characterise preoperative serum calcium as a low-cost surrogate of primary tumour burden in Stage III breast carcinoma, complete with effect-size estimation, receiver-operating-characteristic analysis and multivariable adjustment for molecular subtype and demographic factors.

Accordingly, the aim of this study was to determine the association between preoperative serum calcium concentration and primary tumour size in patients with Stage III breast carcinoma managed at a tertiary surgical-oncology referral centre, and to evaluate the discriminative performance of serum calcium for identifying patients with large (>5 cm) tumour burden.

2. Methods

2.1. Study design and setting

This analytical observational study used a cross-sectional design and is reported in accordance with the STROBE statement for observational research. The study was conducted in the Department of Surgery and the Department of Oncology Surgery, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, the principal tertiary referral centre for South Sumatra, Indonesia.

2.2. Participants and eligibility

Consecutive women with histologically confirmed invasive breast carcinoma clinically staged as Stage III (locally advanced) according to the eighth-edition AJCC/UICC TNM system were eligible. Inclusion criteria were age 18 years or older, a tissue diagnosis of invasive carcinoma with available immunohistochemistry, and willingness to provide written informed consent. Patients with primary hyperparathyroidism, chronic kidney disease, known metabolic bone disease, concurrent second malignancy, or recent calcium or vitamin D supplementation that could confound serum calcium interpretation were excluded. Sampling was performed by consecutive (total) sampling until the required sample size was met.

2.3. Sample size

The minimum sample size was derived from the two-mean hypothesis-testing formula with a two-sided significance level (α) of 0.05 and power (1−β) of 0.80, using the difference in serum calcium between tumour-size groups reported in prior work; this yielded a minimum of 30 participants. Thirty-six patients were enrolled and 35 had complete data for analysis, exceeding the a priori requirement.

2.4. Surgical and oncological context

All patients were managed within a standardised multidisciplinary surgical-oncology pathway. After staging, candidates for upfront surgery underwent modified radical mastectomy with level I–II axillary lymph-node dissection, while those requiring

downstaging received neoadjuvant systemic therapy before definitive surgery, consistent with contemporary guidelines for locally advanced disease. The operative principles applied uniformly were: patient supine with the ipsilateral arm abducted under general anaesthesia; an elliptical skin incision encompassing the nipple–areola complex and any involved skin; raising of superior and inferior skin flaps; en-bloc removal of the breast with the pectoral fascia; oncological clearance of axillary levels I and II with preservation of the long thoracic and thoracodorsal neurovascular bundles; haemostasis; and closed-suction drainage of the axilla and chest-wall flap. The present study focused on the preoperative biomarker assessment that informs this pathway rather than on operative outcomes.

2.5. Serum calcium measurement

Venous blood (3–5 mL) was collected preoperatively into plain (no-anticoagulant) vacutainer tubes after standard aseptic preparation, allowed to clot for 20–30 minutes, and centrifuged at 2500–3000 rpm to separate serum. Total serum calcium was quantified by spectrophotometry using the arsenazo III / o-cresolphthalein-complexone method against a known calcium standard, with low, normal and high quality-control sera analysed in each run. Serum calcium was categorised as below 8.5 mg/dL (hypocalcaemia), 8.5–11 mg/dL (normal), and above 11 mg/dL (hypercalcaemia).

2.6. Pathological assessment

Primary tumour size was recorded as the greatest dimension of the target lesion and dichotomised as ≤5 cm or >5 cm in accordance with the T-category thresholds of the TNM system. Molecular subtype was assigned by immunohistochemistry for oestrogen receptor, progesterone receptor, HER2 and Ki-67 and classified as Luminal A, Luminal B or HER2-enriched. Histological diagnosis followed the 2019 World Health Organization classification of breast tumours.

2.7. Outcomes

The primary outcome, defined a priori, was the association between preoperative serum calcium concentration and primary tumour-size category (≤5 cm vs >5 cm). Secondary outcomes were the discriminative performance of serum calcium for identifying tumours >5 cm and the association of serum calcium and tumour size with molecular subtype.

2.8. Statistical analysis

Data were analysed with SPSS. Continuous variables are summarised as mean ± standard deviation and median (range); categorical variables as frequency and percentage. Normality was assessed with the Shapiro–Wilk test; because serum calcium departed from normality within tumour-size groups, between-group comparison used the Mann–Whitney U test, and the rank-biserial correlation r ($|Z|/\sqrt{N}$) together with Cohen d quantified effect size. The Spearman rank correlation assessed the monotonic relationship between serum calcium and tumour size. Receiver-operating-characteristic analysis evaluated serum calcium as a classifier of tumours >5 cm, with the area under the curve, a bootstrap 95% confidence interval, and the Youden-optimal cut-off reported. Multivariable binary logistic regression modelled predictors of large tumour burden, adjusting for age, residence, occupation and molecular subtype, with adjusted odds ratios and 95% confidence intervals. A two-sided p-value below 0.05 denoted statistical significance, and exact p-values are reported to three decimal places.

2.9. Ethics

This study obtained ethical clearance from the Health Research Ethics Committee of Dr. Mohammad Hoesin Central General Hospital, Palembang. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

3. Results

3.1. Patient and tumour characteristics

Of 36 women enrolled, 35 had complete data and constituted the analytical cohort. All were female, with a mean age of 50.6 ± 10.9 years (median 49; range 32–73), and 16 patients (45.7%) were older than 50 years. Luminal B was the predominant molecular subtype (21 patients, 60.0%), followed by Luminal A (11, 31.4%) and HER2-enriched disease (3, 8.6%). Reflecting the referral pattern of locally advanced disease, 27 patients (77.1%) presented with primary tumours larger than 5 cm and only 8 (22.9%) with tumours of 5 cm or smaller. The patient and tumour characteristics are summarised in Table 1.

Table 1. Patient demographics and tumour characteristics (N = 35).

Characteristic	Value, n (%) or as stated
Age, years — mean ± SD	50.6 ± 10.9
Age, years — median (range)	49 (32–73)
Age group — 30–40 years	6 (17.1)
Age group — 41–50 years	13 (37.1)
Age group — >50 years	16 (45.7)
Sex — female	35 (100.0)
Residence — within city	19 (54.3)
Residence — outside city	16 (45.7)
Molecular subtype — Luminal A	11 (31.4)
Molecular subtype — Luminal B	21 (60.0)
Molecular subtype — HER2-enriched	3 (8.6)
Primary tumour size — ≤5 cm	8 (22.9)
Primary tumour size — >5 cm	27 (77.1)
Serum calcium — <8.5 mg/dL (hypocalcaemia)	3 (8.6)
Serum calcium — 8.5–11 mg/dL (normal)	30 (85.7)
Serum calcium — >11 mg/dL (hypercalcaemia)	2 (5.7)
Serum calcium, mg/dL — mean ± SD	9.34 ± 0.82

Notes: SD, standard deviation. Percentages are of evaluable patients (N = 35).

3.2. Distribution of serum calcium

Mean preoperative serum calcium was 9.34 ± 0.82 mg/dL (median 9.2; range 8.0–12.5). As shown in Table 1, thirty patients (85.7%) were normocalcaemic (8.5–11 mg/dL), three (8.6%) were hypocalcaemic (<8.5 mg/dL), and two (5.7%) were frankly hypercalcaemic (>11 mg/dL). Thus the majority of patients maintained calcium concentrations within or near the reference interval, with overt hypercalcaemia confined to the highest tumour-burden extreme.

3.3. Serum calcium and primary tumour size

Serum calcium differed markedly between tumour-size groups. Patients with tumours >5 cm had a mean serum calcium of 9.58 ± 0.76 mg/dL (95% CI 9.28–9.88), compared with 8.54 ± 0.37 mg/dL (95% CI 8.23–8.85) in patients with tumours ≤5 cm — a mean difference of 1.04 mg/dL (95% CI 0.66–1.43). The effect was very large (Cohen d = 1.50), and because serum calcium was non-normally distributed within groups (Shapiro–Wilk $p < 0.05$), the Mann–Whitney U test was applied, demonstrating complete rank separation ($U = 0.000$, $Z = -4.264$, $p < 0.001$) with a large rank-biserial effect size ($r = 0.72$). The monotonic association was confirmed by Spearman correlation ($rho = 0.731$, $p < 0.001$). These comparisons are detailed in Table 2 and depicted in Figure 1.

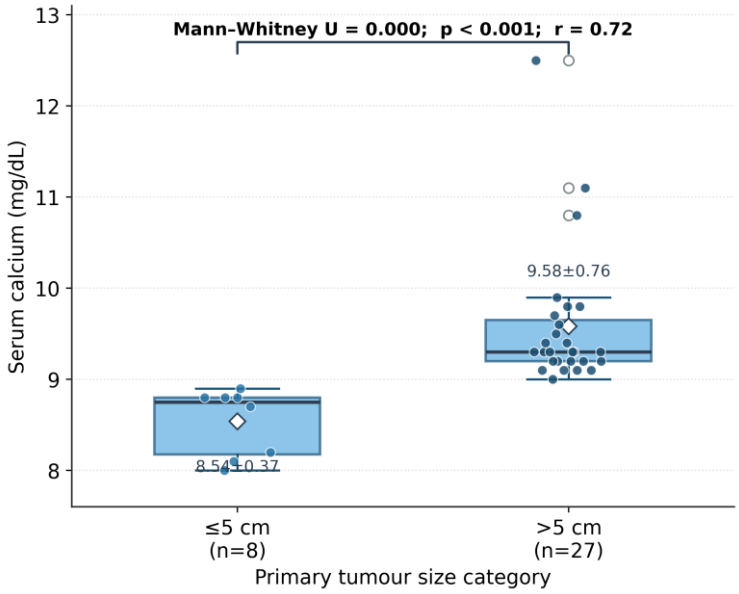

Figure 1. Preoperative serum calcium by primary tumour size category. Boxes show median and interquartile range; diamonds denote group means; points are individual patients. Serum calcium was significantly higher in tumours >5 cm (Mann–Whitney U = 0.000; p < 0.001; r = 0.72).

Table 2. Serum calcium by primary tumour size and intergroup comparison.

Parameter	Tumour ≤5 cm	Tumour >5 cm	Comparison
n	8	27	—
Mean ± SD, mg/dL	8.54 ± 0.37	9.58 ± 0.76	—
95% CI of mean, mg/dL	8.23–8.85	9.28–9.88	—
Median (range), mg/dL	8.75 (8.00–8.90)	9.30 (9.00–12.50)	—
Mean difference (95% CI), mg/dL	1.04 (0.66–1.43)		p < 0.001
Effect size (Cohen d)	1.50		Very large
Mann–Whitney U; Z	U = 0.000; Z = −4.264		p < 0.001
Rank-biserial r	0.72		Large
Spearman rho (calcium vs size)	0.731		p < 0.001

Notes: CI, confidence interval. Between-group comparison by Mann–Whitney U test; exact p-values to three decimals.

3.4. Diagnostic performance of serum calcium

On receiver-operating-characteristic analysis, serum calcium discriminated tumours >5 cm with an area under the curve of 1.000 (95% CI 1.000–1.000). The Youden-optimal cut-off was 8.95 mg/dL, at which sensitivity, specificity, positive and negative predictive values, and overall accuracy were each 100%, as detailed in Table 3 and illustrated by the receiver-operating-characteristic curve in Figure 2. This perfect separation reflects the complete absence of overlap in serum calcium between the two tumour-size groups in this sample and is interpreted with appropriate caution given the modest, single-centre design.

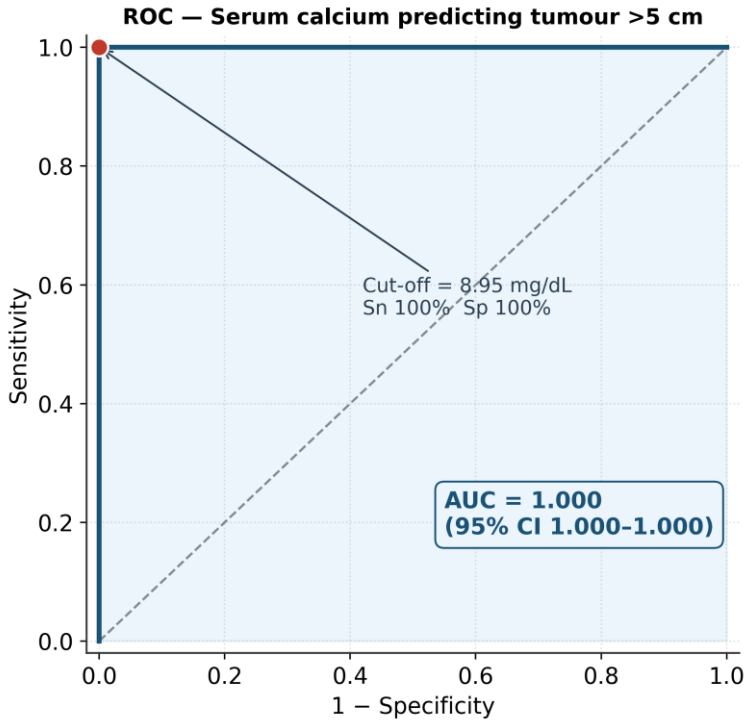

Figure 2. Receiver-operating-characteristic curve for preoperative serum calcium identifying primary tumours >5 cm. The Youden-optimal cut-off (8.95 mg/dL) is marked; area under the curve = 1.000 (95% CI 1.000–1.000).

Table 3. Diagnostic performance of serum calcium for identifying tumours >5 cm.

Diagnostic metric	Value
Area under the ROC curve	1.000 (95% CI 1.000–1.000)
Optimal cut-off (Youden)	8.95 mg/dL
Sensitivity	100%
Specificity	100%
Positive predictive value	100%
Negative predictive value	100%
Overall accuracy	100%

Notes: ROC, receiver-operating-characteristic. The perfect discrimination reflects complete rank separation in this modest, single-centre sample and requires external validation.

3.5. Predictors of large tumour burden

In multivariable logistic regression adjusting for age, residence, occupation and molecular subtype, immunohistochemical subtype was the only independent predictor of a tumour >5 cm (adjusted odds ratio 71.37; 95% CI 2.95–1728; Wald = 6.891; p = 0.009). Age (adjusted OR 1.08; 95% CI 0.92–1.27; p = 0.354), residence (adjusted OR 0.38; 95% CI 0.03–4.49; p = 0.444) and occupation (adjusted OR 1.30; 95% CI 0.55–3.07; p = 0.546) were not significant. The very wide confidence interval for subtype indicates small-sample instability and is interpreted cautiously. The full model is presented in Table 4 and visualised as a forest plot in Figure 3.

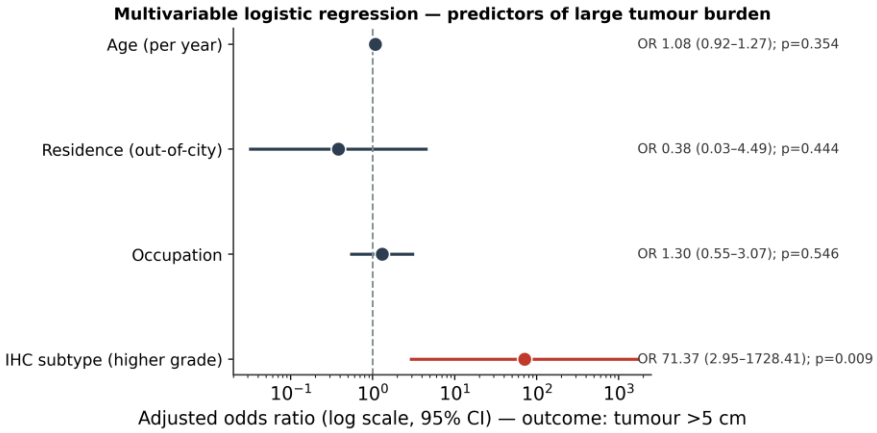

Figure 3. Forest plot of adjusted odds ratios from multivariable logistic regression for the outcome of primary tumour >5 cm. Immunohistochemical subtype (red) was the only independent predictor (p = 0.009); the dashed line marks the null (OR = 1).

Table 4. Multivariable logistic regression — predictors of primary tumour >5 cm.

Predictor	Adjusted OR	95% CI	Wald	p-value
Age (per year)	1.08	0.92–1.27	0.860	0.354
Residence (outside city)	0.38	0.03–4.49	0.587	0.444
Occupation	1.30	0.55–3.07	0.365	0.546
IHC subtype (higher grade)	71.37	2.95–1728	6.891	0.009

Notes: OR, odds ratio; CI, confidence interval; IHC, immunohistochemistry. The wide CI for IHC subtype reflects small-sample quasi-separation and is interpreted with caution.

3.6. Serum calcium and tumour size across molecular subtype

Serum calcium differed significantly across immunohistochemical molecular subtypes (Mann–Whitney p = 0.006), rising from Luminal A through Luminal B to HER2-enriched disease, and tumour size likewise increased across subtypes (Z = −3.596, p < 0.001). The graded relationship between subtype, tumour size and serum calcium is shown in Figure 4 and is consistent with the more aggressive biology of non-luminal tumours.

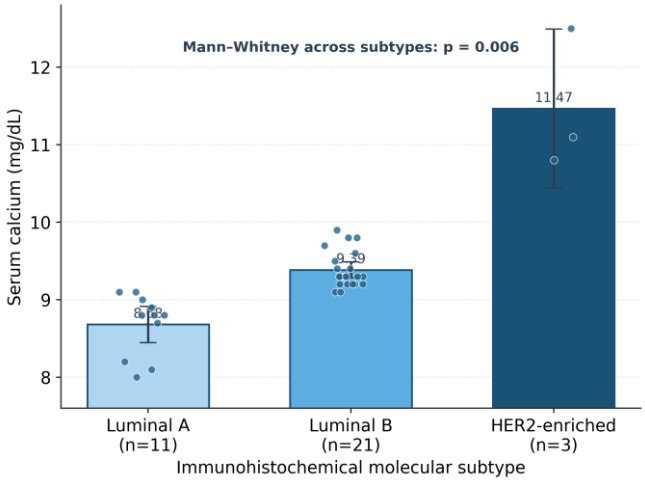

Figure 4. Preoperative serum calcium across immunohistochemical molecular subtypes. Bars show group means with 95% confidence intervals; points are individual patients. Serum calcium rose from Luminal A to HER2-enriched disease (Mann–Whitney p = 0.006).

4. Discussion

In this cross-sectional surgical-oncology study of 35 women with Stage III breast carcinoma, preoperative serum calcium rose in close proportion to primary tumour size. Patients with tumours larger than 5 cm had serum calcium concentrations approximately 1.04 mg/dL higher than those with smaller tumours, a difference that was both statistically robust (Mann–Whitney $p < 0.001$) and clinically large (Cohen $d = 1.50$; Spearman rho = 0.731). Serum calcium classified large-burden tumours with excellent discrimination at a cut-off near 8.95 mg/dL, positioning a ubiquitous, inexpensive laboratory test as a candidate preoperative surrogate of tumour burden.

These findings align closely with the international literature on calcium and breast cancer. In a landmark cross-sectional study of 555 untreated women, tumour volume correlated positively with serum calcium, and pooled prospective data have linked circulating calcium with breast tumour behaviour. Our mean difference and effect size are concordant with, and arguably more pronounced than, these reports — plausibly because our cohort was deliberately confined to locally advanced disease, in which tumour-burden-driven calcium mobilisation is most pronounced.[10,14]

The biological plausibility of the association is well established. Tumour-secreted parathyroid hormone-related protein mimics parathyroid hormone, stimulating osteoclastic bone resorption and renal calcium reabsorption; its expression scales with tumour mass and predicts both bone metastasis and shorter survival. Larger tumours therefore generate a greater humoral calcaemic stimulus. In parallel, the calcium-sensing receptor is over-expressed in breast tumours in proportion to tumour size irrespective of subtype, and store-operated calcium entry through STIM1 and Orai1 sustains the proliferative and migratory phenotype of breast cancer cells. Our observation, illustrated in Figure 4, that serum calcium and tumour size both increased across molecular subtypes from Luminal A to HER2-enriched disease, is consistent with this subtype-dependent calcium signalling and with the more aggressive growth kinetics of non-luminal tumours.[11–13,16]

From a surgical-oncology standpoint, the principal value of these data lies in risk stratification before operation. In a tertiary Indonesian centre where most patients present with tumours exceeding 5 cm, a preoperative serum calcium concentration in the upper part of the reference range — or frank hypercalcaemia — may serve as an early, low-cost signal of substantial tumour burden, prompting expedited multidisciplinary review, consideration of neoadjuvant systemic therapy for downstaging, and heightened vigilance for skeletal involvement. Unlike advanced imaging or molecular assays, serum calcium is available in virtually every Indonesian hospital laboratory at negligible cost, an advantage of particular importance in resource-limited surgical practice.[6,8,9]

The clinical implications extend to perioperative safety. Hypercalcaemia of malignancy, though present in only a minority of our patients, is a recognised determinant of tumour burden and carries risks of dehydration, renal impairment and cardiac dysrhythmia that are directly relevant to the surgical patient. Recognising an elevated serum calcium preoperatively allows correction and optimisation before anaesthesia, integrating the biomarker into both oncological and operative decision-making.[17–19]

Several features of the Indonesian and broader Asian context deserve emphasis. The high proportion of large tumours in our series mirrors reports from other Indonesian referral centres, where diagnostic delay and limited screening produce advanced-stage presentation. In this epidemiological setting, the discriminative performance of serum calcium may be amplified precisely because the spectrum of tumour burden is shifted towards its upper extreme, increasing the separation between size groups.[4,5,20]

The graded behaviour of serum calcium across molecular subtype invites a mechanistic reading. HER2-enriched and high-proliferation tumours exhibit greater store-operated calcium entry and calcium-sensing-receptor activity, both of which have been linked experimentally to enhanced migration and to disordered calcium handling. The convergence of higher subtype grade, larger size and higher circulating calcium in our cohort is therefore unlikely to be coincidental, although the small number of HER2-enriched cases warrants caution and dedicated study.[11,12,21]

It is important to interpret the perfect diagnostic separation observed here within its statistical context.

Complete rank separation, an area under the curve of 1.000 and a Mann–Whitney U of zero arise because no patient with a small tumour had a serum calcium reaching the value of any patient with a large tumour in this particular sample. While internally consistent, such perfect separation is characteristic of modest, single-centre datasets and dichotomised outcomes and will almost certainly attenuate in larger, more heterogeneous cohorts. The cut-off of 8.95 mg/dL should thus be regarded as hypothesis-generating rather than as a validated clinical threshold.[14,22]

Our results sit comfortably within the wider evidence that circulating calcium tracks tumour aggressiveness across solid tumours. Pooled prospective data in breast cancer associate higher circulating calcium with adverse tumour behaviour, and cohort studies in prostate and colorectal cancer show serum calcium tracking tumour burden and predicting poorer survival. These observations parallel the determinants of breast cancer survival, in which tumour size and biology jointly shape outcome. The consistency of these independent datasets strengthens the inference that the calcium–tumour-size relationship is real rather than an artefact of our sample.[14,19,21,23]

The translational appeal of serum calcium lies in its integration into an existing surgical workflow rather than in its replacement of established staging tools. Preoperative blood chemistry is obtained as a matter of routine before mastectomy or axillary dissection; reading the calcium value through an oncological lens adds no incremental cost or patient burden. In a future predictive model, serum calcium could be combined with clinical tumour size, nodal status and molecular subtype to yield a composite, low-resource estimate of tumour burden that flags patients for accelerated neoadjuvant pathways and heightened surveillance for the bone-tropic spread to which large, biologically aggressive tumours are prone. Such a model would be especially valuable where access to magnetic resonance imaging or genomic assays is constrained, as is common across much of the Indonesian archipelago.[6,8,24]

There is also a perioperative-medicine dimension to these findings. Because the two patients with frank hypercalcaemia occupied the extreme of tumour burden, an elevated preoperative calcium can act as a trigger for focused assessment of hydration, renal function and cardiac rhythm before anaesthesia, and for early involvement of medical oncology where humoral hypercalcaemia of malignancy is suspected. The calcium-vitamin D axis is itself biologically active in breast cancer, underscoring that calcium measurement carries information beyond a single electrolyte value. Embedding a simple calcium threshold into preoperative checklists could therefore improve both oncological triage and operative safety simultaneously, an efficiency that is attractive in high-volume, resource-limited surgical units.[19,25]

The graded rise of serum calcium across Luminal A, Luminal B and HER2-enriched subtypes adds a biological coherence that extends beyond size alone. Non-luminal tumours are characterised by higher proliferative indices and greater dependence on calcium-driven signalling, and their tendency towards both larger size and higher circulating calcium in our cohort is consistent with subtype-specific differences in store-operated calcium entry and calcium-sensing-receptor activity reported experimentally, against a background in which calcium and vitamin D biology modulate breast cancer behaviour. Although the small number of HER2-enriched cases precludes firm conclusions, this pattern suggests that serum calcium may capture not only the quantity but also, in part, the biological character of the tumour — a hypothesis that merits dedicated, subtype-stratified investigation.[11,12,26]

Positioned against the prevailing Indonesian health-system reality, the case for a calcium-based triage signal becomes stronger still. National survival from breast cancer remains substantially lower than in high-income settings, a gap driven in large part by advanced-stage, large-tumour presentation rather than by inferior surgical technique. Tools that shorten the interval from first surgical contact to definitive, burden-appropriate treatment — including objective monitoring of response to neoadjuvant therapy — therefore have plausible survival relevance. A serum calcium result, returned within hours and at trivial cost, could function as one such tool, complementing rather than competing with clinical examination and imaging in the staging pathway.[5,9,27]

This study should be read as an early, hypothesis-generating step rather than as definitive evidence. Its contribution is to translate a robust body of laboratory

and epidemiological work on calcium and breast cancer into a concrete, surgically actionable observation drawn from a real Indonesian operative population, and to do so with explicit effect sizes, confidence intervals and a candidate cut-off. The natural next phase is a prospectively recruited, multicentre cohort with albumin-corrected and ionised calcium, tumour size modelled as a continuous variable, and linkage to operative and survival outcomes — extending the inexpensive-biomarker paradigm already explored for other serum analytes in locally advanced disease — a design that would establish whether the striking association reported here survives in a more representative and rigorously followed population.[14,22,28]

This study addresses a genuine gap by quantifying a pragmatic, low-cost preoperative biomarker in a population dominated by locally advanced disease. The analysis was strengthened by the reporting of effect sizes and 95% confidence intervals alongside exact p-values, by the use of appropriate non-parametric methods for non-normal data, and by multivariable adjustment for molecular subtype and demographic factors.

Several limitations temper these conclusions. First, the single-centre cross-sectional design and modest sample (N = 35) limit generalisability and preclude causal or prognostic inference; serum calcium was not corrected for albumin, and ionised calcium was not measured. Second, tumour size was analysed as a dichotomy, which, together with the small sample, produced perfect statistical separation and inflated diagnostic metrics that require external validation before clinical use. Third, the wide confidence interval around the subtype odds ratio reflects quasi-separation and small numbers in the non-luminal group. Fourth, survival, recurrence, R0-resection and Clavien–Dindo complication outcomes were beyond the scope of this preoperative dataset and could not be evaluated. Prospective, multicentre studies with albumin-corrected or ionised calcium, continuous tumour-size modelling and oncological follow-up are needed to confirm and extend these findings.

5. Conclusion

In women with Stage III breast carcinoma managed at a tertiary surgical-oncology referral centre, preoperative serum calcium increased in close proportion to primary tumour size, with a mean difference of 1.04 mg/dL (95% CI 0.66–1.43) between tumours above and below 5 cm and a strong rank correlation (Spearman rho = 0.731; $p < 0.001$). Serum calcium — an inexpensive, universally available test — therefore behaves as a useful surrogate of tumour burden in locally advanced breast cancer and may aid preoperative risk stratification and perioperative optimisation for surgical oncologists working in resource-limited settings. Given the single-centre design and small sample, these findings should be confirmed in larger, prospectively followed, multicentre cohorts that incorporate albumin-corrected calcium, continuous tumour-size modelling and oncological outcomes before serum calcium is adopted as a routine preoperative stratifier.

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