



ORIGINAL ARTICLE

Evaluation of 25-Hydroxyvitamin D Levels and Their Relationship with Breast Cancer Biomarkers CA15-3 and CEA: A Retrospective Study



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KEYWORDS

Vitamin D;
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Abstract

Introduction: Vitamin D deficiency is prevalent and often overlooked, especially in countries like Morocco. Concurrently, breast cancer remains the most common cancer among women globally. Recent interest has focused on the link between vitamin D levels and breast cancer development. This study aims to examine the relationship between serum levels of breast cancer biomarkers and vitamin D status in Moroccan women, while exploring associations with clinicopathological features.

Materials and methods: A retrospective analysis was conducted on 116 Moroccan women. The vitamin D status and serum levels of CA15-3 and CEA were evaluated by Competitive Immunoassay Technique with End-Point Fluorescence Detection (ELFA) and Chemiluminescent Microparticle Immunoassay (CMI). Statistical analyses evaluated the associations between vitamin D status and breast cancer risk, with a particular focus on comparing CA15-3 and CEA levels between vitamin D-deficient and non-deficient patients.

Results: Vitamin D deficiency was significantly associated with elevated CA15-3 levels ($p = 0.041$), with all patients showing elevated CA15-3 being vitamin D deficient. However, no significant correlation was identified between vitamin D levels and CEA ($p = 0.221$). In vitamin D-deficient patients, a negative correlation was observed between vitamin D and CA15-3 levels ($r = -0.244$, $p = 0.017$), suggesting that lower vitamin D levels may contribute to higher CA15-3 concentrations.

Conclusion: Our findings highlight that a significant association was observed between CA15-3 levels (abnormal ≥ 30 U/mL) and vitamin D status ($p = 0.041$), but the logistic regression model did not confirm this association. This suggests that additional factors may influence this association, and further studies are needed to confirm these findings.

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PALABRAS CLAVE

Vitamina D;
CA15-3 sérico;
CEA;
Biomarcadores
tumores;
Cáncer de mama

Evaluación de los niveles de 25-hidroxivitamina D y su relación con los biomarcadores de cáncer de mama CA15-3 y CEA: Un estudio retrospectivo**Resumen**

Introducción: La deficiencia de vitamina D es común y a menudo no se detecta, especialmente en países como Marruecos. El cáncer de mama es el más frecuente entre las mujeres a nivel mundial. Este estudio tiene como objetivo examinar la relación entre los niveles de biomarcadores del cáncer de mama y el estado de vitamina D en mujeres marroquíes, explorando también su asociación con características clinicopatológicas.

Materiales y Métodos: Se realizó un análisis retrospectivo en 116 mujeres marroquíes. El estado de vitamina D y los niveles séricos de CA15-3 y CEA fueron evaluados mediante inmunoensayo competitivo con detección de fluorescencia (ELFA) y quimioluminiscencia de micropartículas (CMI). Se analizaron las asociaciones entre el estado de vitamina D y el riesgo de cáncer de mama, comparando los niveles de CA15-3 y CEA en pacientes con y sin deficiencia de vitamina D.

Resultados: La deficiencia de vitamina D se asoció significativamente con niveles elevados de CA15-3 ($p = 0.041$), siendo todas las pacientes con CA15-3 elevado deficientes en vitamina D. No se encontró correlación significativa entre vitamina D y CEA ($p = 0.221$). En las pacientes deficientes en vitamina D, se observó una correlación negativa entre vitamina D y CA15-3 ($r = -0.244$, $p = 0.017$), sugiriendo que niveles bajos de vitamina D podrían contribuir a concentraciones más altas de CA15-3.

Conclusión: Nuestros hallazgos destacan que se observó una asociación significativa entre los niveles de CA15-3 (anormal ≥ 30 U/mL) y el estado de la vitamina D ($p = 0.041$), pero el modelo de regresión logística no confirmó esta asociación. Esto sugiere que factores adicionales pueden influir en esta relación y que se necesitan más estudios para confirmar estos resultados.

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Introduction

Vitamin D is unique among vitamins, in that it has a dual source it can be acquired through diet or produced endogenously by the skin following exposure to UVB radiation.¹ Whether obtained through ingestion or synthesized in the skin, vitamin D undergoes conversion to 25(OH)D in the liver.² This conversion process is loosely regulated, making the 25(OH)D concentration the most reliable marker of vitamin D status. A second hydroxylation step, catalyzed by 1-alpha-hydroxylase, results in the production of the active metabolite, 1,25-dihydroxyvitamin D, across various tissues. The circulating 1,25-dihydroxyvitamin D is believed to originate predominantly from renal 1-alpha hydroxylation.^{3,4}

Recently, there has been an increase in interest of vitamin D and breast cancer, as evidenced by the growing number of publications on the subject,^{5,6} and this increased interest can be attributed to several reasons, on the one hand, there is a rising prevalence of vitamin D deficiency, on the other hand, the active form of vitamin D, 1,25(OH)₂D₃, binds to the vitamin D receptor (VDR), which then translocates to the nucleus and affects regulatory genes.⁷ These genes are crucial in controlling cell proliferation and differentiation, apoptosis, angiogenesis, as well as the activation of proto-oncogenes and tumor suppressor genes.^{8,9}

Serum biomarkers, notably CA 15-3 and CEA, are particularly useful in detecting breast cancer recurrence or

metastasis early, potentially before it is visible on imaging studies.¹⁰ CEA is one of the first tumor markers to be recognized. While it is specific to tumors, it is not limited to a particular organ.¹¹ CA 15-3 is a mucinous glycoprotein that has been detected at heightened levels in the serum of women diagnosed with breast cancer in combination with CEA; it is one of the first circulating prognostic indicators in breast cancer.¹²

Indeed, breast cancer (BC) is the leading cause of death for women worldwide, with an annual incidence of 2.3 million new cases.¹³ However, vitamin D deficiency is a common and underdiagnosed issue. It is estimated that globally, one billion people are affected.¹⁴

Several studies have confirmed that breast cancer cells contain vitamin D receptors and have identified a link between vitamin D levels and breast cancer development.^{15,16} In addition, preclinical research indicates that combining calcitriol with anticancer drugs can yield promising outcomes.¹⁷ However, the results of clinical trials on patients are contradictory, and the true role of vitamin D in the development of breast cancer is still unknown.^{5,18} For this reason, this study focuses on the growing interest in assessing the association between vitamin D status and breast cancer risk.

Materials and methods

Study population: A retrospective study was conducted on 116 female patients, all of whom were examined at a

medical analysis laboratory in Casablanca, Morocco, between 2020 and 2023. The biomarkers CA15-3 and CEA were monitored for post-diagnostic follow-up of breast cancer. In addition, vitamin D status was measured. Participant recruitment and data collection for this case group were based on the available information from the laboratory records. However, specific clinicopathological parameters, such as tumor grade, stage, or receptor status, were not included, as this information was not available. The study was carried out in full accordance with ethical guidelines, as approved by the Ethics Committee for Biomedical Research in Morocco (Approval No. 3/2018/April 30, 2018).

Inclusion and exclusion criteria: In this study, all included cases are of Moroccan origin from the Casablanca-Settat region, aged between 26 and 83 years, with a historical onset of breast cancer (BC) disease. Participants taking vitamin D supplements were excluded from the study as this could affect the measurement of vitamin D status. Additionally, individuals with other severe diseases such as renal insufficiency, benign liver, or breast pathologies, etc., or those undergoing intensive medical treatment, were also excluded from the study.

Blood Sampling: Blood from the cases was preferably drawn fasting in dry tubes and centrifuged at 3000 rpm for 15 min. The serum was used for the dosage of vitamin D and tumor markers (CA15-3 and CEA).

Vitamin D dosage: The quantification of vitamin D is carried out through a competitive immunoassay technique with end-point fluorescence detection (ELFA), utilizing the VIDAS 25-OH Vitamin D kit in the Vidas system. The measured values are interpreted based on reference ranges: Vitamin D deficiency is indicated by a serum level of 25-D < 10 ng/mL, insufficiency by a level of ≥ 10 to < 30 ng/mL, and normal levels range from ≥ 30 ng/mL to 100 ng/mL.

Marker analysis: Serum concentrations of CA15-3 and CEA were measured using the Architect i1000SR analyzer (Abbott Diagnostics). The CA15-3 assay was conducted with the ARCHITECT CA15-3 reagent, utilizing a chemiluminescent microparticle immunoassay (CMIA). Likewise, CEA levels were assessed on the same automated system using the ARCHITECT CEA reagent, which also employs CMIA technology. The standard cut-offs were used for the usual breast cancer biomarkers: 30 U/mL for CA 15-3 and 10 ng/mL for CEA.¹⁹

Statistical Analysis: The data were analyzed using SPSS version 23 software. Statistical comparisons between the two groups were carried out using the Pearson correlation and chi-square test (χ^2), with a significance level set at $P < 0.05$. Additionally, logistic regression was employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs), allowing for the evaluation of the association between vitamin D status and potential associated factors.

Results

Profile of study participants: In this retrospective cohort, the mean age at diagnosis was 59.5 years (± 9.37 years). The majority of patients (72.4%, or 84 cases) were older than 55 years, while 27.6% (32 cases) were younger than 55 years. Regarding serum CEA levels, 94 patients (92.2%) had normal levels (< 10 ng/mL), while 8 patients (7.8%) had

abnormal levels (≥ 10 ng/mL). Indeterminate values were observed in 14 patients. For serum CA 15-3 levels, 98 patients (84.5%) had normal levels (< 30 U/mL), while 18 patients (15.5%) had abnormal levels (≥ 30 U/mL). The tests were conducted at different times of the year. Among the participants, 52.6% (61 cases) were tested during winter and spring (November 1 to April 30), while 47.4% (55 cases) were tested during summer and autumn (May 1 to October 31). Concerning vitamin D status, 19 patients (16.4%) had normal levels (≥ 30 ng/mL), 75 patients (64.7%) had insufficiency (≥ 20 to < 30 ng/mL), and 22 patients (19.0%) had a deficiency (< 10 ng/mL). Finally, regarding menopausal status, 105 patients (90.5%) were postmenopausal, while 11 patients (9.5%) were premenopausal (Table 1).

Correlation between clinicopathological characteristics and vitamin D status: The correlation between vitamin D status and various patient characteristics is detailed in Table 2. The analysis revealed that among patients younger than 55 years, 84.4% (27 cases) were vitamin D deficient, while 15.6% (5 cases) were non-deficient. Among patients older than 55 years, 83.3% (70 cases) were deficient, and 16.7% (14 cases) were non-deficient. However, the difference in vitamin D status by age was not statistically significant ($p = 0.892$).

Regarding serum CEA levels, 100% (8 cases) of patients with abnormal CEA levels (≥ 10 ng/mL) were vitamin D deficient, whereas none of these patients were non-deficient. In contrast, 84.0% (79 cases) of patients with normal CEA levels were deficient, and 16.0% (15 cases) were non-deficient. Although deficiency was more prevalent

Table 1 Clinical data of the subjects studied.

Features	n	Percentage (%)
Age at diagnosis (years): Mean age = 59,5 ($\pm 9,37$)		
< 55	32	27.6
> 55	84	72.4
Serum CEA levels		
Normal (< 10 ng/mL)	94	92.2
Anormal (≥ 10 ng/mL)	8	7.8
Indeterminate values	14	—
Serum CA 15-3 levels		
Normal (< 30 U/mL)	98	84.5
Anormal (≥ 30 U/mL)	18	15.5
Dosage by season		
Winter/Spring (1 November to 30 April)	61	52.6
Summer/Autumn (1 May to 31 October)	55	47.4
Vitamin D status		
Normal (≥ 30 ng/mL)	19	16.4
Insufficiency (≥ 20 to < 30 ng / mL)	75	64.7
Deficiency (< 10 ng/mL)	22	19.0
Menopausal status		
Premenopausal	11	9.5
Postmenopausal	105	90.5

n: Number of patients.

Table 2 Correlation of Vitamin D Levels with age, Serum Markers, Menopausal status, and Seasonal Variation.

Characteristics	Vitamin D status				<i>P</i>
	Non-deficient		Deficient		
	N	Percentage %	N	Percentage %	
Age at diagnosis					0.892
<55	5	15.6	27	84.4	
>55	14	16.7	70	83.3	
Serum CEA levels					0.221
Normal (<10 ng/mL)	15	16.0	79	84.0	
Anormal (≥10 ng/mL)	0	0	8	100.0	
CA 15-3 levels					0.041
Normal (< 30 U/mL)	19	19.4	79	80.6	
Anormal (≥ 30 U/mL)	0	0	18	100.0	
Menopausal status					0.865
Premenopausal	2	18.2	9	81.8	
Postmenopausal	17	16.2	88	83.8	
Dosage by season					0.012
Winter/Spring	15	24.6	46	75.4	
Summer/Autumn	4	7.3	51	92.7	

n: Number of patients / p values less than 0.05 are highlighted in bold.

among patients with abnormal CEA levels, the association was not statistically significant ($p = 0.221$).

A significant correlation was observed between CA 15-3 levels and vitamin D status ($p = 0.041$). All patients with abnormal CA 15-3 levels (≥ 30 U/mL) were vitamin D deficient (100%, 18 cases), while among those with normal CA 15-3 levels, 19.4% (19 cases) were non-deficient, and 80.6% (79 cases) were deficient. No significant difference in vitamin D status was observed between premenopausal and postmenopausal patients ($p = 0.865$). Among premenopausal patients, 81.8% (9 cases) were deficient, and 18.2% (2 cases) were non-deficient. Similarly, among postmenopausal patients, 83.8% (88 cases) were deficient, and 16.2% (17 cases) were non-deficient. Seasonal variations in vitamin D levels were significant ($p = 0.012$). Deficiency was more prevalent during summer and autumn (92.7%, 51 cases) compared to winter and spring (75.4%, 46 cases). Conversely, non-deficiency was more common during winter and spring (24.6%, 15 cases) compared to summer and autumn (7.3%, 4 cases).

Potential risk factors associated with Vitamin D Deficiency: According to Table 2, several factors are analyzed for their potential influence on vitamin D deficiency among the patients. Additionally, Table 3 explores both risk and protective elements associated with vitamin D deficiency. Notably, the diagnosis age at diagnosis shows an odds ratio

Table 3 Influential Factors in Vitamin D Deficiency.

Factors	Odds ratio value	95% Confidence interval
Age at diagnosis	0.575	[0.304; 2.82]
CEA levels	1.131	[0.793; 1.81]
CA 15-3 levels	1.012	[0.963; 1.09]
Menopausal status	0.170	[0.228; 5.80]
Dosage by season	2.381	[1.287; 13.43]

(OR) of 0.575, indicating a possible protective effect where younger patients at diagnosis might be less likely to experience vitamin D deficiency compared to older patients. However, the 95% confidence interval (CI) [0.304; 2.82], suggests that this association is not statistically significant. CEA levels present an OR of 1.131, which suggests no strong association between CEA levels and vitamin D deficiency. The 95% CI for this factor [0.793; 1.81] includes values around 1, reinforcing the interpretation that this relationship is not statistically significant. Similarly, CA 15-3 levels have an OR of 1.012, with a 95% CI [0.963; 1.09] is narrow and centers around 1, confirming that CA 15-3 levels do not significantly influence vitamin D status. Menopausal status has an OR of 0.170, with a 95% CI [0.228; 5.80] indicating that this association is not statistically significant. Finally, the dosage by season shows an OR of 2.381, with a 95% CI [1.287; 13.43], indicating that this association is statistically significant.

Correlation between serum vitamin D levels and the breast cancer marker CA15-3: In Fig. 1A, the correlation between vitamin D and CA15-3 levels in non-deficient patients shows a Pearson correlation coefficient (r) of -0.181 . This value indicates a very low negative correlation between the two variables. The P-value of 0.445, well above 0.05, suggests that there is no significant association. Consequently, we can conclude that in non-deficient patients, no significant correlation was observed between vitamin D levels and CA15-3 levels.

On the other hand, the correlation in vitamin D-deficient patients (Fig. 1, B) reveals a Pearson correlation coefficient (r) of -0.244 , implying a slightly stronger negative correlation than in non-deficient patients. This could suggest a minor trend where lower vitamin D levels might be associated with slightly elevated CA15-3 levels. However, the P value of 0.017 is statistically significant ($P < 0.05$), indicating that there is indeed a significant negative correlation between vitamin D and CA15-3 levels in vitamin D-deficient patients.

Discussion

Breast cancer is the most prevalent malignancy in women and ranks as the second leading cause of cancer-related mortality, accounting for 24% of all cancers diagnosed in women.²⁰ Serum biomarkers, especially cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA), are highly valuable in tracking treatment response and detecting early signs of recurrence or metastasis. CA15-3, a glycoprotein derived from the mucin-1 (MUC-1) protein, is notably overexpressed in approximately 90% of breast cancers,

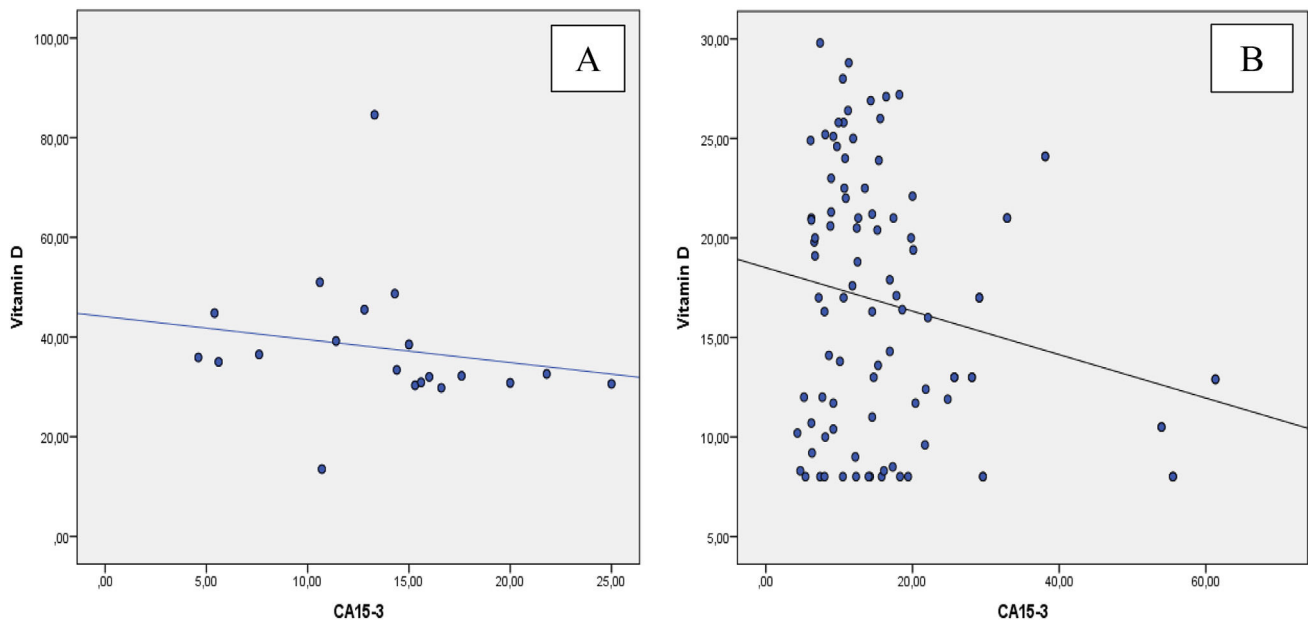


Figure 1 A: Correlation between vitamin D and CA15-3 in non-deficient, B: Correlation between vitamin D and CA15-3 in deficiency patients.

highlighting its value as a diagnostic and prognostic biomarker.²¹

In this study, we investigated not only the relationship between vitamin D levels and factors such as age, seasonal variations, and menopausal status but also how these levels relate to the tumor markers CA15-3 and CEA in breast cancer. This is particularly relevant as the majority of women suspected of having breast cancer were found to have a serum 25-(OH)D deficiency at the time of diagnosis. In the study cohort, a significant proportion, 64.7% had vitamin D insufficiency, with nearly 19% of these women suffering from severe vitamin D deficiency. Our findings are consistent with a diverse literature on the decline in serum 1,25(OH)₂D levels as breast cancer progresses.^{22,23} This suggests that even in a country like ours, where the sun shines year-round, hypovitaminosis D is highly prevalent.²⁴ Other factors, such as recent climate changes through heat stress, may also play a role.²⁵ This is supported by our findings, which show that vitamin D deficiency was more common in autumn and spring (92.7%). With a p-value of 0.012, this result is statistically significant, as blood vitamin D levels increase in response to sun exposure, leading to seasonal variations.²⁶

In addition, 90.5% of the population studied had a postmenopausal status, as the age of the onset of menopause can be a contributing factor to breast cancer.²⁷ Furthermore, vitamin D deficiency is a critical issue in postmenopausal women,²⁸ but in our study, deficiency was high in both menopausal statuses.

CA 15-3 and CEA are the most widely investigated serum tumor markers in breast cancer. Thus, marker analysis is appropriate for patients with a prior diagnosis who are at high risk for tumor recurrence, as it helps detect early disease dissemination. Additionally, it is valuable in patients with metastatic disease for evaluating their therapeutic response.²⁹ Among these, CA15-3 is the most widely utilized

marker due to its significant overexpression in breast cancer.³⁰

The study found a significant inverse correlation between vitamin D levels and CA15-3 concentrations in vitamin D-deficient patients ($p = 0.017$), suggesting that lower vitamin D levels may be associated with higher expression of CA15-3, but the logistic regression model did not confirm this association (OR 1.012 [0.963–1.09]). Comparable findings were reported in an Iraqi study where lower serum 25-hydroxyvitamin D levels corresponded with elevated CA15-3 levels in breast cancer patients.³¹ These results are consistent with other studies that have reported an inverse and independent association between vitamin D levels and breast cancer risk.³² These findings align with broader epidemiological evidence pointing to an inverse relationship between serum 25(OH)D levels and breast cancer risk, although the strength of this association varies across studies.^{33,34}

Nevertheless, our analysis did not reveal a significant association between vitamin D levels and CEA concentrations or patient age. This lack of correlation with CEA contrasts with some studies that have reported a more direct link between vitamin D status and cancer risk, though findings in this area are inconsistent.^{32,33} While an observed trend suggested a slight increase in breast cancer risk among vitamin D-deficient individuals, the association did not reach statistical significance.

It is important to acknowledge the limitations of our study. Firstly, the lack of complete data on clinico-pathological parameters, such as tumor grade, stage, and receptor status (estrogen and progesterone receptors), hinders a comprehensive assessment of the relationship between vitamin D and these key prognostic factors in breast cancer. Additionally, the absence of data on skin color, and data on vitamin D-related gene variants which may influence

vitamin D synthesis, represents another limitation. These factors may influence the biomarkers studied (CA15-3 and CEA) and warrant further investigation in future research to better understand the role of vitamin D in the development and progression of breast cancer.

In conclusion, this study demonstrates a significant negative correlation between vitamin D levels and CA15-3 in vitamin D-deficient patients ($r = -0.244$, $p = 0.017$), suggesting a possible trend where lower vitamin D levels might be associated with slightly higher CA15-3 levels in this subgroup. However, logistic regression analysis revealed that CA15-3 levels do not significantly influence vitamin D status (OR 1.012 [0.963–1.09]), indicating that the observed associations may be influenced by other covariates. Further research with larger sample sizes and adjustments for additional confounding factors is required to clarify the relationship between vitamin D status and CA15-3, a tumor marker associated with breast cancer. As a cross-sectional analysis, this research provides a snapshot of the relationship between these variables but does not establish any causal links. The study's retrospective limits the ability to draw direct cause-and-effect conclusions. Future investigations, including longitudinal studies and genetic analyses, are necessary to better elucidate the underlying mechanisms and potential clinical implications of these findings.

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Ethical disclosures

This study was ethically approved by the Committee of Biomedical Research Ethics in Morocco (n°3/2018/April 30/2018- Morocco).

Patients consent

Free consent was obtained from all recruited patients, and the confidentiality of their personal information was kept according to ethical rules.

Authors' contributions

ZS. was involved in the conceptualization of the study, as well as in the study methodology, data collection & processing, formal analysis & interpretation, project administration, and in the writing, reviewing, and editing of the original draft of the manuscript. KN. was involved in the reviewing and editing of the manuscript and in the formal analysis. KAT. was involved in the formal analysis, reviewing and editing of the manuscript. MME. was involved in project administration, in data validation, in writing, reviewing, and editing of the manuscript, and in project supervision. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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