

## Serum 25-Hydroxy D3 Levels in Different Severity of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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### ABSTRACT

**Aim:** The aim of this study was to evaluate serum 25-hydroxyvitamin D3 levels across different stages of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) severity. **Materials and Methods:** Fifty-three participants with morbid obesity (Body Mass Index (BMI)  $\geq 40$  kg/m<sup>2</sup>) were included in the study. MASLD activity scores (NAS) were calculated based on liver biopsies, and participants were divided into three groups: mild MASLD (n=15, NAS  $\leq 2$ ), moderate MASLD (n=23, NAS 3–4), and severe MASLD (n=15, NAS  $\geq 5$ ). Blood samples were collected, and serum vitamin D levels were analyzed using liquid chromatography–tandem mass spectrometry. **Results:** Serum 25-hydroxyvitamin D3 levels were significantly lower in the moderate and severe MASLD groups ( $25.9 \pm 9.10$  ng/mL and  $21.9 \pm 7.14$  ng/mL, respectively) compared with the mild MASLD group ( $34.5 \pm 10.19$  ng/mL). Total cholesterol and HDL cholesterol levels were lower in the severe MASLD group compared to other groups ( $165.0 \pm 38.64$  mg/dL and  $39.8 \pm 8.33$  mg/dL, respectively). Furthermore, serum folic acid levels were significantly lower in the moderate and severe MASLD groups ( $13.8 \pm 4.00$  nmol/L and  $14.9 \pm 4.38$  nmol/L, respectively) compared with the mild MASLD group ( $17.9 \pm 3.98$  nmol/L). Serum 25-hydroxyvitamin D3 levels and NAS were not significantly different between genders. Serum vitamin D levels showed an inverse correlation with NAS ( $r = -0.332$ ,  $p < 0.05$ ). **Conclusion:** These findings suggest that lower serum 25-hydroxyvitamin D3 levels are associated with increasing severity of MASLD. Vitamin D deficiency may play a potential role in disease progression and could serve as a biomarker for disease severity. Future studies are warranted to explore whether vitamin D supplementation could improve clinical outcomes in patients with MASLD.

**Keywords:** Vitamin D, metabolic dysfunction-associated steatotic liver disease, 25-hydroxy D3

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## **INTRODUCTION**

Vitamin D is a fat-soluble vitamin synthesized from 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation. It is subsequently hydroxylated in the liver to form 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D. This metabolite is then transported to the kidney, where it is further converted into its biologically active form, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). The active form of vitamin D exerts its physiological effects primarily by binding to the nuclear vitamin D receptor (VDR) (1).

Over the last decade, the importance of vitamin D has become increasingly evident. Beyond its classical role in calcium and bone metabolism, vitamin D has been implicated in modulating immune responses, reducing inflammation, and influencing cellular differentiation (2).

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly termed Non-Alcoholic Fatty Liver Disease (NAFLD), is now recognized as the most prevalent form of chronic liver disease, strongly associated with obesity, type 2 diabetes mellitus, and cardiometabolic risk factors, particularly in Western countries (3). MASLD is characterized by macrovesicular accumulation of triglycerides in hepatocytes (hepatic steatosis) in the absence of significant alcohol consumption (4). Its spectrum ranges from simple steatosis (MASL) to more severe stages such as steatohepatitis (MASH), fibrosis, cirrhosis, and eventually hepatocellular carcinoma, which can lead to liver failure (5, 6).

Obesity is both a major risk factor for MASLD and a significant cause of vitamin D insufficiency. In turn, MASLD progression can lead to necroinflammation and fibrosis (7). Although the exact pathogenesis of MASLD is not yet fully understood, several factors are implicated, including excess intracellular fatty acids, oxidative stress, inflammatory cytokines and adipocytokines, as well as mitochondrial dysfunction. These processes appear to play a critical role in the transition from simple steatosis to advanced fibrosis (8).

Vitamin D has been suggested to have protective effects against hepatic inflammation and fibrosis by modulating immune responses, reducing oxidative stress, and influencing fibrogenic pathways (9). Mechanistically, vitamin D and VDR signaling have been shown to suppress the activation of hepatic stellate cells, downregulate pro-fibrotic cytokines such as TGF-β1, and reduce the expression of pro-inflammatory mediators including TNF-α and IL-6. Additionally, vitamin D may mitigate lipotoxicity and mitochondrial dysfunction by enhancing antioxidant defenses and improving insulin sensitivity. These actions collectively help limit the progression from simple steatosis to fibrosis and inflammation in MASLD (10-12).

Therefore, MASLD severity may be affected by vitamin D status, given its hormonal, immunological, and cellular regulatory effects (13, 14). However, previous studies have reported inconsistent results regarding the relationship between serum vitamin D levels and MASLD severity (15-18). While some studies have found significantly lower vitamin D levels in patients with steatohepatitis or advanced fibrosis, others reported no clear association or even contradictory findings. These discrepancies may be attributed to differences in study populations, geographical variations in sun exposure, vitamin D assessment methods, and diagnostic criteria used for MASLD. Clarifying these inconsistencies could help determine whether vitamin D status serves as a reliable marker of disease severity.

From a clinical perspective, evaluating serum vitamin D levels in MASLD patients may have prognostic and therapeutic implications. Identifying vitamin D deficiency could help stratify patients at higher risk of disease progression and guide potential supplementation strategies. Optimizing vitamin D status may represent a simple, low-cost adjunctive approach to reduce inflammation, prevent fibrosis, and improve overall liver health in MASLD.

The aim of this study was to evaluate serum 25-hydroxyvitamin D3 levels in patients with different stages of MASLD severity, and to explore potential associations between vitamin D status and disease progression.

## **MATERIALS AND METHODS**

### **Participants**

This study was conducted as a retrospective analysis using patient data from a Texas Tech University Institutional Review Board-approved study. All participants provided written informed consent. Data were retrieved from patient files and hospital records. Data collection was performed between January 2010 and December 2012. A total of 53 participants with severe obesity (15 males and 38 females), aged between 19 and 70 years, were evaluated. Severe obesity was defined according to the World Health Organization (WHO) classification as a body mass index (BMI)  $\geq 40$  kg/m<sup>2</sup>. All patients underwent a standardized diagnostic work-up, including abdominal ultrasonography performed by a radiologist and comprehensive laboratory tests conducted at the Texas Tech University Health Center.

All participants diagnosed with MASLD had liver biopsy confirmation. None of the patients had concomitant conditions such as cancer, alcoholism, hemochromatosis, Wilson's disease, rickets, or any other structural and/or metabolic disorders that could cause hepatic steatosis or

vitamin D deficiency. In addition, there were no prior dietary interventions, and none of the participants were taking vitamin D supplements. To minimize the confounding effect of seasonal variation on vitamin D levels, all blood samples and liver biopsies were obtained during the late winter and early spring months (February–April), when sunlight exposure was relatively stable across participants.

Exclusion criteria included previous abdominal or bariatric surgery, autoimmune diseases, chronic metabolic diseases, documented organic gastrointestinal diseases, mental health disorders, and pregnancy. Liver biopsy and strict exclusion criteria were applied to ensure accurate diagnosis of MASLD, minimize potential confounding factors, and increase the reliability of the study findings.

The final sample size ( $n = 53$ ) was based on the availability of biopsy-confirmed MASLD cases that met the strict inclusion and exclusion criteria during the data collection period. Although the sample size was modest, it provided sufficient statistical power ( $>80\%$ ) to detect medium-to-large effect sizes (Cohen's  $d = 0.6$ ) at  $\alpha = 0.05$ , which is acceptable for exploratory retrospective studies.

### Subgroups

MASLD (previously Nonalcoholic Fatty Liver Disease-NAFLD) activity scores (NAS) were calculated based on liver biopsy findings (Table 1). According to NAS, participants were categorized into three groups: mild MASLD ( $n=15$ ,  $NAS \leq 2$ ), moderate MASLD ( $n=23$ ,  $NAS 3-4$ ), and severe MASLD ( $n=15$ ,  $NAS \geq 5$ ). The histopathological evaluation and NAS scoring were performed jointly by an experienced pathologist and a hepatologist using the standardized MASLD Activity Score criteria.

**Table 1.** MASLD activity score (NAS) grading

| MASLD Activity Score   |            |
|------------------------|------------|
| Steatosis Grade        | 0-3        |
| Lobular Inflammation   | 0-3        |
| Hepatocytes Ballooning | 0-2        |
| <b>Total</b>           | <b>0-8</b> |

### Laboratory Tests

Fasting blood samples were collected in EDTA-coated tubes. Samples were centrifuged for at least 25 minutes at  $11,000 \times g$  at  $4^\circ\text{C}$ , and plasma was aliquoted and stored at  $-80^\circ\text{C}$  until

analysis. Participants' age, weight, body mass index (BMI), sex, fasting blood glucose, triglycerides, total cholesterol, high density lipoprotein (HDL)-cholesterol, hemoglobin A1c (HbA1c), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), iron, folic acid, and vitamin B12 levels were measured using standardized laboratory methods at Texas Tech University Medical Center.

Plasma insulin levels were determined using a commercially available human insulin direct enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen, Grand Island, New York). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula:

$$\text{HOMA-IR} = (\text{Fasting blood glucose (mmol/L)} \times \text{Fasting plasma insulin (mU/L)}) / 22.5$$

Serum 25-hydroxyvitamin D levels were measured using liquid chromatography–tandem mass spectrometry (LC-MS/MS).

### **Statistical Analysis**

Statistical analyses were performed using PASW Statistics version 18.0 (IBM, USA). The distribution of variables was assessed using the Kolmogorov–Smirnov test. One-way ANOVA was used for comparison of more than two group means, while Student's t-test was applied for pairwise comparisons. For post hoc analysis, the least significant difference (LSD) and Bonferroni tests were used when equal variances were assumed, whereas the Games–Howell test was applied when variances were unequal.

Correlations among variables were evaluated using Pearson's correlation coefficient. Nominal data were analyzed using the chi-square test. Results were expressed as mean  $\pm$  standard deviation and frequencies. A p-value  $<0.05$  was considered statistically significant. There were no missing data in the dataset.

## **RESULTS**

All participants had severe obesity, with an average BMI of  $49.2 \pm 8.76$  kg/m<sup>2</sup>. Based on the NAS scores (Table 1), participants were divided into Mild MASLD (n = 15), Moderate MASLD (n = 23), and Severe MASLD (n = 15) groups (Table 2).

**Table 2.** Classification of subjects according to NAS

| Mild MASLD<br>(NAS = 1-2) |      | Moderate MASLD<br>(NAS = 3-4) |      | Severe MASLD<br>(NAS ≥ 5) |      |
|---------------------------|------|-------------------------------|------|---------------------------|------|
| n                         | %    | n                             | %    | n                         | %    |
| 15                        | 28.3 | 23                            | 43.4 | 15                        | 28.3 |

Age, BMI, blood glucose, HbA1c, and insulin levels did not show significant differences among the groups (Table 3). In all three groups, blood glucose, HbA1c, plasma insulin, and HOMA-IR levels were higher than normal reference values, with averages of  $118.7 \pm 47.12$  mg/dL for blood glucose,  $6.34 \pm 4.03\%$  for HbA1c,  $27.2 \pm 11.76$   $\mu$ IU/mL for plasma insulin, and  $6.5 \pm 3.42$  for HOMA-IR. These findings indicate pre-diabetes and diabetes.

Although triglyceride levels did not differ significantly among groups, total cholesterol levels were higher in the Severe MASLD group ( $206.7 \pm 35.30$  mg/dL) compared to the Mild and Moderate MASLD groups ( $165.0 \pm 38.64$  mg/dL and  $192.3 \pm 36.72$  mg/dL, respectively). Post hoc analysis revealed that total cholesterol levels were significantly higher in the Severe group compared to the Mild group ( $p < 0.05$ ), while the difference between the Severe and Moderate groups did not reach statistical significance.

**Table 3.** Comparison of physical, blood lipid, and insulin resistance characteristics between different MASLD groups <sup>€,‡</sup>.

|                               | MASLD                          |                                |                                | P     |
|-------------------------------|--------------------------------|--------------------------------|--------------------------------|-------|
|                               | Mild<br>(n=15)                 | Moderate<br>(n=23)             | Severe<br>(n=15)               |       |
| Age                           | 52.2 $\pm$ 9.88                | 44.0 $\pm$ 10.86               | 44.8 $\pm$ 11.43               | 0.128 |
| Weight (kg)                   | 140.0 $\pm$ 28.61              | 140.3 $\pm$ 32.45              | 139.4 $\pm$ 21.65              | 0.315 |
| BMI (kg/m <sup>2</sup> )      | 48.9 $\pm$ 7.29                | 49.2 $\pm$ 9.93                | 49.4 $\pm$ 7.17                | 0.268 |
| Blood glucose (mg/dL)         | 126.7 $\pm$ 61.48              | 112.4 $\pm$ 38.73              | 119.8 $\pm$ 42.96              | 0.298 |
| HbA1c (%)                     | 6.4 $\pm$ 1.11                 | 6.1 $\pm$ 1.31                 | 6.6 $\pm$ 1.45                 | 0.148 |
| Plasma insulin ( $\mu$ IU/mL) | 29.2 $\pm$ 17.82               | 27.3 $\pm$ 5.90                | 25.4 $\pm$ 11.22               | 0.812 |
| HOMA-IR                       | 6.5 $\pm$ 4.03                 | 6.8 $\pm$ 3.67                 | 6.3 $\pm$ 2.76                 | 0.098 |
| Triglycerides (mg/dL)         | 173.2 $\pm$ 105.98             | 162.5 $\pm$ 65.56              | 134.6 $\pm$ 41.06              | 0.112 |
| Total cholesterol (mg/dL)     | 206.7 $\pm$ 35.30 <sup>a</sup> | 192.3 $\pm$ 36.72 <sup>a</sup> | 165.0 $\pm$ 38.64 <sup>b</sup> | 0.025 |
| HDL cholesterol (mg/dL)       | 49.9 $\pm$ 18.55 <sup>a</sup>  | 40.7 $\pm$ 10.86 <sup>a</sup>  | 39.8 $\pm$ 8.33 <sup>b</sup>   | 0.018 |
| VLDL cholesterol (mg/dL)      | 34.7 $\pm$ 21.21               | 32.6 $\pm$ 13.11               | 25.8 $\pm$ 7.64                | 0.618 |
| Alkaline phosphatase (U/L)    | 70.1 $\pm$ 13.53 <sup>b</sup>  | 89.0 $\pm$ 29.11 <sup>a</sup>  | 83.1 $\pm$ 20.69 <sup>a</sup>  | 0.037 |
| AST (U/L)                     | 24.3 $\pm$ 6.01                | 26.2 $\pm$ 10.31               | 27.5 $\pm$ 2.86                | 0.556 |
| ALT (U/L)                     | 26.8 $\pm$ 9.01                | 31.04 $\pm$ 16.63              | 33.2 $\pm$ 11.28               | 0.734 |
| Iron (mcg/dl)                 | 85.1 $\pm$ 33.29               | 80.1 $\pm$ 19.25               | 77.4 $\pm$ 30.05               | 0.287 |
| Folic acid (nmol/L)           | 17.9 $\pm$ 3.98 <sup>a</sup>   | 13.8 $\pm$ 4.00 <sup>b</sup>   | 14.9 $\pm$ 4.38 <sup>b</sup>   | 0.007 |
| B 12 (ng/L)                   | 668.5 $\pm$ 369.08             | 641.4 $\pm$ 293.78             | 536.6 $\pm$ 254.77             | 0.332 |
| 25-Hydroxy D3 (ng/mL)         | 34.5 $\pm$ 10.19 <sup>a</sup>  | 25.9 $\pm$ 9.10 <sup>b</sup>   | 21.9 $\pm$ 7.14 <sup>b</sup>   | 0.002 |

<sup>€</sup> Data were analyzed by ANOVA.

<sup>‡</sup> Data are presented as means  $\pm$  SD.

<sup>a, b</sup> There is a significant difference between MASLD groups;  $p < 0.05$ .

HDL cholesterol levels were also significantly different among the groups ( $p = 0.018$ ). Post hoc tests indicated that the Severe group ( $39.8 \pm 8.33$  mg/dL) had significantly lower HDL cholesterol compared with the Mild group ( $49.9 \pm 18.55$  mg/dL,  $p < 0.05$ ), whereas the

difference between the Moderate ( $40.7 \pm 10.86$  mg/dL) and Severe groups was not statistically significant. Although the mean difference between the Moderate and Severe groups was small, this trend supports the overall pattern of lower HDL levels with increasing disease severity (Table 3).

**Figure 1.** Serum 25-Hydroxy D<sub>3</sub> levels in different MASLD groups.

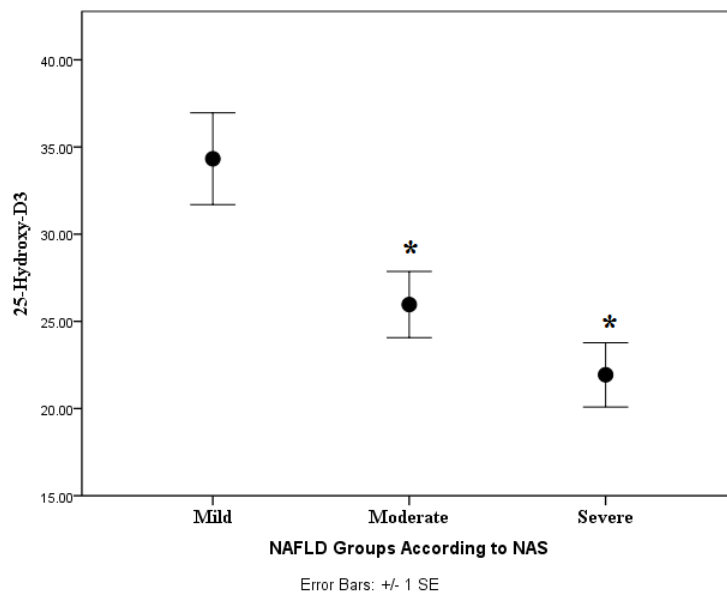
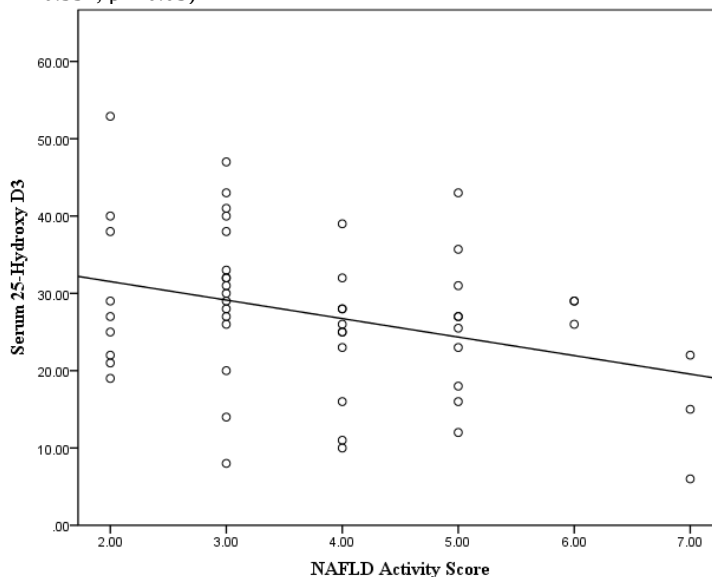


**Figure 2.** Correlation between NAFLD activity score and serum 25-Hydroxy D<sub>3</sub>.  
( $r = -0.332$ ,  $p < 0.05$ )



Although blood ALT and AST levels did not differ among MASLD groups, alkaline phosphatase levels were significantly lower in the Mild MASLD group ( $70.1 \pm 13.53$  U/L) compared to the Moderate and Severe MASLD groups ( $89.0 \pm 29.11$  U/L and  $83.1 \pm 20.69$  U/L,

respectively). Iron and vitamin B12 levels showed no significant differences among groups. Folic acid levels were significantly higher in the Mild MASLD group.

Serum 25-hydroxyvitamin D3 levels were significantly higher in the Mild MASLD group ( $34.5 \pm 10.19$  ng/mL) than in the Moderate and Severe MASLD groups ( $25.9 \pm 9.10$  ng/mL and  $21.9 \pm 7.14$  ng/mL, respectively) (Figure 1). A significant negative correlation was observed between NAS and serum 25-hydroxyvitamin D3 levels ( $r = -0.332$ ,  $p < 0.05$ ), indicating a moderate inverse relationship between vitamin D status and histological disease severity (Figure 2).

The average NAS score was  $4.1 \pm 1.50$  in males and  $3.7 \pm 1.34$  in females (Table 4, Figure 3). Serum 25-hydroxyvitamin D3 levels were not significantly different between males ( $24.8 \pm 9.01$  ng/mL) and females ( $28.1 \pm 10.33$  ng/mL) (Table 4).

**Table 4.** Comparison of NAFLD activity score and serum 25-Hydroxy D<sub>3</sub> mean values between different gender groups <sup>€,‡</sup>.

|                                         | Gender          |                  | p value         |
|-----------------------------------------|-----------------|------------------|-----------------|
|                                         | Male (n = 15)   | Female (n = 38)  |                 |
| NAFLD Activity Score                    | $4.1 \pm 1.50$  | $3.7 \pm 1.34$   | NS <sup>Ω</sup> |
| Serum 25-Hydroxy D <sub>3</sub> (ng/ml) | $24.8 \pm 9.01$ | $28.1 \pm 10.33$ | NS              |

<sup>€</sup> Data were analyzed by Student's t-test.

<sup>‡</sup> Data are presented as means  $\pm$  SD.

<sup>Ω</sup> NS: Not significant

## DISCUSSION

In the current study, we classified MASLD patients according to NAFLD Activity Scores (NAS) and demonstrated that serum 25-hydroxyvitamin D3 levels were significantly lower in the Moderate and Severe MASLD groups compared to the Mild MASLD group. This finding suggests a potential link between vitamin D status and disease severity in MASLD.

MASLD is one of the most common liver diseases worldwide, with an increasing prevalence in parallel with the global rise in obesity and metabolic syndrome (12, 13). Extensive research has established strong associations between MASLD, metabolic syndrome, and insulin resistance, highlighting the multifactorial nature of the disease (14–21). Consistent with this, in our cohort, 34% of the subjects were classified as pre-diabetic, and 30.2% were diabetic, indicating a high burden of impaired glucose metabolism among patients with MASLD.

Vitamin D deficiency is a widespread public health concern, affecting approximately 50% of the healthy population globally (1). Clinically, vitamin D deficiency is defined as a serum 25-hydroxyvitamin D3 level below 20 ng/mL, while insufficiency refers to levels below 30 ng/mL (22). It is estimated that around one billion people worldwide suffer from vitamin D deficiency

or insufficiency, underscoring its global impact (22). Notably, numerous studies have reported an even higher prevalence of vitamin D deficiency among individuals with chronic liver diseases, including MASLD (11, 23–26). Our findings align with this evidence, as vitamin D insufficiency was prevalent in the Moderate and Severe MASLD groups. Specifically, 22.6% of participants exhibited vitamin D deficiency, and 43.4% showed vitamin D insufficiency.

The observed association between lower vitamin D levels and increased MASLD severity supports the hypothesis that vitamin D may play a role in the pathogenesis and progression of MASLD, possibly through its anti-inflammatory, immunomodulatory, and metabolic regulatory effects. However, it remains unclear whether vitamin D deficiency is a contributing factor or a consequence of liver disease progression.

In conclusion, while our study adds to the growing body of evidence linking vitamin D status to MASLD severity, further prospective and interventional studies are required to clarify the causal relationship and evaluate the potential benefits of vitamin D supplementation in the management of MASLD. Such research could pave the way for novel adjunctive therapies aimed at improving outcomes for patients suffering from this increasingly prevalent liver condition.

**Ethics approval:** Texas Tech University Institutional Review Board, 03-2010.

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Author contributions:** Study design: ZG, SG, SW, MB; Data collection: ZG; SG, DS; Data analysis: ZG, SG, EKA; Draft preparation: ZG, SG; Critical review for content: ZG, SG, DS, EKA, SW, MB; Final approval of the version to be published: ZG, SG, DS, EKA, SW, MB.

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