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Original Article

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Bone Mineral Density as a Predictor of Cardiovascular Disease in Women: A Real-World Retrospective Study

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Abstract

Background: Atherosclerotic cardiovascular disease (ASCVD) in women remains understudied, under-diagnosed, and under-treated. Traditional risk factors affect men's and women's hearts differently. However, the current risk stratification tools do not consider such sex-specific factors. We aimed to investigate the utility of bone mineral density (BMD) with dual-energy X-ray absorptiometry (DXA) scoring as a predictor of ASCVD in women.

Methods: Data of 1,995 patients who underwent DXA scanning from 2012 to 2014 at multiple centers within our health system were collected through a chart review and using the SlicerDicer tool of Epic electronic medical records (EMR) to identify comorbidities and outcomes. Age, sex, race, history of hypertension (HTN), hyperlipidemia (HLD), diabetes mellitus (DM), body mass index (BMI), and smoking status were noted. The primary outcome was the composite of ASCVD events (stroke, myocardial infarction (MI) and cardiac death). Osteoporosis was defined as a T score of < -2.5, and osteopenia was defined as a combined T score between -1.5 to -2.5 in either hip, one of the femurs or combined.

Results: Of the 1,995 female participants who underwent DXA scanning, 245 patients (10.8%) experienced ASCVD events during the mean follow-up of 9 years. After adjusting covariables, women with osteoporosis and combined low BMD have higher odds of the composite ASCVD events compared to normal BMD (odds ratio (OR) 4.60 (2.783 - 7.867), P < 0.0001). Low BMD in each site, the right femur, left femur, and hip is associated with an increased risk of ASCVD events (OR 6.50 (3.637 - 11.608), P < 0.0001; OR 5.07 (3.166 - 8.108), P < 0.000; OR 3.36 (2.127 - 5.312), P < 0.0001, respectively). Osteoporosis is independently linked to a 4.25-fold rise in MI incidence and a 3.64-fold rise in stroke. Osteopenia was not associated with ASCVD events (OR 1.29 (0.754 - 2.204), P = 0.35416).

Conclusions: BMD measurement with DXA scan could stratify and predict the risk of ASCVD events in women, with no additional economic strain on healthcare. Further wide-scale studies are needed to utilize this potentially promising predictor and a commonly used test.

Keywords: Atherosclerotic cardiovascular disease; Bone mineral density; DXA; Women

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women. One in three fatalities among females are attributable to it [1]. Women with ischemic heart disease have worse outcomes and a greater mortality rate even though cardiovascular mortality in both sexes has significantly decreased over the past few decades [2-4]. The most likely reason is that risk variables and outcomes differ according to gender [5]. Gender-specific risk factors for cardiovascular disease in women include menopause, polycystic ovary disease, pre-eclampsia, gestational hypertension (HTN), depression and autoimmune inflammatory disease.

Osteoporosis is a major health problem with a significant risk of serious fractures, disability and mortality. It is estimated that more than 200 million have the disease worldwide, with an expected rise given the steady increase in the ageing population [6]. In postmenopausal women, osteoporosis and cardiovascular disease are prevalent disorders with shared underlying risk factors like obesity, HTN, diabetes mellitus (DM), smoking, and physical inactivity. Low bone mineral density (BMD) is linked to female cardiovascular mortality in numerous epidemiological studies [7-9]. Regardless of any risk factors, the majority of societies in the United States and Canada, including the United

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States Preventive Services Task Force, advocate screening for BMD in postmenopausal women when they are over 65 years old [10]. BMD can be determined at a low cost and in large quantities using dual-energy X-ray absorptiometry (DXA) scanning. Our study aim was to investigate lower BMD as a predictor of ASCVD events in females who underwent DXA scanning. The DXA scan has the potential to be an excellent tool for risk classification in women due to its low cost and widespread use. Given that it is a routine test used for women's osteoporosis screening, it will offer an efficient screening tool without placing a financial burden on the healthcare system.

Materials and Methods

Study design and population

A retrospective observational study was conducted in multiple Rochester Regional Health centers in New York. Women aged 50 - 80 years who underwent DXA scanning from 2012 to 2014 were enrolled in the study. For women who underwent repeated DXAs during the study period, only the first DXA was included. Patients who had scanning of the right hip, left hip and spine were noted. Scanning at other sites like the elbow was not included in the study. We excluded patients with a history of previous myocardial infarction (MI), transient ischemic attack (TIA) or stroke, history of malignant tumor, previous pathological fracture, chronic kidney disease ≥ stage 3a, previous osteoporosis treatment, patients without complete BMD measurements and those without follow-up data (185 patients had no follow-up). Finally, a total of 1,995 patients were included in the analysis.

Data were collected through a chart review and using the Epic electronic medical records (EMR) SlicerDicer tool to identify comorbidities and outcomes. The Institutional Review Board approved the study (approval number 2111A). The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Baseline characteristics were noted from reviewing the chart and using the Epic EMR SlicerDicer tool (Table 1). Age, sex, race, history of HTN, hyperlipidemia (HLD), DM, body mass index (BMI), and smoking status were noted. Smoking status was noted from the history taken at the initial provider encounter. HTN was defined by blood pressure of more than 140/90 or the use of antihypertensive medication within the last 6 months. DM was defined by hemoglobin A1c or more than 6.5% or the use of insulin or oral hypoglycemic medications within the previous 6 months. Smoking status was noted from the history taken at the initial provider encounter.

BMD measurement

BMD was measured at the left femur, right femur and total hip using a single DXA scanner. Osteopenia was defined as a T score between -1.0 and -2.5, and osteoporosis was defined as a T score below -2.5 in either hip or one of the femurs, in accordance with World Health Organization guidelines.

Table 1. Baseline Characteristics of the Enrolled Population

Baseline characteristics	N = 1,995
Age (years)	
N	1,995
Mean (SD)	72.55 (10.067)
SEM	0.225
Median	73
Q1 - Q3	66 - 79
Min - Max	32 - 100
Race, n (%)	
Asian	3 (0.2%)
Black	135 (6.8%)
Hispanic	29 (1.5%)
Other	95 (4.8%)
Unknown	24 (1.2%)
White	1,709 (85.7%)
Status	
Alive	1,798 (90.1%)
Dead	197 (9.9%)
Hypertension	
No	797 (39.9%)
Yes	1,198 (60.1%)
Hyperlipidemia	
No	791 (39.6%)
Yes	1,204 (60.4%)
Diabetes mellitus	
No	1,771 (88.8%)
Yes	224 (11.2%)
Stroke	
No	1919 (96.2%)
Yes	76 (3.8%)
Myocardial infraction	
No	1,909 (95.7%)
Yes	86 (4.3%)
Cardiac death	
No	102 (5.1%)
Yes	39 (2.0%)
Cardiac event	
No	1,827 (91.6%)
Yes	168 (8.4%)
Smoking status	
Active smoker	385 (19.3%)
Former smoker	1,610 (80.7%)
BMD hip	
Normal	1,126 (56.4%)
Osteopenia	692 (34.7%)

Table 1. Baseline Characteristics of the Enrolled Population - *(continued)*

Baseline characteristics	N = 1,995
Osteoporosis	166 (8.3%)
Right femur	
Normal	445 (22.3%)
Osteopenia	965 (48.4%)
Osteoporosis	158 (7.9%)
Left femur	
Normal	544 (27.3%)
Osteopenia	1,119 (56.1%)
Osteoporosis	325 (16.3%)
Combined (hip, right and left femur)	
Normal	413 (20.7%)
Osteopenia	1,142 (57.2%)
Osteoporosis	440 (22.1%)
Height	
N	1,572
Mean (SD)	63.37 (2.770)
SEM	0.070
Median	63
Q1 - Q3	62 - 65
Min - Max	54 - 73
Weight	
N	1,634
Mean (SD)	166.84 (42.318)
SEM	1.047
Median	160
Q1 - Q3	136 - 189
Min - Max	82 - 340
BMI	
N	1,579
Mean (SD)	29.29 (7.185)
SEM	0.181
Median	28
Q1 - Q3	24 - 33
Min - Max	14 - 64
BMD-hip score	
N	1,984
Mean (SD)	-0.55 (1.573)
SEM	0.035
Median	-1
Q1 - Q3	-2 - 0
Min - Max	-5 - 6
Right femur score	
N	1,568
Mean (SD)	-1.38 (1.047)
SEM	0.026
Median	-2
Q1 - Q3	-2 to -1
Min - Max	-8 - 3
Left femur score	
N	1,988
Mean (SD)	-1.51 (1.132)
SEM	0.025
Median	-2
Q1 - Q3	-2 to -1
Min - Max	-7 - 3

Osteopenia was defined as a BMD T score between -1.0 and -2.5, and osteoporosis was defined as a T score below -2.5. SD: standard deviation; SEM: standard error of the mean; BMD: bone mineral density.

Outcomes

The primary outcome of interest is the composite of MI, stroke, and cardiovascular death. Cardiovascular death was defined as death during the same hospitalization for an acute cardiac event or stroke. Primary endpoint analysis was done by chart review and chart follow-up.

Analysis

In this study, statistical analyses were performed with the use of SAS Studio (SAS Institute) to conduct logistic regression to assess the relationship between cardiovascular events and T scores (normal range, osteopenia, and osteoporosis). Cardiac event was defined as if a patient experienced stroke, MI or cardiac death. Descriptive statistics for all the study variables were reported. Logistic regression results of these analyses were reported with point estimates, 95% confidence intervals (CIs) and P values. Mixed linear regression results were reported with estimates, 95% CIs and P values. P value ≤ 0.05 was considered to be statistically significant.

Results

Demographic characteristics and cardiovascular risk factors

Of the 1,995 patients who underwent DXA scanning, 1,709 patients were white (85.7%), 135 (6.8%) were black, and the average age was 72.5 years. Of the patients, 22.1% were found to have osteoporosis, and 57.2% had osteopenia based on combined BMD of the hip, right femur or left femur. All demo-

graphics collected at baseline, as noted in Table 1, included age, gender, race, height, weight, BMI, and baseline BMD of the hip, left and right femur. Traditional risk factors for coronary artery disease included HTN, DM, smoking, HLD, history of cardiac events and MI, and history of stroke.

The primary outcome (cardiovascular event) included MI, stroke, or cardiac death. During the mean follow-up of 9 years, patients with osteoporosis had higher odds of the primary outcome (cardiovascular events) independent of other risk factors. Combined low BMD was independently associated with a significant risk of ASCVD events (odds ratio (OR) 4.68 (2.783 - 7.867), P < 0.0001 (Tables 2, 3)). Low BMD at each site, the right femur, left femur, or hip was independently associated with an increased risk of ASCVD events (OR 6.50 (3.637 - 11.608), P < 0.0001; OR 5.07 (3.166 - 8.108), P < 0.000; OR 3.36 (2.127 - 5.312), P < 0.0001, respectively) (Table 2). After adjusting other covariables, osteoporosis is mainly associated with significant increase in the risk of MI (OR 4.25 (2.105 - 8.593), P < 0.0001) and stroke (OR 3.64 (1.720 - 7.703), P < 0.0007) (Tables 4-7). There was no increase in the risk of cardiovascular death in the osteoporosis group (Tables 8, 9). The linear regression model shows an inverse relationship between the BMD score and cardiac event risk (Table 10). T scores in the osteopenia range did not have any statistically significant increased risk of ASCVD events (OR 1.31 (0.779 - 2.212), P < 0.3062).

Table 2. Logistic Regression Model for ASCVD and BMD

Parameter	OR	CI	P-value
Combined			
Normal	Reference		
Osteopenia	1.31	0.779 - 2.212	0.3062
Osteoporosis	4.68	2.783 - 7.867	< 0.0001
Right femur			
Normal	Reference		
Osteopenia	1.69	1.014 - 2.809	0.0441
Osteoporosis	6.50	3.637 - 11.608	< 0.0001
Left femur			
Normal	Reference		
Osteopenia	1.34	0.849 - 2.104	0.2106
Osteoporosis	5.07	3.166 - 8.108	< 0.0001
Hip			
Normal	Reference		
Osteopenia	1.49	1.050 - 2.119	0.0255
Osteoporosis	3.36	2.127 - 5.312	< 0.0001

Only non-missing values were included. Cardiac event = "Yes", if a patient had (stroke, MI or cardiac death). ASCVD: atherosclerotic cardiovascular disease; BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

Discussion

Even though there is ample evidence of the association between cardiovascular disease and osteoporosis, BMD is not used for risk assessment of cardiovascular disease. Accord-

Table 3. Logistic Regression Model for ASCVD, BMD and Other Covariates

Parameter	OR	CI	P-value
Combined (hip, right and left femur)			
Normal	Reference		
Osteopenia	1.26	0.736 - 2.157	0.3987
Osteoporosis	4.44	2.559 - 7.701	< 0.0001
Age (years)	1.02	1.005 - 1.043	0.0137
Smoking status, n (%)			
No/former smoker	Reference		
Active smoker	1.41	0.905 - 2.186	0.1292
Diabetes mellitus			
No	Reference		
Yes	2.33	1.529 - 3.551	< 0.0001
Hypertension			
No	Reference		
Yes	2.30	1.456 - 3.622	0.0003
Hyperlipidemia			
No	Reference		
Yes	1.47	0.970 - 2.236	0.0693

Only non-missing values were included. Cardiac event = "Yes", if a patient had (stroke, MI or cardiac death). ASCVD: atherosclerotic cardiovascular disease; BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

Table 4. Logistic Regression Model for BMD and MI

Parameter	OR	CI	P-value
Combined			
Normal	Reference		
Osteopenia	1.24	0.605 - 2.526	0.5600
Osteoporosis	4.25	2.105 - 8.593	< 0.0001
Right femur			
Normal	Reference		
Osteopenia	1.49	0.727 - 3.062	0.2755
Osteoporosis	5.59	2.523 - 12.400	< 0.0001
Left femur			
Normal	Reference		
Osteopenia	1.10	0.603 - 1.995	0.7617
Osteoporosis	3.86	2.093 - 7.105	< 0.0001
Hip			
Normal	Reference		
Osteopenia	1.47	0.913 - 2.380	0.1126
Osteoporosis	2.92	1.567 - 5.455	0.0007

Only non-missing values were included. BMD: bone mineral density; MI: myocardial infarction; OR: odds ratio; CI: confidence interval.

Table 5. Logistic Regression Model for Stroke and BMD

Parameter	OR	CI	P-value
Combined			
Normal	Reference		
Osteopenia	1.38	0.655 - 2.897	0.3986
Osteoporosis	3.64	1.720 - 7.703	0.0007
Right femur			
Normal	Reference		
Osteopenia	1.78	0.880 - 3.612	0.1083
Osteoporosis	4.90	2.175 - 11.045	0.0001
Left femur			
Normal	Reference		
Osteopenia	1.32	0.692 - 2.514	0.4004
Osteoporosis	3.85	1.965 - 7.548	< 0.0001
Hip			
Normal	Reference		
Osteopenia	1.46	0.882 - 2.401	0.1415
Osteoporosis	2.50	1.269 - 4.938	0.0081

Only non-missing values were included. BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

ing to the current study, women with osteoporosis have an increased risk of MI, stroke, and cardiovascular death. Osteopenia, on the other hand, did not appear to be related to cardiovascular events. The present findings support prior studies, which revealed a similar connection. In a meta-analysis of 25 studies with around 10,299 patients, decreased BMD was an independent risk factor for ASCVD events in postmenopausal women [11]. The MORE study enrolled 2,576 postmenopausal women with an average age of 66.5 years and followed for 4 years. There was a strong linear association between the severity of osteoporosis and the future risk of cardiovascular disease [12].

In a recent longitudinal study conducted in Korea with over 12,000 women, BMD has prognostic significance for ASCVD events [13]. Even after considering age and other risk variables, they also demonstrated incremental predictive value. Our study is the first to examine the predictive power of BMD for ASCVD in a mixed group of American women, with a preponderance of white and African American women.

The pathological relation between osteoporosis and atherosclerotic disease is poorly understood and cannot be explained only by age. The most plausible mechanisms include shared risk factors, shared pathophysiology, or a combination of both. Although DM, dyslipidemia, HTN, obesity and smoking are associated with an increased risk of osteoporosis, fracture and coronary artery disease, our study and earlier investigations revealed that osteoporosis is a risk factor for coronary artery disease independent of those conventional risk factors. This is suggestive of the common underlying pathophysiology. The two most frequently suggested hypotheses are a biological mechanism through circulating cytokines and a hormonal mechanism. Osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor, is a soluble glycoprotein cytokine found in various tissue cells that is crucial to bone metabolism. Clinical studies reported an association between increased level of OPG and decreased BMD and consequently increased fracture risk [14-17]. On the other side, Bjerre et al, in a prospective cohort study of 4,063 patients with stable coronary artery disease, reported that OPG level was independently predictive of all-cause mortality and cardiovascular death in patients with stable coronary artery disease [18]. Several other studies showed that OPG levels correlate with the severity of coronary artery disease, low BMD and fractures [19-22]. In a study of 490 white postmenopausal women, OPG level was independently linked to the risk and severity of DM, stroke, cardiovascular disease and mortality and may be used as a marker for vascular calcification [21]. The hormonal mechanism relies on postmenopausal estrogen deficiency, which is associated with cardiovascular disease and low BMD [23, 24].

Cardiovascular disease is a leading cause of death in women. Compared to men, they are less likely to be diagnosed early and receive preventive management [25, 26]. In particular, women without traditional risk factors like HTN, DM, smoking, or HLD were assumed to have a lower risk of cardiovascular disease. However, there are substantial and underappreciated gender disparities in risk factors. Many non-traditional risk factors are specific to women that have been linked to cardiovascular disease. Pregnancy-associated complications like pre-eclampsia, gestational DM and preterm delivery are associated with increased ASCVD [27-29]. Autoimmune diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis are associated with a significantly

Table 6. Logistic Regression Model for MI, BMD and Other Covariates

Parameter	OR	CI	P-value
Combined (hip, right and left femur)			
Normal	Reference		
Osteopenia	1.16	0.556 - 2.409	0.6952
Osteoporosis	3.80	1.810 - 7.979	0.0004
Age (years)	1.02	0.995 - 1.047	0.1098
Smoking status, n (%)			
No/former smoker	Reference		
Active smoker	1.87	1.059 - 3.299	0.0311
Diabetes mellitus			
No	Reference		
Yes	1.59	0.907 - 2.775	0.1054
Hypertension			
No	Reference		
Yes	4.43	2.029 - 9.690	0.0002
Hyperlipidemia			
No	Reference		
Yes	2.38	1.234 - 4.595	0.0097

Only non-missing values were included. BMD: bone mineral density; MI: myocardial infarction; OR: odds ratio; CI: confidence interval.

increased risk of cardiovascular disease in women [30]. The current risk stratification and prediction algorithm are limited in assessing women and do not consider gender differences in the traditional risk factors. The 10-year ASCVD estimate with the pool cohort equation has not shown remarkable accuracy in the lower-risk women [31]. This necessitates the use of additional risk-stratification techniques for women. DXA scan is an easy, widely accessible test used to screen

Table 7. Logistic Regression Model for Stroke, BMD and Other Covariates

Parameter	OR	CI	P-value
Combined (hip, right and left femur)			
Normal	Reference		
Osteopenia	1.33	0.620 - 2.834	0.4674
Osteoporosis	3.40	1.551 - 7.447	0.0022
Age (years)	1.02	0.998 - 1.052	0.0669
Smoking status, n (%)			
No/former smoker	Reference		
Active smoker	0.99	0.508 - 1.924	0.9727
Diabetes mellitus			
No	Reference		
Yes	2.89	1.630 - 5.132	0.0003
Hypertension			
No	Reference		
Yes	1.29	0.709 - 2.337	0.4072
Hyperlipidemia			
No	Reference		
Yes	1.11	0.628 - 1.968	0.7152

Only non-missing values were included. BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

Table 8. Logistic Regression Model for BMD and Cardiac Death

Parameter	OR	CI	P-value
Combined			
Normal	Reference		
Osteopenia	0.59	0.327 - 1.065	0.0802
Osteoporosis	0.21	0.114 - 0.375	< 0.0001
Right femur			
Normal	Reference		
Osteopenia	0.38	0.210 - 0.704	0.0019
Osteoporosis	0.16	0.081 - 0.328	< 0.0001
Left femur			
Normal	Reference		
Osteopenia	0.50	0.297 - 0.855	0.0110
Osteoporosis	0.18	0.104 - 0.316	< 0.0001
Hip			
Normal	Reference		
Osteopenia	0.88	0.600 - 1.282	0.4972
Osteoporosis	0.43	0.256 - 0.707	0.0010

Only non-missing values were included. BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

for osteoporosis in women over 65 and women under 65 with a high risk of fracture. According to our results, osteoporosis diagnosed with a low T score in the hip, left femur, or right femur is associated with a significantly increased risk of ASCVD. Therefore, BMD can be a reliable screening test for identifying women at risk for ASCVD or risk stratification. Further research is needed to determine the accuracy of BMD measurement in predicting ASCVD, and it may be necessary to compare the computed tomography coronary calcium score to BMD in assessing cardiovascular disease.

Table 9. Logistic Regression Model for Cardiac Death, BMD and Other Covariates

Parameter	OR	CI	P-value
Combined (hip, right and left femur)			
Normal	Reference		
Osteopenia	0.65	0.356 - 1.198	0.1684
Osteoporosis	0.24	0.130 - 0.457	< 0.0001
Age (years)	0.96	0.940 - 0.978	< 0.0001
Smoking status, n (%)			
No/former smoker	Reference		
Active smoker	0.72	0.444 - 1.181	0.1957
Diabetes mellitus			
No	Reference		
Yes	0.38	0.241 - 0.586	< 0.0001
Hypertension			
No	Reference		
Yes	0.39	0.235 - 0.643	0.0002
Hyperlipidemia			
No	Reference		
Yes	1.07	0.698 - 1.641	0.7561

Only non-missing values were included. BMD: bone mineral density; OR: odds ratio; CI: confidence interval.

Table 10. Linear Regression for BMD and ASCVD

Parameter	Estimate	CI	P-value
Hip score			
No cardiac event	Reference		
Cardiac event	-0.58	-0.83, -0.33	< 0.0001
Left femur score			
No cardiac event	Reference		
Cardiac event	-0.79	-0.96, -0.61	< 0.0001
Right femur score			
No cardiac event	Reference		
Cardiac event	-0.58	-0.77, -0.39	< 0.0001
Combined			
No cardiac event	Reference		
Cardiac event	-0.78	-0.95, -0.60	< 0.0001

ASCVD: atherosclerotic cardiovascular disease; BMD: bone mineral density; CI: confidence interval.

Limitations

The retrospective medical records review design of the study is a limitation of the study. Since we used the SlicerDicer tool and coding from the Epic EMR, time to death or ASCVD outcome was not calculated. We were not able to use Cox proportional hazards regression due to the lack of this information. Steroid use and menopausal status were not checked. Another limitation is that the blood pressure and lipid levels were not measured. Instead, they were included as a binary variable depending on if the diagnosis of HTN or HLD was added to the chart for the analysis, so the severity of these conditions was not taken into consideration. Another limitation is that we did not account for any cardiovascular deaths or diagnosis occurring outside the medical system. But the change in outcome would be minimal as the chart would reflect such diagnosis from outside centers from updating of the chart by system primary care physician or subspecialist.

The strength of the study is that even in a mixed racial population group, typical of any US city, results were suggestive of a strong association between low BMD and ASCVD in females.

Conclusion

Osteoporosis is associated with an increased risk of cardiovascular disease in women. BMD measurement with DXA scan is widely used in postmenopausal women. Hence, it could stratify and predict the risk of ASCVD events in women. Further wide-scale studies are needed to determine the utility of this commonly used test as a predictor for ASCVD.

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No funding was obtained from any source for this study.

Conflict of Interest

All authors declare that they have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Sarath Lal Mannumbeth Renjithlal, Sarah Mohamed, and Mohammed Magdi: conception or design of the work. Mostafa Reda Mostafa, Keerthi Renjith, Parvathi Pillai, and Viqarunnisa Zahid: data collection. Musaib Syed: data analysis. Nathan Ritter and Mallory Balmer-Swain: final approval of the version to be published. Amjad Makaryus and Nisha Pillai: critical revision of the article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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