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The Prognostic Significance of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Patients With Multiple Myeloma

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Object: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are simple, inexpensive prognostic markers for various conditions. The objective of this study was to determine the prognostic significance of NLR and PLR in patients with multiple myeloma (MM) in terms of survival. *Method:* A retrospective chart review study was conducted for 175 patients who met the criterion of diagnosis for MM between January 2004 and September 2014. *Result:* The median age of diagnosis was 69 years. Patients were divided into high and low NLR and PLR groups according to cutoff points from the receiver operating characteristic curve (2.78 and 155.58, respectively). The high NLR and PLR groups were associated with lower albumin level and higher staging. The high NLR group experienced inferior median survival compared with the low NLR group (37 vs. 66 months; log-rank *P*-value 0.005). However, there was no significant difference in median survival between the high and low PLR groups (45 vs. 62 months; $P = 0.077$). Multivariate analysis demonstrated that NLR is an independent predictor for OS of MM (HR 2.892; $P = 0.009$). *Conclusion:* We conclude that NLR is an independent prognostic factor for OS in MM. J. Clin. Lab. Anal. **30**:1208–1213, 2016.

Key words: multiple myeloma; neutrophil-to-lymphocyte ratio; overall survival; platelet-to-lymphocyte ratio; prognostic marker

INTRODUCTION

With a prevalence of approximately 13% of hematologic malignancies and 1–1.4% of all tumors, multiple myeloma (MM) is the second most common hematologic malignancy after lymphoma (1, 2). This malignancy is characterized by abnormal clonal proliferation of malignant clonal plasma cells in the bone marrow, abnormal monoclonal paraprotein, and evidence of end-organ damage (3). In 2014, the Revised International Myeloma Working Group diagnostic criteria for multiple myeloma were published. Several conditions without end-organ damage to be the diagnostic criteria for myeloma were added. These include clonal bone marrow plasma cell percentage ≥60%, involved per uninvolved serum free light chain ratio ≥100, and more than one focal lesions on MRI studies (4).

Multiple myeloma is considered to be a disease of the elderly because the median age of diagnosis is 70 years (5). Clinical manifestations of MM include anemia (70%), renal dysfunction (20–40%), bone lesion (80%), and hypercalcemia (13%) (6). Therefore, complete blood count (CBC) is considered as a baseline investigation for MM at the time of diagnosis. For the past two decades, thalidomide, lenalidomide, and bortezomib have been used to treat MM, resulting in a drastic improvement in median survival from 29.9 to 44.8 months (2, 7).

Cytogenetic analysis, serum beta 2-microglobulin level, lactate dehydrogenase level, serum free light chain ratio (3), gene expression profiling (8), and the International staging system (ISI), in particular stage III, have been used in previous studies to determine prognosis for MM (5). The platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with adverse prognosis in several malignancies (9–13). However, the

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utility of PLR in MM patients is unknown, and there are limited reports in the literature regarding the use of NLR as a prognostic marker for MM. Therefore, this study aimed to investigate an association between NLR and PLR as well as their prognostic value in terms of survival outcome in patients with MM.

METHODS

Subjects

All adult patients (older than 18 years at the time of diagnosis) who were diagnosed with MM and went to Albert Einstein Medical Center as an outpatient and/or inpatient between January 2004 and September 2014 were included in this study. All of the patients included in the analysis met three essential criteria: namely (a) monoclonal plasma cells in the bone marrow ≥10 percent, (b) monoclonal protein present in the serum and/or urine, and (c) at least one of the following: serum calcium >10.5 mg/l, creatinine >2 mg/100 ml, hemoglobin <10 g/100 ml, or evidence of lytic bone lesions.

All subjects with (a) acute infection, (b) human immunodeficiency virus infection, (c) chronic liver disease, (d) collagen vascular disease, (e) previous or concomitant other malignancies, and (f) primary or secondary thrombocytopenia, as well as (g) chronic anti-inflammatory medication users, were excluded from our study.

From 216 patients, 175 patients fulfilled the criteria for diagnosis of MM, and 161 patients fulfilled the inclusion criteria. This study was approved by the Institutional Review Board of Philadelphia.

Study design

We conducted a retrospective chart review to obtain data regarding the patients, including age at diagnosis, gender, race, follow-up duration, disease staging, percentage bone marrow infiltration, immunoglobulin (Ig) subtypes, number of deaths, and losses to follow-up. We also obtained the following laboratory parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count (PC), glomerular filtration rate (GFR), and levels of calcium, albumin, and beta-2 microglobulin. Overall survival (OS) was defined as the period between the date of diagnosis and the date of death from any cause or the month of last follow-up.

Laboratory parameters

Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula. The International Staging System (ISS) (5) was used as the staging criteria for MM patients in this study. The NLR was defined by the ANC divided by the ALC, and the PLR was defined by the PC divided by the ALC. All laboratory parameters including NLR and PLR were obtained within 4 weeks before or after the diagnosis of multiple myeloma.

Chemotherapy

The chemotherapy that the patients received in this study refers to either the conventional or the novel agents. Conventional chemotherapy includes melphalan, dexamethasone, vincristine, and doxorubicin. Novel agents, however, include bortezomib, and immunomodulatory agents include lenalidomide.

Statistical analysis

Data were entered analyzed using SPSS statistics 17.0 (Chulalongkorn University, Bangkok, Thailand). Demographic and descriptive characteristics were summarized using descriptive statistics. The relationship between NLR and PLR, and baseline characteristics, laboratory parameters, OS, staging, and MM subtype were analyzed using a chi-square test or independent *t*-test as appropriate. We determined the optimum cutoff points for the NLR and PLR as a predictor for OS based on the receiver operating characteristic (ROC) curve. The optimum cut points were the point on ROC curve which yielded the highest specificity and sensitivity. This process was performed by visual inspection. Cox proportional hazard regression analysis was used to examine an association between prognostic predictors and OS. The overall cumulative probability of survival was analyzed by Kaplan–Meier survival analysis. A two-sided *P*-value less than 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

The baseline characteristics of the patients in this study are shown in Table 1. Among 161 MM patients, 50.6% were male and 49.4% were female. The median age at diagnosis was 69 years, with an age range of 41–91 years. The majority of the patients were African-American (82.7%). In terms of ISS staging, patients had been diagnosed with stage I (29.0%),

TABLE 1. Demographics of Multiple Myeloma Patients by Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios

Characteristics	NLR > 2.79 (n = 39)	NLR ≤ 2.78 (n = 92)	P-value	PLR > 155.59 (n = 45)	PLR ≤ 155.58 (n = 85)	P-value
Age	66.59 (11.14)	68.34 (10.74)	0.315*	69.75 (11.28)	67.18 (10.68)	0.203*
Race			0.275**			0.770**
Caucasian	8	8		5	6	
African-American	53	80		38	74	
Asian	1	1		0	1	
Other	7	3		2	4	
Gender (% male)	65.2	40.2	0.002**	48.9	45.9	0.744**
Loss to follow-up	5.8	5.4	0.921**	2.2	7.1	0.245**
Hb (g/dl)	9.27 (1.83)	10.98 (3.54)	0.001*	9.80 (1.93)	10.89 (3.69)	0.067*
MCV (μm^3)	89.51 (13.02)	89.42 (10.45)	0.963*	90.16 (6.63)	89.35 (13.79)	0.714*
MCH (pg/cell)	32.49 (11.85)	30.63 (6.10)	0.214*	31.27 (7.95)	31.68 (9.67)	0.807*
MCHC (g/l)	33.17 (1.41)	33.32 (1.06)	0.459*	33.24 (1.46)	33.27 (1.08)	0.880*
RDW (%)	17.27 (4.62)	16.39 (3.30)	0.190*	16.81 (4.59)	16.60 (3.70)	0.779*
WBC ($/mm^3$)	8302.69 (3420.63)	6228.58 (5324.97)	0.013*	5861.55 (2842.87)	7241.41 (5497.43)	0.118*
ANC ($/mm^3$)	5907.21 (2571.78)	3218.68 (2734.06)	0.000*	3953.59 (2759.59)	4039.37 (3072.03)	0.876*
ALC ($/mm^3$)	1237.70 (606.45)	2365.65(2314.40)	0.000*	1143.89 (554.02)	2743.95 (2355.78)	0.000*
Platelet (×10 3 μl)	220.65 (106.78)	216.50 (117.82)	0.834*	281.77 (150.26)	183.28 (73.62)	0.000*
GFR (ml/min/1.73 m^2)	46.80 (33.14)	63.25 (28.13)	0.003*	54.38 (33.46)	59.39 (29.17)	0.395*
Calcium (mg/dl)	8.73 (1.25)	8.97 (1.56)	0.353*	8.72 (1.15)	8.94 (1.65)	0.461*
Albumin (g/dl)	2.74 (0.66)	3.42 (1.47)	0.002*	2.84 (0.64)	3.38 (1.54)	0.009*
Beta-2 microglobulin (mg/l)	10.82 (13.82)	4.89 (5.27)	0.026*	7.33 (6.87)	7.41 (11.57)	0.975*
ISS staging (%)			0.001**			0.028**
I	9	37		16.7	40.0	
II	26	35		54.8	36.3	
II	21	13		28.6	23.8	
Ig (%)			0.674**			0.317**
IgG	63.6	61.7		21	49	
IgA	16.4	20.3		10	13	
IgM	0	0		0	0	
Light chain (L)	9.1	6.8		4	3	
Light chain (K)	10.9	11.3		3	9	
Bone marrow infiltration (%)	47.25 (31.80)	45.94 (23.82)	0.803*	45.58 (28.16)	47.44 (25.84)	0.743*
Chemotherapy (%)	53.6	64.1	0.179**	60.0	62.4	0.793**
Stem cell transplant (%)	8.7	12.0	0.505**	6.7	11.8	0.357**
Death (%)	56.5	43.5	0.101**	66.4	44.7	0.017**

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; WBC, white blood count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; PC, platelet count; GFR, glomerular filtration rate.
*Independent t-test, **chi-square test.

stage II (37.7%), or stage III (21.0%) MM. The most common paraprotein type was IgG (50.9), followed by IgA (16.8%), lambda light chain (5.6), and kappa light chain (9.3). At the time of the study, patient deaths represented 49.4% (n = 80) of the total patient group. Regarding treatment, 59.9% of patients had received chemotherapy, while 10.5% had undergone stem cell transplantation.

NLR and PLR

Histograms of the NLR and PLR of the patients, excluding outliers for PLR (1959.60) and NLR (36.23), are shown in Figure 1. The median NLR was 1.93 (range: 0.10–36.23), and the median PLR was 127.69 (range: 0.46–1959.60).

The optimum cutoff points for the NLR and PLR yielded from the ROC curve plots between sensitivity and specificity for OS were 2.783 (with a sensitivity of 83.3% and a specificity of 43.1%) and 155.58 (with a sensitivity of 67.7% and specificity of 36.9%), respectively.

Based on the cutoff points for the NLR and PLR, patients were divided into the following groups: high NLR (NLR > 2.78), low NLR (NLR ≤ 2.78), high PLR (PLR > 155.58), and low PLR (PLR ≤ 155.58). The high NLR and PLR groups were associated with lower albumin level and higher staging. Patients in the high NLR group were predominately male (P = 0.002), with lower Hb level (P = 0.001), lower GFR (P = 0.003), higher WBC (P = 0.013), and lower beta 2-microglobulin level (P = 0026). Patients in the

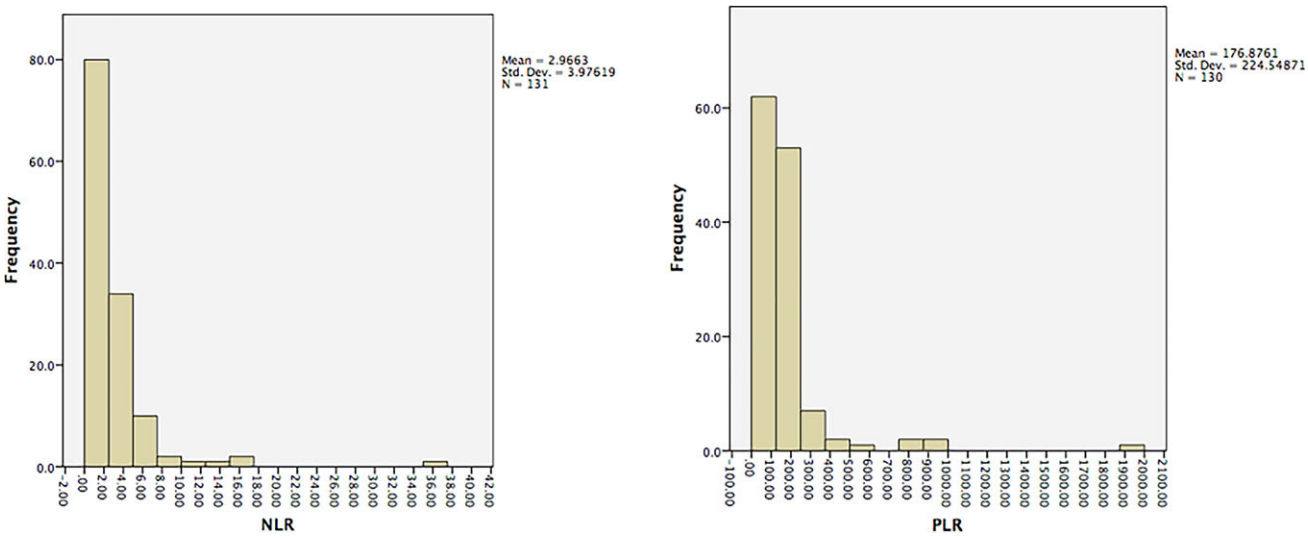

Fig. 1. Histograms of the neutrophil-to-lymphocyte ratio (left) and platelet-to-lymphocyte ratio (right) in patients with multiple myeloma.

high PLR group tended to display a lower albumin level ($P = 0.009$) and higher staging ($P = 0.028$) (Table 1). In addition, from Pearson correlation analysis, there was no significant linear correlation between the NLR and PLR of the patients ($r = 0.312$, R square 0.097).

OS according to NLR and PLR

From the Kaplan–Meier curve, median survival in the high NLR group was determined as 37 months (95% confidence interval (CI): 21.80–52.19 months) and 66 months in the low NLR group (95% CI: 53.19–78.80 months), with a log-rank *P*-value of 0.005 (Fig. 2a). In the high PLR group, median survival was 45 months (95% CI: 0.00–91.18), and in the low PLR group, median survival was 62 months (95% CI: 45.67–78.33), with a log-rank *P*-value of 0.077 (Fig. 2b).

Univariate analysis using Cox proportional hazard regression between OS and each variable was analyzed (Table 2). We allowed all variables with a univariate *P*-value less than 0.2 to enter into a multivariate analysis. Once in a multivariate analysis, a backward elimination procedure was used to remove variables with a *P*-value greater than 0.05. After performing the model

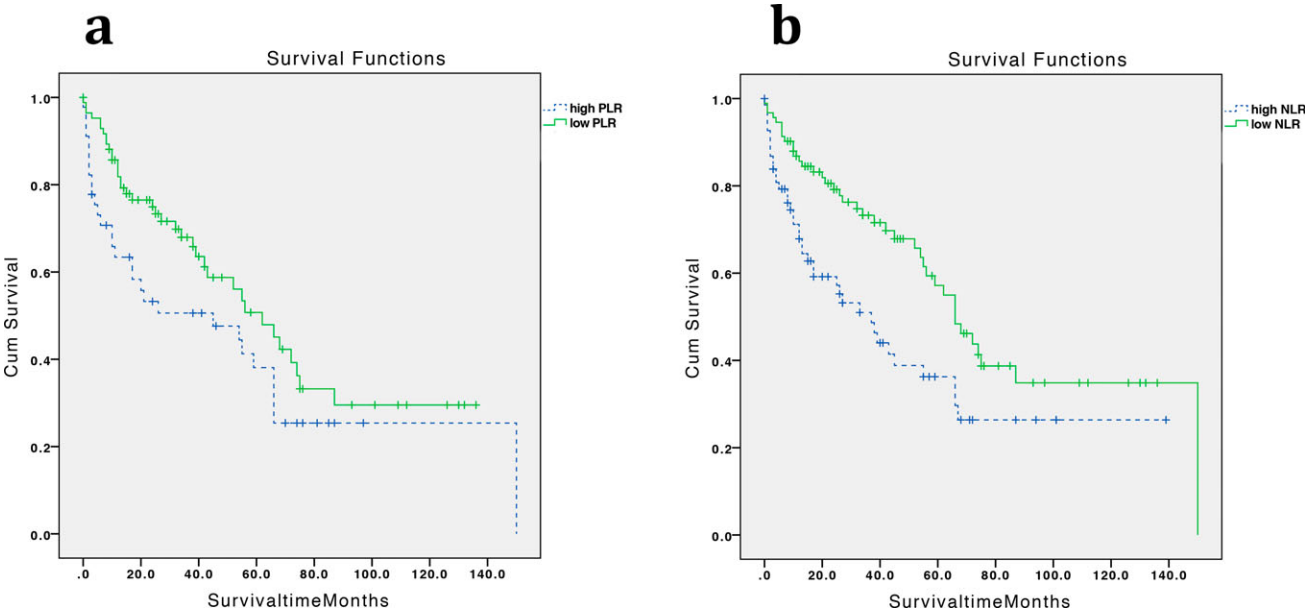

Fig. 2. Kaplan–Meier survival analysis for overall survival based on platelet-to-lymphocyte ratio (a) and neutrophil-to-lymphocyte ratio (b).

TABLE 2. Univariate Analysis of the Neutrophil-to-Lymphocyte Ratio in Patients with Multiple Myeloma

Characteristics	Hazard ratio	95% Confident interval	*P*-value
Age at diagnosis (≤ 65 vs. 65)	1.289	0.808–2.055	0.287
Race			
Caucasian	1		
African-Americans	0.449	0.130–1.554	0.206
Asian	0.949	0.383–2.355	0.911
Other	0.000	0.000–1.931	0.970
Gender (male vs. female)	0.662	0.423–1.038	0.072
ISS staging			
I	1		
II	3.090	1.098–8.695	0.033
III	4.873	1.675–14.181	0.004
Immunoglobulin			
IgG	1		
IgA	1.860	0.912–3.796	0.088
IgM	1.974	0.853–4.566	0.112
Lambda light chain	1.522	0.468–4.944	0.485
Kappa light chain	0.846	0.260–2.748	0.781
Hb (≤10 vs. > g/dl)	0.371	0.228–0.64	0.000
GFR (≤60 vs. >60 ml/min/1.73 m^2)	0.615	0.381–0.993	0.047
Calcium (<9 vs. >9 mg/dl)	0.692	0.414–1.157	0.160
Beta-2-microglobulin (≤3.5 vs. >3.5 mg/l)	2.813	1.483–5.336	0.002
Albumin (≤3.5 vs. >3.5 g/dl)	1.874	1.044–3.362	0.035
BM infiltration (≤2 5 vs. >25%)	0.844	0.483–1.474	0.551
NLR (>2.78 vs. ≤2.78)	0.536	0.343–0.837	0.006
PLR (>155.58 vs. ≤155.59)	0.651	0.400–1.058	0.083
Chemotherapy	0.929	0.586–1.473	0.755
Stem cell transplantation	1.690	0.810–3.523	0.162

Hb, hemoglobin; GFR, glomerular filtration rate; BM, bone marrow NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

TABLE 3. Multivariate Analysis of the Neutrophil-to-Lymphocyte Ratio Using a Backward Elimination Model

Characteristics	Hazard ratio	95% Confident interval	*P*-value
Type of immunoglobulin	0.816	0.619–1.075	0.147
Beta-2-microglobulin (>3.5 vs. ≤3.5 mg/l)	2.292	1.028–5.112	0.043
Stem cell transplantation	0.368	0.132–1.030	0.057
NLR (>2.78 vs. ≤2.78)	2.892	1.307–6.396	0.009

NLR, neutrophil-to-lymphocyte ratio.

selection procedure, four variables remained, namely Beta-2 microglobulin, types of immunoglobulin, stem cell transplantation, and NLR (Table 3). We, therefore, concluded that NLR was a statistically significant independent predictor for overall OS.

DISCUSSION

The median age of MM diagnosis in our study was 69 years, and this finding agrees with the previously reported median age of diagnosis of 69–70 years (5, 8). Most MM patients in our study were African-Americans (82.7%). Even though, it has been reported that the prevalence of MM among African-Americans is 2- to 3-fold greater than that in the white population, disparities in terms of race in our study may limit the generalization of our results to other population groups (14).

A high NLR has recently been shown to be associated with poor survival for various malignancies, including advanced pancreatic (9), esophageal, rectal, lung, gastric, breast, ovarian, and bladder cancer (10). Aside from malignancies, NLR can also be a predictive factor in several other disease conditions, including brucellosis (15), advanced heart failure (16), and cystic fibrosis (17).

Platelet-to-lymphocyte ratio has also been known to be a predictive factor for several malignancies, for example, esophageal (18), ovarian (12), and fallopian tube cancer (13). In addition, PLR is used as a marker in other conditions, in particular in cardiovascular disease (19, 20). However, in our study, we found no significant difference in median survival between patients with high and low PLR (45 vs. 62 months; $P = 0.077$).

In this study, we found that only NLR can be used as an independent predictor of OS for MM patients (HR 2.59, $P = 0.049$). These findings support those of Kelkitli et al. (21), who carried out the first and only reported study regarding the relationship between NLR and MM in 2013 (21). Using a NLR cutoff point of 2, they divided 151 MM patients into two groups and found a superior OS in patients with a NLR ≥ 2 compared with patients with a NLR < 2. As a result, they concluded that NLR was a potential prognostic factor for OS and event-free survival in MM patients.

The pathophysiology of an association between NLR, PLR, and poor prognostic outcome of MM is largely unknown. One possible hypothesis for this concerns lymphopenia in malignancy. Several studies have been shown that lymphopenia serves as a poor prognostic marker in solid tumors and hematologic malignancies, including MM (11, 22). In 2008, Ege et al. (23) performed a retrospective study in 537 MM patients and demonstrated that low ALC is associated with lower OS. The second hypothesis is IL-6-mediated neutrophil response. Apart from producing monoclonal protein, malignant plasma cell can also produce chemokines such as IL-6 (24). This chemokine can regulate and stimulate neutrophil recruitment process, including mobilization from the bone marrow, rolling along and attaching to endothelial cells, and transmigration through cell membranes (25, 26). We hypothesized that increased number of malignant plasma cell can

cause increasing IL-6 production, which leads to increase NLR would act as poorer prognosis for multiple myeloma. The third possible hypothesis regarding pathophysiology is the tumor-associated inflammatory response, which is now considered as one of hallmarks of cancer. Inflammation does indeed appear to play a role from the very earliest to the advanced stages of cancer (27).

Apart from disparities in terms of population groups, the potential limitations of this study include the limited sample size. In addition, despite the exclusion from this study of patients with conditions that may interfere with the NLR and PLR, other confounding factors may affect the NLR and PLR, including uncontrolled hypertension, uncontrolled diabetes, previous history of infection (within 3 months), and certain medications (28).

In conclusion, our study demonstrated that a high NLR (>2.78) is associated with shorter OS and can be a potential independent prognostic marker in patients with MM.

AUTHORS' CONTRIBUTIONS

SW, VM, and GV conceived the study and together with GG and WC collaborated on the design of the study. SW, GG, WC, SB, and NC carried out the data collection. SW and SP performed the data analysis. SW and GV drafted the manuscript. All authors contributed substantially and approved the final manuscript.

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