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Synergistic Effect of Low Neutrophil–Lymphocyte Ratio With Physical Activity on Quality of Life in Type 2 Diabetes Mellitus: A Community-Based Study

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Abstract

Background: Physical inactivity and Type 2 diabetes mellitus (T2DM)–associated inflammatory biomarkers are correlated with poor quality of life (QoL). However, no study has investigated the synergistic effect of physical activity (PA) and lower neutrophil–lymphocyte ratio (NLR) on QoL. **Objective:** We examined the independent and synergistic effects of PA and inflammatory biomarkers on three domains of QoL in T2DM. **Methods:** This cross-sectional study included 294 patients with T2DM from community clinics in Indonesia. The 36-item Short Form Survey and a questionnaire about PA engagement were used to measure QoL and metabolic equivalent of task (MET)-hr/week, respectively. Inflammatory biomarkers were measured in fasting blood. Adjusted coefficients β and 95% confidence interval (CI) were estimated using multiple linear regression. The synergistic effect was analyzed using additive interaction for linear regression. **Results:** Patients with PA ≥ 7.5 MET-hr/week exhibited significantly higher total QoL (β = 8.41, 95% CI = [6.04, 10.78]) and physical component score (PCS; β = 13.90, 95% CI = [10.52, 17.29]) than those with PA < 7.5 MET-hr/week. Patients with NLR < 1.940 had significantly higher total QoL (β = 4.76, 95% CI = [3.41, 6.11]), mental component score (MCS; β = 2.62, 95% CI = [0.75, 4.49]), and PCS (β = 6.89, 95% CI = [4.97, 8.82]) than patients with NLR ≥ 1.940. PA ≥ 7.5 MET-hr/week and NLR < 1.940 exhibited a synergistic effect on total QoL, MCS, and PCS. **Conclusions:** High PA level and low NLR had a positive synergistic effect on QoL among patients with T2DM.

Keywords

type 2 diabetes mellitus, quality of life, physical activity, neutrophil–lymphocyte ratio

Type 2 diabetes mellitus (T2DM) is a group of complex metabolic disorders distinguished by increased blood glucose concentration (American Diabetes Association, 2018). The prevalence of T2DM is increasing at the fastest rate of all global health burdens (Cho et al., 2018; Saeedi et al., 2019), and patients with T2DM have a higher risk of mortality than the general population (Ogurtsova et al., 2017). The International Diabetes Federation has estimated that 578 million people globally will have diabetes by 2030, and by 2045, the number will increase to 700 million (Saeedi et al., 2019). In Indonesia, specifically, it is estimated that the number of people with T2DM will increase from 10.7 million in 2019 to 16.6 in 2045. The rapidly increasing prevalence of T2DM necessitates an increase in our understanding of the factors that affect the burden of T2DM. These factors, which include demographic characteristics as well as physiological and lifestyle factors, may impair the quality of life (QoL) of patients with the disease (Jing et al., 2018).

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Patients with T2DM need regular medical treatment and face physical and mental limitations, leading to disruption in personal relationships and social life (Kalra et al., 2018). Some characteristics of T2DM and its management regimen, patient lifestyles, and complications are associated with QoL (Arifin et al., 2019; Davies et al., 2018). Recognizing the predictors of QoL, particularly those that are modifiable, may be valuable for future interventions for improving QoL and, consequently, promote life satisfaction of patients with T2DM (Jing et al., 2018). Notably, only one study has investigated sociodemographic characteristics and clinical factors contributing to QoL outcomes in patients with T2DM among Indonesians (Arifin et al., 2019). Clinical factors such as complications of T2DM, using oral antidiabetic drugs versus insulin injections, blood sugar level, and duration since T2DM onset were not significantly associated with QoL. However, sociodemographic characteristics including physical inactivity, requiring help from caregivers, and treatment in secondary care were significantly correlated with decreased QoL in patients with T2DM after adjustment for confounding factors.

Physical activity (PA) can improve QoL in patients with T2DM (Eckert, 2012; Thiel et al., 2017b). The Canadian Diabetes Association and American Diabetes Association established guidelines for managing T2DM and demonstrated that participating in at least 150 min of moderate-to-strenuous PA, such as aerobics or gym exercise, at least 3 days per week significantly improves glycemic control and reduces mortality in these patients (American Diabetes Association, 2015; Sigal et al., 2018). Findings of a prospective cohort study indicated that $\geq$150 min of moderate-to-vigorous PA per week was associated with a 3.31-fold increase in the QoL physical component score (PCS) and a 1.40-fold increase in the mental component scores (MCS) compared with <150 min of moderate-to-vigorous PA per week in patients with T2DM (Thiel et al., 2017a). Approximately 46% of general population of Indonesia engages in low levels of PA (Pengpid & Peltzer, 2017). In the present study, we hypothesized that the level of PA is a predominant factor for QoL among patients with T2DM in Indonesia. However, no study has investigated the relationship between PA and QoL among patients with T2DM in Indonesia. Hence, estimating this relationship is necessary for promoting a healthy lifestyle and increasing QoL among Indonesians with T2DM.

The neutrophil–lymphocyte ratio (NLR), a measure derived from white blood cell (WBC) count, is a reproducible and inexpensive test that can serve as a biomarker of inflammatory abnormalities and has emerged as a key pathogenetic mechanism triggering T2DM (Imtiaz et al., 2012; Lee et al., 2014). Additionally, high NLRs in patients with T2DM have been significantly associated with complications in geriatric diabetic patients, with NLR > 2.89 considered an independent predictor of microvascular complication for T2DM (Öztürk et al., 2013). Moreover, a cohort study demonstrated that high NLRs were significantly associated with low physical QoL in patients with multiple sclerosis (Hemond et al., 2019). Gialluisi et al. (2019) conducted a population-based cohort study in Molise in central Italy and reported that low NLRs were significantly associated with high MCSs measured using the 36-item Short Form Health Survey (SF-36). However, the roles of NLR and WBC count in QoL among patients with T2DM remain undetermined. Because they indicate lower levels of pathogenic progression and complication in T2DM, we further hypothesized that both low NLRs and low WBC counts are associated with high QoL scores in patients with T2DM. In the present study, we assessed the effect of PA and low NLRs and WBC counts, as well as their synergistic effect, on QoL in Indonesians with T2DM.

Materials and Methods

Study Design and Participants

We conducted this community-based, cross-sectional study with stratified multistage cluster sampling between July 1 and November 30, 2018, in the province of East Java, Indonesia. For the first stage, we divided the province into 38 regions. For the second, we selected 4 regions, including 2 rural and 2 urban areas, from the 38 regions. In the final stage, we randomly selected eight community clinics from the four regions for data collection, three of which declined our invitation to participate in this research. In the end, we recruited participants from five community clinics (Figure 1). The inclusion criteria included (1) Indonesian nationality and age of 17–79 years, (2) having visited the outpatient community clinic and completed the questionnaires, (3) agreement to participate in the study, and (4) a diagnosis of T2DM confirmed by a physician with 2-hr plasma glucose test results >200 mg/dL or fasting plasma glucose > 126 mg/dL (American Diabetes Association, 2018). Patients who (1) scored $\leq$24 on the Mini-Mental State Exam, (2) had auditory deficiencies, (3) were pregnant, (4) used antidepressants, or (5) had limb amputation or could not walk were excluded from the study.

Sample Size Calculation

To calculate sample size, we used G-Power Version 3.1 with Cohen's effect size (f^2) of $-.47$ (Xu et al., 2018), an α level of .01, and a power value of .9. With 14 predictors, we calculated a sample size of 262 participants. Considering an estimated dropout rate of 12%, we increased our total sample size to 294 participants with T2DM.

Instruments

Trained professional nurses collected study data using a survey containing questions regarding participants' demographic characteristics including age, diabetes duration, gender, marital status, income, education (Arifin et al., 2019) and smoking status (Tsai et al., 2007). The validity and reliability of the questionnaire have been reported in previous studies (Arifin et al., 2019; Tsai et al., 2007).

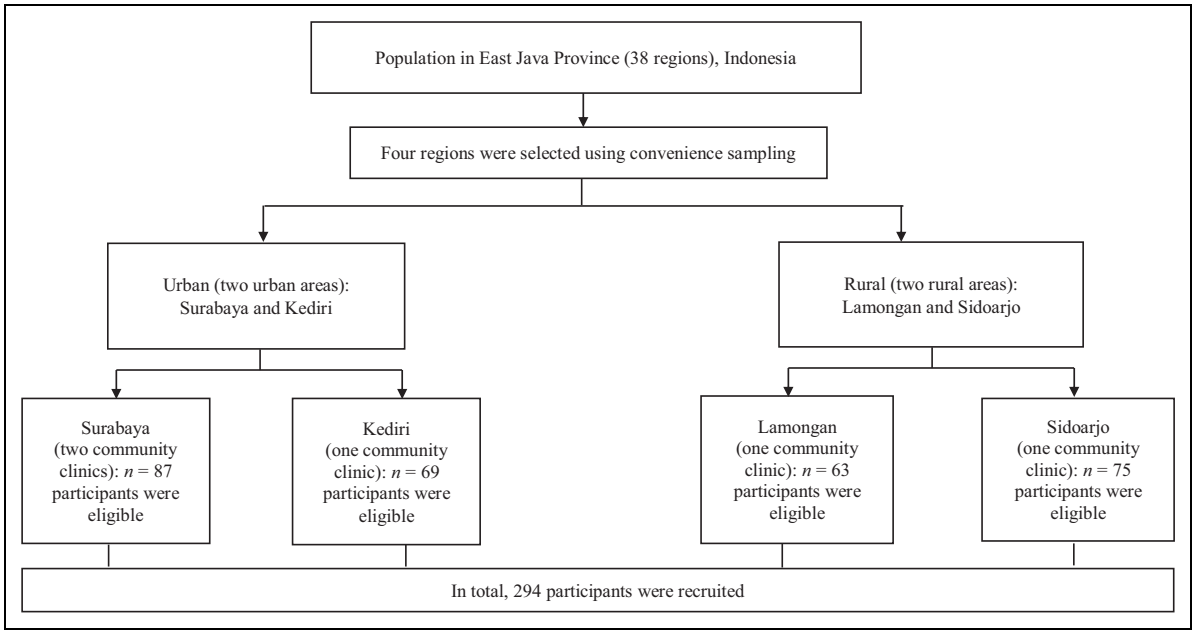

Figure 1. Study sample flowchart.

Assessment of QoL

We used the 36-item Short Form Survey (SF-36) to measure QoL. Instructions for the SF-36, which is one of the most widely used instruments to measure self-reported QoL, are publicly available on the RAND Corporation website (Hays & Morales, 2001). In comparison to diabetes-specific tools, the general SF-36 has the ability to assess an individual's MCSs and PCSs separately as well as evaluating total QoL. Moreover, the SF-36 has been widely used in diabetes research, and researchers have suggested that it is a reasonable choice for both diabetes research and diabetes treatment applications, with reference to the inclusion both of physical and mental concepts to assess the validity and responsiveness of SF-36 tools specifically related to T2DM (Eckert, 2012; Hays & Morales, 2001; Jing et al., 2018). The version of the SF-36 Questionnaire translated into Indonesian has a test–retest reliability of $r = 0.626$–1 and good internal consistency, with a Cronbach's α of .789 (Salim et al., 2017). The SF-36 comprises eight subscales: Mental Health (MH), Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and General Health (GH). These eight scales can be simplified into three main domains, namely, total QoL, MCS, and PCS. MCS is the sum of the scores of the RE, VT, MH, and SF subscales, while PCS is the sum of the scores of the GH, PF, RP, and BP subscales. Total QoL is the sum of the MCS and PCS. Total QoL, MCS, and PCS range from 0 to 100, with scores standardized to a normal distribution (cutoff point = 50 and standard deviation [*SD*] = 10). Higher scores indicate high QoL (Hays & Morales, 2001).

Assessment of PA

We estimated participants' level of PA as metabolic equivalent of task (MET)-hr/week over the last 12 months using three questions based on the modified Physical Activity Guidelines from the Advisory Committee for Americans (Shiroma et al., 2014) and the Godin Leisure-Time Exercise Questionnaire (GLTEQ; Godin & Shephard, 1997). We then classified participants based on the type, duration in minutes, and intensity of exercise they performed during a typical week, with exercise types divided into the following categories: mild (e.g., yoga, bowling, or floor sweeping), moderate (e.g., gym exercise, baseball, or badminton), and strenuous exercise (e.g., hiking, soccer, or running). We multiplied the number of hours and frequency of mild, moderate, and strenuous exercise by 3, 5, and 9, respectively. We categorized the calculated MET-hr/week for each participant into one of five levels: very high ($\geq$25.50 MET-hr/week), high (16.50–25.49 MET-hr/week), moderate (7.50–16.49 MET-hr/week), low (3.75–7.49 MET-hr/week), and inactive (<3.75 MET-hr/week; Godin & Shephard, 1997; Shiroma et al., 2014). We calculated total weekly PA in arbitrary units by summing the exercise pattern of the separate items. For example, if a participant performed 30 min of yoga (mild) 5 times per week, played 30 min of badminton (moderate) once per week, and did 30 min of running (strenuous) once per week, we calculated the weekly total MET-hr/week score as (3 [mild] $\times$ 0.5 hr/time $\times$ 5 times/week) + (5 [moderate] $\times$ 0.5 hr/time $\times$ 1 time/week) + (9 [strenuous] $\times$ 0.5 hr/time $\times$ 1 time/week) = 7.5 + 2.5 + 4.5 = 14.5 MET-hr/week (moderate PA [7.50–16.49 MET-hr/week] or PA of $\geq$7.5 MET-hr/week).

Assessment of Depression, Anxiety, and Stress

We estimated levels of depression, anxiety, and stress by using the Depression, Anxiety, and Stress Scale–21 (DASS-21) after adjusting for confounding factors (Oei et al., 2013). The DASS-21 is widely used to measure the three domains of depression, anxiety, and stress and comprises 21 items. The Cronbach's α values for the Indonesian version are .87, .85, and .72 for the depression, anxiety, and stress subscales, respectively. For the present study, we defined DASS-21 scores as categorical data for anxiety (yes = score $\geq$ 8, no = score < 8), stress (yes = score $\geq$ 15, no = score < 15), and depression (yes = score $\geq$ 10, no = score < 10).

Assessments of Clinical and Biochemical Variables

The primary biological and clinical measures in the present study were body mass index (BMI) and inflammatory markers (NLR and WBC count). We calculated BMI as body weight (kg)/height^2 (m^2) and classified participants into two groups including nonobese (BMI < 25 kg/m^2) and obese (BMI $\geq$ 25 kg/m^2; Purnell, 2018). We measured NLR and WBC count using a fasting blood sample (5 ml) withdrawn from the antecubital vein. The blood was mixed with dipotassium ethylenediaminetetraacetic acid (1.5–2.2 mg/ml) and analyzed using the automated hematology cell counter XP-100 (Sysmex, Kobe, Japan). We defined WBC as either <7.950 or $\geq$7.950 (10^3/μl) based on the area under the curve (AUC) of .660, with 63% sensitivity and 61% specificity. We calculated NLR as the ratio of neutrophil count to lymphocyte count and defined the measure as <1.940 or $\geq$1.940 based on the AUC of .828 with 80% sensitivity and 80% specificity.

Statistical Analysis

Distributions of demographic characteristics and determinant factors between groups are expressed as frequency (*n*) and percentage (%). Continuous variables are expressed as means with *SD*s and were evaluated using an independent *t* test, Pearson's correlation, or Spearman's rank correlation, as appropriate. *Z*-scores for skewness and kurtosis were used to assess the normality of data, with *Z*-scores < 3.29 indicating normal distributions (Kim, 2013). Multicollinearity was assessed using a variance inflation factor (VIF) of <10 (García et al., 2015). The present study had a maximum VIF of 2.23, indicating that our data had low impact for multicollinearity. Adjusted β coefficients and 95% confidence intervals (CIs) were obtained by performing a multiple linear regression for QoL in relation to exposures of interest after adjustment for potential confounding variables including gender, age, marital status, income, education, duration of diabetes, BMI, active smoker, WBC count, nonsmoker, and stress, anxiety, and depression levels. The synergistic interaction effect of low NLR and PA on QoL was investigated after creating four dummy variables for the following four (2 × 2) conditions: (1) PA of <7.5MET-hr/weeks and NLR of $\geq$1.940 (the reference condition or β00), (2) PA of <7.5MET-hr/weeks and NLR of <1.940 (β10), (3) PA of $\geq$7.5 MET-hr/week and NLR of $\geq$1.940 (β01), and (4) PA of $\geq$7.5 MET-hr/week and NLR of <1.940 (β11). We calculated the additive interaction or synergistic effect using the following categories: (1) if $\beta 11 = \beta 01 + \beta 10$, no interaction as departure from additivity, (2) if $\beta 11 > \beta 01 + \beta 10$, positive interaction as departure from additivity, and (3) if $\beta 11 < \beta 01 + \beta 10$, negative interaction as departure from additivity (Knol et al., 2007; Slinker, 1998). We also calculated the 95% CI for our synergistic effect. Statistical analyses were performed using SPSS Version 25.0 (Chicago, IL), with a p value of <.05 considered statistically significant.

Ethical Considerations

The institutional review board (IRB) of Siti Khodijah Muhammadiyah Sepanjang Hospital Ethics Committee reviewed and approved the study protocol (IRB: 009/KET-TPEP/X-2018), and the protocol conformed to the provisions of the Declaration of Helsinki. We obtained informed written consent from each participant after providing them with both verbal and written information about the research.

Results

Table 1 presents the demographic characteristics of the participants. There were no significant differences by age, gender, or education in total QoL, PCS, and MCS. However, we did find a significant difference by marital status and income in total QoL and PCS, but no significant difference in MCS, whereby the mean (*SD*) total QoL and PCS were significantly higher in married participants than in unmarried participants (total QoL $p = .02$; PCS $p = .003$). Total QoL and PCS were also significantly higher in participants with high income compared to those with low income (total QoL $p = .001$; PCS: $p = .001$).

We have presented the determinantal factors for QoL in Table 2. We observed significant negative correlations between duration since diabetes onset and total QoL ($p < .001$), MCS ($p < .001$), and PCS ($p < .001$). Moreover, mean (*SD*) total QoL, MCS, and PCS were significantly higher ($p < .05$) in participants with PA $\geq$ 7.5 MET-hr/week, NLR < 1.940, WBC count (10^3/μl) < 7.950, DASS-21 stress score < 15, DASS-21 anxiety score < 8, and DASS-21 depression score < 10.

The adjusted β coefficients and 95% CIs of PA status, NLR, and WBC count for QoL, including total QoL, MCS, and PCS, are presented in Table 3. Participants with $\geq$7.5 MET-hr/week of PA were significantly more likely to have higher total QoL (β = 8.41, 95% CI = [6.04, 10.78]) and PCS (β = 13.90, 95% CI = [10.52, 17.29]) compared to those with <7.5 MET-hr/week of PA after adjustment for covariates, but PA was not significantly associated with MCS after adjustment for confounding factors. Participants with a low NLR (<1.940) were significantly more likely to have higher total QoL (β = 4.76, 95% CI = [3.41, 6.11]), MCS (β = 2.62, 95% CI = [0.75, 4.49]), and PCS (β = 6.89, 95% CI = [4.97, 8.82]) compared

Table 1. Relationships of Distributions of Demographic Characteristics With Quality-of-Life Scores from the SF-36 in Participants With Type 2 Diabetes Mellitus.

	Total Participants	Total Quality-of-Life Score		Mental Component Score (MCS)		Physical Component Score (PCS)	
Characteristic	*n* (%)	Mean (*SD*)/*r*	*p* Value	Mean (*SD*)/*r*	*p* Value	Mean (*SD*)/*r*	*p* Value
Age (years) [a]	294 (100)	0.05	.377	0.04	.453	0.05	.377
Gender [b]			.134		.057		.550
Female	237 (80.6)	47.85 (8.63)		49.87 (10.33)		45.82 (9.722)	
Male	57 (19.4)	45.97 (7.73)		46.96 (9.93)		44.98 (8.37)	
Marital status [b]			.028		.404		.003
Not married	159 (54.1)	46.48 (8.16)		48.84 (10.62)		44.13 (8.34)	
Married	135 (45.9)	48.66 (8.73)		49.86 (10.11)		47.46 (10.39)	
Income (IDR) [b]			.001		.146		.001
Low income	255 (86.7)	46.87 (8.29)		48.96 (10.52)		44.77 (8.74)	
High income	39 (13.3)	55.12 (8.71)		51.56 (9.29)		51.48 (11.86)	
Education [b]			.550		.759		.159
ISCED < 3	169 (57.5)	47.23 (8.63)		49.47 (10.58)		44.99 (9.42)	
ISCED ≥ 3	125 (42.5)	47.83 (8.29)		49.09 (10.15)		46.56 (9.49)	

Note. $N = 294$. IDR = Indonesian Rupiah rate; ISCED = International Standard Classification of Education; *SD* = standard deviation; SF-36 = 36-item Short Form Health Survey.
[a]Pearson's correlation. [b] Independent *t* test.

Table 2. Relationships of Distributions of Determinantal Factors With Quality-of-Life Scores on the SF-36 in Participants With Type 2 Diabetes Mellitus.

	Total Participants	Total Quality-of-Life Score		Mental Component Score (MCS)		Physical Component Score (PCS)	
Variables	*n* (%)	Mean (*SD*)/*r*	*p* Value	Mean (*SD*)/*r*	*p* Value	Mean (*SD*)/*r*	*p* Value
Duration of diabetes (years) [a]	294 (100)	−0.23	<.001	−0.20	<.001	−0.21	<.001
BMI (kg/m^2) [b]			.098		.122		.206
≥25	116 (39.5)	46.47 (8.74)		48.15 (10.67)		44.79 (9.13)	
<25	178 (60.5)	48.14 (8.26)		50.06 (10.16)		46.22 (9.66)	
Physical activity (MET-hr/week) [b]			<.001		<.001		<.001
<7.5	273 (92.9)	46.37 (7.37)		48.44 (9.96)		44.30 (7.78)	
≥7.5	21 (7.1)	61.93 (8.84)		60.59 (9.39)		63.28 (11.80)	
Smoking status [b]			.104		.062		.387
Active smoker	33 (11.2)	45.22 (8.00)		46.13 (10.69)		44.31 (8.54)	
Nonactive smoker	261 (88.8)	47.77 (8.51)		49.71 (10.30)		45.83 (9.58)	
NLR [b]			<.001		<.001		<.001
≥1.940	186 (63.3)	43.91 (6.11)		45.86 (8.95)		41.96 (6.21)	
<1.940	108 (36.7)	53.63 (8.48)		55.24 (10.03)		52.02 (10.68)	
WBC count (10^3/μl) [b]			<.001		.001		.003
≥7.950	157 (53.4)	45.75 (7.32)		47.39 (9.61)		44.11 (7.86)	
<7.950	137 (46.6)	49.47 (9.27)		51.51 (10.83)		47.43 (10.79)	
DASS-21 stress [b]			<.001		<.001		.001
Yes (score ≥ 15)	168 (57.1)	45.59 (7.90)		47.21 (9.83)		43.98 (8.14)	
No (score < 15)	126 (42.9)	50.00 (8.60)		52.11 (10.48)		47.89 (10.62)	
DASS-21 anxiety [b]			<.001		<.001		<.001
Yes (score ≥ 8)	232 (78.9)	44.79 (6.31)		46.05 (8.13)		43.52 (7.30)	
No (score < 8)	62 (21.1)	57.57 (7.97)		61.48 (8.79)		53.67 (12.09)	
DASS-21 depression [b]			<.001		<.001		<.001
Yes (score ≥ 10)	206 (70.1)	43.41 (5.22)		44.19 (6.54)		42.64 (6.48)	
No (score < 10)	88 (29.9)	57.01 (6.85)		61.29 (7.43)		52.72 (11.44)	

Note. $N = 294$. BMI = body mass index; DASS-21 = Depression, Anxiety, and Stress Scales–21; MET = metabolic equivalent of task; NLR = neutrophil–lymphocyte ratio; *SD* = standard deviation; SF-36 = 36-item Short Form Health Survey; WBC = white blood cell.
[a]Pearson's correlation. [b] Independent *t* test.

Table 3. Adjusted β Coefficients and 95% Confidence Intervals (CIs) of Physical Activity (PA) Status, Neutrophil–Lymphocyte Ratio (NLR), White Blood Cell (WBC) Count for Quality of Life in Participants With Type 2 Diabetes Mellitus.

	Total Quality-of-Life Score		Mental Component Score (MCS)		Physical Component Score (PCS)	
Variables	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients β (95% CI)	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients β (95% CI)	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients β (95% CI)
Physical activity (MET-hr/week)						
<7.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥7.5	15.56 [12.23, 18.90]**	8.41 [6.04, 10.78]**	12.16 [7.74, 16.58]**	2.91 [−0.38, 6.20]	18.97 [15.36, 22.59]**	13.90 [10.52, 17.29]**
NLR						
≥1.940	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<1.940	9.742 [8.03, 11.40]**	4.76 [3.41, 6.11]**	9.38 [7.15, 11.61]**	2.62 [0.75, 4.49]*	10.06 [8.12, 12.00]**	6.89 [4.97, 8.82]**
WBC count ($10^3/\mu l$)						
≥7.950	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<7.950	3.72 [1.82, 5.63]*	−0.13 [−1.28, 0.88]	4.12 [1.77, 6.47]*	0.33 [−1.27, 1.92]	3.32 [1.18, 5.47]*	−0.59 [−2.24, 1.06]

Note. $N = 294$. Adjusted β coefficients and 95% CI were estimated using multiple linear regression after adjusting for gender, age, marital status, income, education, duration of diabetes, body mass index, smoking status, and stress, anxiety, and depression levels. CI = confidence interval; MET = metabolic equivalent of task; NLR = neutrophil–lymphocyte ratio; WBC = white blood cell.
*$p < .05$. **$p < .001$.

Table 4. Synergistic Effect of Physical Activity (PA) Level and NLR for Quality of Life in Participants With Type 2 Diabetes Mellitus.

	Total Quality-of-Life Score		Mental Component Score (MCS)		Physical Component Score (PCS)	
Variables	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients (95% CI)	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients β (95% CI)	Unadjusted Coefficients β (95% CI)	Adjusted Coefficients β (95% CI)
Both MET-hr/week < 7.5 and NLR ≥ 1.940	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Both MET-hr/week < 7.5 and NLR < 1.940	8.51 [6.97, 10.05]**	4.52 [3.18, 5.85]**	8.36 [6.12, 10.59]**	2.27 [0.42, 4.12]*	8.66 [6.94, 10.38]**	6.76 [4.85, 8.67]**
Both MET-hr/week ≥ 7.5 and NLR ≥ 1.940	11.67 [7.29, 16.05]**	6.05 [2.41, 9.68]**	7.68 [1.32, 14.04]**	−0.52 [−5.56, 4.53]	15.67 [10.76, 20.57]**	12.61 [7.40, 17.82]**
Both MET-hr/week ≥ 7.5 and NLR < 1.940	22.74 [19.25, 26.23]**	14.31 [11.36, 17.27]**	19.61 [14.55, 24.66]**	7.20 [3.09, 11.31]**	25.88 [21.98, 29.77]**	21.43 [17.19, 25.67]**

Note. $N = 294$. Adjusted for gender, age, marital status, income, education, duration of diabetes, body mass index, active smoker, nonsmoker, white blood cell level, stress level, anxiety level, and depression level. CI = confidence interval; MET = metabolic equivalent of task; NLR = neutrophil–lymphocyte ratio.
*$p < .05$. **$p < .001$.

to those with NLR ≥ 1.940 after adjustment for confounders. However, we observed no significant associations between WBC count and total QoL or either of the QoL components after controlling for confounding factors.

In Table 4, we present the synergistic effects of PA of ≥7.5 MET-hr/week and the T2DM-related predictor NLR on QoL among participants with T2DM. Patients with both PA ≥ 7.5 MET-hr/week and NLR < 1.940 had synergistically increased total QoL, MCS, and PCS compared with patients with both PA < 7.5 MET-hr/week and NLR ≥ 1.940. The adjusted β coefficients (95% CI) of total QoL, MCS, and PCS were 14.31 (11.36–17.27), 7.20 (3.09–11.31), and 21.43 (17.19–25.67), respectively, in patients with both PA ≥ 7.5 MET-hr/week and NLR < 1.940 compared with patients with both PA < 7.5 MET-hr/week and NLR ≥ 1.940. Results indicate that there were positive synergistic effects (additive interactions) from the combination of PA of MET-hr/week ≥ 7.5 and NLR < 1.940 for total QoL ($14.31 > 6.05 + 4.52$), MCS ($7.20 > -0.52 + 2.27$), and PCS ($21.43 > 12.61 + 6.76$).

Discussion

To the best of our knowledge, the present study is the first to investigate the association of NLR with QoL among patients with T2DM in an Indonesian population. Our results demonstrated that both NLR < 1.940 and PA ≥ 7.5 MET-hr/week were associated with improved total QoL, PCS, and MCS among patients with T2DM in Indonesia.

Prior research has shown that PA, and not physical inactivity, was positively associated with higher QoL (Adeniyi et al., 2015; Thiel et al., 2017a). In the present study, patients with T2DM who participated in ≥7.5 MET-hr/week of PA had higher β coefficients for total QoL and PCS than those who participated in <7.5 MET-hr/week of PA, after adjustment for other variables. This result is consistent with those of previous research (Adeniyi et al., 2015) in which investigators concluded that individuals with moderate-to-high levels of PA (≥10 to ≥ 25 MET-hr/week) had a 0.4-fold risk (95% CI = [0.2, 0.8]) of having a reduced total QoL compared with those who had lower levels of PA (<10 MET-hr/week). In that study, PA was the strongest predictor for PCS (β = 0.09; standard error [*SE*] = .04, $p < .05$) for those with T2DM. Eckert (2012) reported that PA was positively correlated with MCS (β = 0.13; *SE* = .04, $p < .001$) after adjustment for age, sex, and BMI. In the present study, PA of ≥7.5 MET-hr/week was not significantly related to MCS after adjustment for confounding factors. This finding is consistent with that of a study to identify potential factors affecting QoL among participants with T2DM in Alberta, Canada, in which researchers observed no association between PA and MCS (pooled β = 0.50; *SE* = .42, $p = .234$) at 1-year follow-up after analysis adjustment (Thiel et al., 2017b). There are a number of possible explanations for the finding that PA level is associated with higher total QoL and PCS but not MCS. First, because mental disorders are prevalent among patients with T2DM, other factors such as depression, anxiety, and worry likely influence a patient's mental status more than PA does (Jing et al., 2018). Second, high levels of PA effectively reduce chronic inflammation and improve common physical functions, such as muscle strength, and prevent disability (Nicklas & Brinkley, 2009), which may be a risk factor for reduced PCS. Third, moderate-to-high-intensity PA contributed to an increased fit–fat index, indicating that reduced adiposity is among the most prominent predictors of increased PCS (Sloan et al., 2015).

Another key finding in the present study was that lower NLR was positively associated with higher total QoL, MCS, and PCS, but we observed no significant relationship between WBC count and any domain of QoL. In a previous cohort study, authors reported that lower levels of WBCs were not significantly correlated with increases in SF-36 MCS (β = 0.0003; *SE* = .0019, $p = .89$) among participants with several chronic diseases including hypertension, cancer, cardiovascular diseases, and diabetes (Gialluisi et al., 2019). However, the effects of WBC count and NLR on total QoL, MCS, and PCS in patients with T2DM have not been fully investigated. Notably, our finding that low NLR is significantly related to high total QoL, MCS, and PCS is consistent with the findings of previous studies in which higher NLR was significantly associated with lower PCS (β = −0.037, 95% CI = [−0.067, −0.007], $p = .015$) in patients with multiple sclerosis (Hemond et al., 2019), and lower NLR was significantly associated with higher MCS (β = −0.034; *SE* = .007, $p < .0001$) in Italian adults (Gialluisi et al., 2019). The immune–inflammation response to specific physiological problems is characterized by increased neutrophil and decreased lymphocyte counts. Decreased lymphocyte counts can induce cytotoxic cell death and lower the insulin sensitivity index (Kang et al., 2019; Lee et al., 2014). In another study, higher NLRs played a crucial role in the progression of diabetic nephropathy and were associated with major adverse cardiac events and related mortality (DiGangi, 2016). Öztürk et al. (2013) reported that higher NLRs were powerful contributors to the development of microvascular complications (β = 2.217, 95% CI = [1.086, 4.526], $p = .029$) among participants with T2DM. In addition, Eraldemir et al. (2016) found that higher NLRs indicated a robust inflammatory response and may thus have stimulated increased levels of malondialdehyde, a marker of oxidative stress (β = 0.422, 95% = [CI 0.048, 0.796], $p = .029$). Increases in oxidative stress are associated with β cell dysfunction, endothelial cell dysfunction, insulin resistance, and increased levels of adipokines and cytokines (Tangvarasittichai, 2015). This mechanism might provide new insight into the pathways that affect both physical health and MH in patients with T2DM.

Our results further demonstrate that the combination of an NLR < 1.940 and levels of PA ≥ 7.5 MET-hr/week synergistically increased total QoL, PCS, and MCS compared with the combination of an NLR ≥ 1.940 and levels of PA < 7.5 MET-hr/week. The potential mechanism for this synergistic effect on total QoL, MCS, and PCS might be explained by the relationship between PA and NLR. Kim et al. (2018) reported that moderate-intensity PA was negatively associated with NLR (β = −0.07, 95% CI = [−0.14, 0.01], $p = .038$). Additional research has demonstrated that lower NLR was associated with a better QoL (Gialluisi et al., 2019; Hemond et al., 2019). These previous results support our finding that patients with T2DM with a high level of PA and low NLR had higher QoL scores than individuals with only one of these factors. Moreover, the etiological factors of weight loss, and low intake of energy, fat, and carbohydrates as well as PA help patients with T2DM effectively control their lipid concentrations and maintain low levels of inflammatory biomarkers, thus reducing the risks of dyslipidemia and hyperglycemia in patients with T2DM (Tangvarasittichai, 2015). Management of hyperglycemia can delay or prevent complications and ultimately optimize QoL in these patients (Davies et al., 2018).

Our findings thus indicate that patients with T2DM who maintain regular PA of ≥7.5 MET-hr/week and have an NLR ≥ 1.940 are likely to have higher total QoL, MCS, and PCS than those performing less PA or with a lower NLR. Moreover, regular PA of ≥7.5 MET-hr/week is a potentially vital factor for reducing high NLR and preventing the decline of QoL. We

would thus encourage patients who perform regular PA at levels of ≥7.5 MET-hr/week to commit to reducing high NLRs so as to improve their total QoL, PCS, and MCS. Reduction of the NLR would also reduce fasting glucose and hemoglobin A1c levels and contribute to reducing the risk of microvascular complications in these patients, particularly in individuals with high levels of inflammatory biomarkers (Adeniyi et al., 2015; Nicklas & Brinkley, 2009; Tangvarasittichai, 2015). More generally, based on our findings, we suggest that increasing regular PA to ≥7.5 MET-hr/week and avoiding high NLRs are potentially effective strategies for improving QoL and reducing disease complications as well as mortality among patients with T2DM.

Among the limitations of the present study was that we collected self-reported PA data using the GLTEQ, which includes leisure-time activities but does not capture PA during work time. It could thus cause an underestimation of the effect of PA on QoL. Furthermore, even though we adjusted for a considerable number of potential confounding factors, we cannot exclude the possibility that NLR is affected by factors other than T2DM. The NLR is reliable, easily measurable, reproducible, and inexpensive, but nonspecific for T2DM. However, our finding that the combination of high levels of PA with low NLRs had a positive synergistic effect on QoL among patients with T2DM is potentially valuable and could contribute to the identification and promotion of strategies for improving QoL in patients with T2DM that target PA and the NLR. Also, we described only inflammatory biomarkers in the present study. Future research should examine biomarkers of other pathways such as oxidative stress among participants with T2DM. Finally, a large cluster-randomized multisite study would provide more comprehensive evidence regarding the individual and combined effects of PA and biomarkers of inflammation and other pathways on QoL in patients with T2DM that could help guide future nursing research and practice.

Conclusions

The present research revealed that levels of PA ≥7.5 MET-hr/week were independently associated with higher total QoL and PCS, but not MCS, in adults with T2DM. Lower NLRs were related to higher total QoL, MCS, and PCS. The combination of PA of ≥7.5 MET-hr/week and an NLR < 1.94 had a positive synergistic effect of promoting QoL, including total QoL, MCS, and PCS, among these patients in Indonesia. These results suggest crucial roles for nurse educators and health professionals in identifying and promoting treatment-targeted strategies such as maintaining a low NLR and increasing PA to ≥7.5 MET-hr/week to improve QoL among patients with T2DM.

Authors' Note

Our data sets generated during the current research are available from the corresponding author upon reasonable request.

Author Contributions

Yohanes Andy Rias contributed to conception, design, acquisition, analysis, and interpretation of data; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Maria Dyah Kurniasari contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Victoria Traynor and Shu Fen Niu contributed to conception and interpretation, critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Bayu Satria Wiratama contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Ching Wen Chang contributed to conception and interpretation, critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Hsiu Ting Tsai contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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