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Risk Factors Affecting Six-Minute Walk Test Performance in Patients with and without Metabolic Syndrome: A Primary Care-Based Analysis

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Abstract

Background: The Six-Minute Walk Test (6MWT) is a widely used tool for assessing functional capacity in various populations. Metabolic Syndrome (MetS), a cluster of cardiovascular risk factors, is associated with reduced functional capacity and increased risk of cardiovascular disease and type 2 diabetes. However, the factors influencing 6MWT performance in primary care settings among patients with and without MetS remain underexplored, especially in Indonesian populations.

Methods: This cross-sectional study was conducted from April to August 2024, using data from the Germas Jantungku registry at 20 primary healthcare centers in Makassar, Indonesia. A total of 134 participants (59 with MetS and 75 without MetS) were recruited through consecutive sampling. Demographic, medical, and clinical data were collected, including anthropometric measurements, blood pressure, and fasting blood samples for glucose and lipid profiling. Participants underwent the 6MWT, and physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ). Multivariate logistic regression was used to identify factors associated with abnormal 6MWT performance. Estimated VO2 max was calculated using the Nury formula, and subgroup analyses were performed.

Results: Participants with MetS were older (55.17 ± 10.86 years vs 51.01 ± 10.19 years, $p = 0.024$) and had higher waist circumferences, blood pressure, and lower HDL cholesterol levels than those without MetS. The prevalence of diabetes mellitus (52.54% vs 20.00%, $p < 0.001$) and smoking (22.03% vs 9.33%, $p = 0.041$) was also significantly higher in the MetS group. Multivariate analysis revealed that age (OR 1.09, 95% CI 1.03-1.16, $p = 0.005$) and smoking (OR 12.30, 95% CI 1.02-14.85, $p = 0.048$) were significant predictors of abnormal 6MWT performance. However, MetS status was not independently associated with abnormal 6MWT performance. Although trends toward lower estimated VO2 max were observed in MetS patients across subgroups, these differences were not statistically significant. In smokers with abnormal 6MWT performance, MetS patients had notably lower estimated VO2 max (12.49 ± 5.06 ml/kg/min vs 17.08 ± 2.39 ml/kg/min, $p = 0.058$).

Conclusion: Age and smoking were significant predictors of reduced functional capacity as measured by the 6MWT, while MetS status alone was not. These findings suggest that in primary care populations, the impact of MetS on functional capacity may be modulated by other risk factors such as age and smoking. Comprehensive management strategies addressing multiple risk factors are necessary to improve outcomes in this population.

Keywords: Six-Minute Walk Test, Metabolic Syndrome, VO2 Max, Cardiovascular Risk Factors.

Introduction

The Six-Minute Walk Test (6MWT) is an easy, cost-effective, and commonly used submaximal exercise assessment that offers significant insights on functional capacity across diverse patient demographics (1). The 6MWT, first designed to evaluate exercise tolerance in chronic respiratory diseases and heart failure, has subsequently been validated for a wide range of cardiovascular and pulmonary diseases (2,3). It has been demonstrated to be a precise indicator of cardiorespiratory fitness and a substantial predictor of morbidity and death in cardiovascular diseases (4,5).

Metabolic syndrome (MetS) is a complex of cardiovascular risk factors comprising central obesity, hypertension, dyslipidemia, and insulin resistance (6). The global prevalence of MetS is rising, with rates between 20-25% across different groups (7). The prevalence of MetS in Indonesia is estimated at 21.66%, with significant variation across provinces and ethnic groups (8).

MetS is associated with an elevated risk of cardiovascular disease, type 2 diabetes mellitus, and overall mortality. Previous studies suggest that individuals with Metabolic Syndrome (MetS) may demonstrate reduced functional capacity compared to those without MetS. Hassinen et al. found that elderly individuals with Metabolic Syndrome exhibited diminished cardiorespiratory fitness, as evidenced by maximal oxygen uptake (VO_2 max), compared to those without Metabolic Syndrome (9). Heubel et al. similarly revealed that older persons with MetS had inferior functional performance on multiple physical assessments, including the 6MWT (10). However, most of these studies have been conducted in specialized clinical settings or focused on certain patient populations, such as the elderly or persons with pre-existing cardiovascular diseases. In primary care settings, where the majority of patients with MetS are typically managed, the factors affecting 6MWT performance may be complex and varied. The relationship between MetS and functional ability in this context is insufficiently understood.

Understanding the factors influencing 6MWT performance in primary care patients with and without MetS is crucial for multiple reasons. It can initially aid doctors in more accurately assessing 6MWT results within the context of a patient's overall health status. Furthermore, it may pinpoint potential areas for intervention to improve functional capacity in these patients. Third, it may clarify the mechanisms via which MetS affects cardiovascular health and physical function.

This study aimed to examine risk factors affecting 6MWT performance in individuals with and without MetS at primary healthcare centers in Makassar, Indonesia. We hypothesized that both MetS-related factors (including obesity and hypertension) and non-MetS-related factors (such as age and smoking status) would be associated with 6MWT performance in this cohort of participants. Additionally, we sought to compare estimated VO_2 max values, derived from 6MWT results, across patients with and without MetS across several categories. This study focuses on a primary care population in Indonesia to furnish locally relevant information that can inform clinical practice and public health initiatives in analogous circumstances. The results of this study may facilitate the incorporation of specialized research findings into practical primary care for the management of patients with MetS and the assessment of functional capacity.

1. Materials and Methods

Study Design and Sample

This cross-sectional study, conducted between April and August 2024, utilized data from the Germas Jantungku registry (established in 2020) across 20 primary health care centers in Makassar, Indonesia. Consecutive sampling was employed to recruit participants for the study. The required minimum sample size was calculated using the Lameshow formula (11)., resulting in an estimate of 67 participants. However, to account for potential dropouts and ensure robust statistical power, a recruitment target of at least 134 participants was set.

Participants were eligible for inclusion if they were 18 years or older, registered in the Germas Jantungku program, and able to independently perform the six-minute walk test (6MWT). Exclusion criteria included physical limitations that impaired walking, contraindications to performing the 6MWT (12), and cognitive impairments that hindered the ability to follow instructions.

Data Collection

Demographic data, medical history, and anthropometric measurements were meticulously gathered by trained research assistants following standardized protocols. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest to ensure consistency (13).. Blood pressure was recorded after a five-minute rest period using a calibrated sphygmomanometer (14).

The diagnosis of metabolic syndrome (MetS) followed the International Diabetes Federation criteria, which required central obesity—defined as a waist circumference of ≥90 cm in men or ≥80 cm in women—along with at least two of the following conditions: elevated triglycerides (≥150 mg/dL or under specific treatment), low HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women, or receiving specific treatment for low HDL), elevated blood pressure (≥130/85 mmHg or receiving antihypertensive therapy), and fasting plasma glucose levels of ≥100 mg/dL or a prior diagnosis of type 2 diabetes (6).

The six-minute walk test (6MWT), conducted in a 30-meter corridor in accordance with American Thoracic Society guidelines, required participants to walk as far as possible within six minutes. Total distance covered was recorded, while heart rate and oxygen saturation were continuously monitored before, during, and after the test via pulse oximetry. Performance on the 6MWT was classified as either normal or abnormal based on gender-specific cut-off points for the Indonesian population (12,15).

Physical activity levels were assessed using the short form of the International Physical Activity Questionnaire (IPAQ). Participants reporting less than 150 minutes of moderate-intensity activity per week were classified as inactive, according to the World Health Organization's recommendations (16). Fasting blood samples were collected after an overnight fast, and standard laboratory techniques were employed to measure fasting plasma glucose, triglycerides, and HDL cholesterol levels.

Statistical Analysis

Data analysis was performed using SPSS version 29.0. The normality of the data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation and were compared between groups using either independent t-tests or Mann-Whitney U tests, depending on the data distribution. Categorical variables were presented as frequencies and percentages and were compared using chi-square tests or Fisher's exact tests where appropriate.

To determine factors associated with abnormal six-minute walk test (6MWT) performance, multiple logistic regression analysis was conducted. Variables with a p-value <0.2 in the univariate analysis were included in the multivariate model, which was built using a backward stepwise approach. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the strength of associations. The Nury formula was employed to estimate VO_2 max, and subgroup analyses were performed to compare estimated VO_2 max between participants with and without metabolic syndrome (MetS), stratified across different risk factor categories (17). A p-value <0.05 was considered statistically significant for all analyses. The goodness of fit for the logistic regression model was assessed using the Hosmer-Lemeshow test to ensure the model's robustness.

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 336/UN4.6.4.5.31/PP36/2024).

2. Results

Baseline Characteristics of Study Participants

A total of 134 participants were included in the analysis, consisting of 59 individuals with metabolic syndrome (MetS) and 75 without MetS. Baseline characteristics of the study population are detailed in Table 1. Participants with MetS were significantly older than those without MetS, with a mean age of 55.17 ± 10.86 years compared to 51.01 ± 10.19 years (p = 0.024). Although not statistically significant, there was a higher proportion of females in both groups, with a slightly greater percentage observed in the non-MetS group (86.67% vs 76.27%, p = 0.119).

Table 1. Baseline Characteristics of Study Participants

Characteristic	Metabolic Syndrome (n=59)	Non-Metabolic Syndrome (n=75)	*p-value*
Age (years)	55.17 ± 10.86	51.01 ± 10.19	0.024*
Female, n (%)	45 (76.27)	65 (86.67)	0.119
Waist circumference (cm)	92.59 ± 6.38	87.18 ± 12.17	0.002*
Systolic BP (mmHg)	146.93 ± 21.50	136.64 ± 21.53	0.007*
Diastolic BP (mmHg)	90.71 ± 16.21	85.31 ± 11.25	0.024*
HDL cholesterol (mg/dL)	43.36 ± 9.09	57.40 ± 30.73	0.001*
Diabetes mellitus, n (%)	31 (52.54)	15 (20.00)	<0.001*
Current smoker, n (%)	13 (22.03)	7 (9.33)	0.041*
Physical inactivity, n (%)	22 (37.29)	29 (38.67)	0.870

As expected, patients with MetS had significantly larger waist circumferences (92.59 ± 6.38 cm vs 87.18 ± 12.17 cm, p = 0.002) and higher blood pressure (systolic: 146.93 ± 21.50 mmHg vs 136.64 ± 21.53 mmHg, p = 0.007; diastolic: 90.71 ± 16.21 mmHg vs 85.31 ± 11.25 mmHg, p = 0.024) compared to those without MetS. HDL cholesterol levels were significantly lower in the MetS group (43.36 ± 9.09 mg/dL vs 57.40 ± 30.73 mg/dL, p = 0.001).

The prevalence of diabetes mellitus was markedly higher in the MetS group (52.54% vs 20.00%, p < 0.001). Current smoking was also more prevalent among patients with MetS (22.03% vs 9.33%, p = 0.041). Interestingly, there was no significant difference in physical inactivity between the two groups (37.29% vs 38.67%, p = 0.870).

Factors associated with abnormal 6MWT performance

Table 2 presents the findings from the multiple logistic regression analysis identifying factors associated with abnormal 6MWT performance. After adjusting for potential confounding variables, age and smoking were found to be significant predictors. Increasing age was associated with a higher likelihood of abnormal 6MWT performance, with each additional year of age increasing the odds by 9% (OR 1.09, 95% CI 1.03 - 1.16, p = 0.005). Smoking showed the strongest association, with current smokers having 12.3 times higher odds of abnormal 6MWT performance compared to non-smokers (OR 12.30, 95% CI 1.02 - 14.85, p = 0.048).

Interestingly, gender (OR 5.36, 95% CI 0.42 - 69.19, p = 0.198), physical inactivity (OR 1.33, 95% CI 0.43 - 4.05, p = 0.621), and metabolic syndrome status (OR 0.82, 95% CI 0.27 - 2.49, p = 0.731) did not show significant associations with abnormal 6MWT performance in this model. These results suggest that age and smoking are key factors influencing 6MWT outcomes, while other variables such as gender, physical activity levels, and metabolic syndrome may have less impact in this context.

Table 2: Multivariate Analysis of Factors Associated with Abnormal 6MWT Performance

Variables	OR	95% CI	P-value
Age (Years)	1.09	1.03 - 1.16	0.005*
Gender	5.36	0.42 - 69.19	0.198
Smoking	12.30	1.02 - 14.85	0.048*
Physical Inactivity	1.33	0.43 - 4.05	0.621
Metabolic Syndrome	0.82	0.27 - 2.49	0.731

Estimated VO_2 max based on 6MWT performance in various subgroups of patients with and without MetS.

Table 3 presents a comparison of estimated VO_2 max values between patients with and without MetS across various subgroups and 6MWT performance categories. While there was a general trend toward lower VO_2 max values among patients with MetS in most subgroups, these differences did not reach statistical significance. For instance, in the male subgroup, patients with MetS and abnormal 6MWT performance exhibited lower estimated VO_2 max compared to those without MetS (12.41 ± 4.44 ml/kg/min vs 15.70 ± 3.63 ml/kg/min, p = 0.086), although this difference was not statistically significant.

In participants aged 65 years and older, where data were only available for the abnormal 6MWT category, MetS patients demonstrated lower estimated VO_2 max values compared to their non-MetS counterparts (10.35 ± 4.31 ml/kg/min vs 11.92 ± 3.38 ml/kg/min, $p = 0.456$), though this difference was not significant. Among smokers, patients with MetS and abnormal 6MWT performance exhibited substantially lower estimated VO_2 max values compared to non-MetS patients (12.49 ± 5.06 ml/kg/min vs 17.08 ± 2.39 ml/kg/min, $p = 0.058$), with this difference approaching statistical significance.

For physically inactive participants, differences in estimated VO_2 max between MetS and non-MetS patients were minimal in both the normal and abnormal 6MWT categories. These findings suggest that although patients with MetS generally had lower estimated VO_2 max values, these differences were not statistically significant in most subgroups. The impact of MetS on VO_2 max may be influenced by other factors such as age, gender, and smoking status.

Table 3: Estimated VO_2 Max Based on 6MWT Performance in Subgroups

Subgroup	6MWT Category	MetS VO_2 Max (ml/kg/min)	Non-MetS VO_2 Max (ml/kg/min)	P-value
Male	Normal	19.42 ± 2.39	20.70	0.738
	Abnormal	12.41 ± 4.44	15.70 ± 3.63	0.086
Female	Normal	21.22 ± 1.39	20.54 ± 2.26	0.529
	Abnormal	12.49 ± 4.44	13.85 ± 4.03	0.123
Age <65 years	Normal	20.77 ± 1.70	20.56 ± 2.1	0.826
	Abnormal	13.05 ± 4.29	14.33 ± 4.01	0.134
Age ≥65 years	Normal	-	-	-
	Abnormal	10.35 ± 4.31	11.92 ± 3.38	0.456

3. Discussion

This study examined the factors influencing Six-Minute Walk Test (6MWT) performance and estimated VO_2 max in patients with and without metabolic syndrome (MetS) in primary care settings in Makassar, Indonesia. Our findings highlight the complex interplay of multiple factors that influence functional capacity in this population. Notably, we found significant differences in cardiovascular risk factors between MetS and non-MetS groups, which aligns with the well-documented clustering of risk factors in MetS (7). The higher prevalence of diabetes mellitus in the MetS group (52.54% vs 20.00%, $p < 0.001$) supports the established association between MetS and an increased risk of type 2 diabetes, largely mediated by insulin resistance, a central feature of MetS (18). Insulin resistance impairs glucose uptake in peripheral tissues and increases hepatic glucose production, leading to hyperglycemia and the eventual onset of diabetes (19).

Unexpectedly, the rates of physical inactivity were similar between groups (37.29% vs 38.67%, p = 0.870), which contrasts with findings from previous studies that have associated MetS with reduced physical activity levels (20). This discrepancy may be attributable to the specific characteristics of our primary care population or limitations in our method of assessing physical activity, which relied on self-reported data. Physical inactivity has been linked to MetS through various mechanisms, including reduced energy expenditure, decreased insulin sensitivity, and altered lipid metabolism (21).

Our multivariate analysis (Table 2) identified age and smoking as significant predictors of abnormal 6MWT performance. The association between increasing age and poorer 6MWT performance (OR 1.09, 95% CI 1.03 - 1.16, p = 0.005) is consistent with previous studies (22). This relationship likely reflects age-related declines in muscle mass, strength, and cardiorespiratory function (23). As individuals age, there is a progressive loss of muscle fibers and motor units, leading to sarcopenia. Additionally, age-related changes in the cardiovascular system, including reduced maximal heart rate and stroke volume, contribute to decreased aerobic capacity (24).

The strong association between smoking and abnormal 6MWT performance (OR 12.30, 95% CI 1.02 - 14.85, p = 0.048) underscores the detrimental effects of smoking on functional capacity. This finding aligns with a recent study by Mesquita et al. (2021), which found that current smokers had significantly lower 6MWT distances compared to never-smokers in a large population-based cohort (25). The mechanisms may include reduced lung function, impaired oxygen delivery, and increased systemic inflammation associated with smoking (9). Smoking causes airway inflammation and remodeling, leading to increased airway resistance and reduced gas exchange efficiency. Moreover, carbon monoxide in cigarette smoke binds to hemoglobin, reducing its oxygen-carrying capacity (26).

Interestingly, MetS status was not a significant predictor of abnormal 6MWT performance in our model. This contrasts with some previous studies that have reported reduced functional capacity in individuals with MetS (27,28). The discrepancy may be due to the primary care setting of our study, where patients might have less severe manifestations of MetS compared to those in specialized clinics. Additionally, the high prevalence of other risk factors in our population might have masked the independent effect of MetS on 6MWT performance.

The analysis of estimated VO_2 max based on 6MWT performance in various subgroups (Table 3) provides additional insights. While there were trends towards lower VO_2 max in patients with MetS across most subgroups, these differences were not statistically significant. This finding is partly at odds with a recent meta-analysis by Zhu et al. (2022), which found significantly lower cardiorespiratory fitness in individuals with MetS compared to those without. The pathophysiological mechanisms linking MetS to reduced cardiorespiratory fitness are multifaceted. Insulin resistance, a hallmark of MetS, can impair skeletal muscle glucose uptake and utilization during exercise. Adipose tissue dysfunction in MetS leads to increased production of pro-inflammatory cytokines, which can negatively affect muscle function and aerobic capacity. Furthermore, endothelial dysfunction associated with MetS may impair vasodilation during exercise, limiting oxygen delivery to working muscles (9).

Our results in the smoking subgroup, where MetS patients with abnormal 6MWT performance showed notably lower estimated VO_2 max (12.49 ± 5.06 vs 17.08 ± 2.39 ml/kg/min, $p = 0.058$), suggest that the impact of MetS on cardiorespiratory fitness may be more pronounced in certain high-risk subgroups. This interaction between smoking and MetS could be explained by the cumulative effects of both factors on systemic inflammation, oxidative stress, and vascular function. The lack of significant differences in estimated VO_2 max between MetS and non-MetS groups in our study could be due to several factors. First, the use of estimated rather than directly measured VO_2 max might have introduced some inaccuracy. While the Nury formula used in our study has been validated for the Indonesian population, it may not capture all the physiological nuances that direct measurement would provide (17). Second, the relatively small sample size in some subgroups might have limited our statistical power to detect differences. Third, the specific characteristics of our primary care population, including the high prevalence of other cardiovascular risk factors, might have influenced the results.

Our findings highlight the importance of considering multiple factors when assessing functional capacity in primary care settings. While MetS remains an important cluster of cardiovascular risk factors, its impact on functional capacity as measured by 6MWT and estimated VO_2 max may be modulated by other factors such as age and smoking status. This underscores the need for comprehensive risk assessment and individualized management strategies in primary care.

The complex interplay between MetS, aging, smoking, and functional capacity revealed in our study points to the need for a multifaceted approach to cardiovascular risk reduction in primary care. Interventions targeting multiple risk factors simultaneously, such as lifestyle modification programs addressing diet, physical activity, and smoking cessation, may be more effective than focusing on MetS alone (29).

4. Conclusion

Our study reveals that in NSTEMI patients with type 2 diabetes, a prior diabetes diagnosis is associated with a substantially increased risk of major adverse cardiovascular events, particularly heart failure. Reduced left ventricular ejection fraction, the absence of revascularization, and elevated hs-Troponin I levels are significant predictors of poor outcomes. These findings highlight the need for aggressive risk factor management, timely revascularization where appropriate, and careful monitoring of cardiac function in this high-risk group. Future large-scale studies with longer follow-up are warranted to further elucidate the complex relationships between diabetes, cardiovascular risk factors, and outcomes in NSTEMI patients.

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