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Research Article

Influence of Therapy Compliance Using Medication Possession Ratio Method for Patients with Metabolic Syndrome

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Abstract
Metabolic syndrome is still a major problem in developing countries and it has an association with high blood pressure, blood glucose, and lipid profile abnormalities, which can cause cardiovascular disease. This indicates that it is important to provide adequate treatment, but patient compliance has effects on the outcome. Improving patients' compliance to treatment can provide a better control of the condition. Therefore, this study aimed to determine the association between medication compliance and the therapeutic outcome of metabolic syndrome. This observational analytic study was conducted using a retrospective cohort design for one year of observation, namely April 2020-March 2021. The influence of patient compliance with therapy outcomes in terms of blood pressure, blood glucose, and lipid profile was assessed using the medication possession ratio method. This study was carried out by examining patients' medical records from the Bethesda Lempuyangwangi Hospital as parameters for compliance, while the outcome parameters were assessed by experts. The data obtained were analyzed using Anova (homogeneous data) or Kruskal-Wallis (not homogeneous data) to determine the differences in the compliance based on patients' characteristics. The relationship of adherence to therapeutic outcomes was analyzed using logistic bivariate. From 174 patients' data that was observed, only 151 had a blood test. The average systolic blood pressure, total cholesterol, triglyceride, and HbA1c levels were above the standard threshold. The three levels of compliance had no significant relationship with blood pressure, HbA1c, and lipid profiles ($p>0.05$). The adjusted data for age and gender on adherence showed patients with low compliance, and they have a 2.08 times risk of having high triglyceride levels compared to others ($p<0.05$). The results indicated the patients' low compliance to therapy, hence, health professionals must strengthen education to improve this condition.

Keywords: Blood glucose, blood pressure, compliance, lipid profile, medication possession ratio

Pengaruh Ketaatan Terapi menggunakan Metode *Medication Possession Ratio* pada Penderita Sindrom Metabolik

Abstrak
Sindrom metabolik masih menjadi masalah besar di negara berkembang. Sindrom metabolik berkorelasi dengan tekanan darah tinggi, peningkatan gula darah, dan kelainan profil lipid. Seiring waktu sindrom metabolik akan menyebabkan penyakit kardiovaskular. Terapi yang memadai merupakan hal penting, tetapi seringkali kepatuhan pasien akan memengaruhi hasil terapi. Peningkatan kepatuhan pasien terhadap pengobatan diduga dapat menghasilkan kondisi sindrom metabolik yang lebih baik, sehingga perlu ditentukan hubungan antara kepatuhan pengobatan dan hasil terapi sindrom metabolik. Penelitian ini merupakan penelitian observasional analitik dengan desain kohort retrospektif selama satu tahun (April 2020–Maret 2021). Kami menyelidiki kepatuhan terhadap hasil terapi pasien (tekanan darah, glukosa darah, dan profil lipid) menggunakan metode *medication possession ratio*. Penelitian dilakukan dengan mengambil rekam medis pasien di RS Bethesda Lempuyangwangi sebagai parameter kepatuhan pasien sedangkan hasil terapi dilihat dari pemeriksaan darah dan pemeriksaan fisik yang dilakukan oleh tenaga ahli. Data yang diperoleh dianalisis menggunakan *Anova* (data homogen) atau *Kruskal-Wallis* (data tidak homogen) untuk melihat perbedaan kepatuhan berdasarkan karakteristik pasien. Hubungan kepatuhan terhadap hasil terapi dianalisis menggunakan bivariat logistik. Sebanyak 174 data pasien dikumpulkan dan hanya 151 responden yang datang pada hari pengecekan darah. Rata-rata tekanan darah sistolik, kolesterol total, trigliserida, dan kadar HbA1c pasien berada di atas ambang standar. Tingkat kepatuhan yang terdiri dari 3 tingkatan tidak memiliki hubungan yang signifikan dengan tekanan darah, HbA1c, dan profil lipid ($p>0,05$). Penyesuaian untuk data usia dan jenis kelamin pada tingkat kepatuhan pada statistik menyatakan pasien dengan kepatuhan rendah memiliki peluang 2,08 kali untuk memiliki kadar trigliserida tinggi dibandingkan pasien dengan kepatuhan tinggi ($p<0,05$). Hasil penelitan mengindikasikan rendahnya kepatuhan terapi pasien sehingga profesional kesehatan harus memperkuat edukasi untuk meningkatkan kepatuhan pengobatan.

Kata kunci: Glukosa darah, kepatuhan, *medication possession ratio*, profil lipid, tekanan darah

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Introduction

Metabolic syndrome (MetS) is a collection of various cardiovascular risk factors, including central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension. This syndrome can increase risks for heart disease, stroke, diabetes, chronic kidney disease, and death.[1,2] The causes of metabolic syndrome are excess calorie intake compared to energy expenditure, a genetic, sedentary lifestyle, and other factors, like quality and composition of food. This epidemic problem does not instantly happen and cannot be controlled immediately either. An in-depth understanding of metabolic syndrome is needed to address this problem properly, including pathophysiological mechanisms, pharmacological and non-pharmacological therapies, and lifestyle changes.[3,4]

More specifically, metabolic syndrome is confirmed when a person has three or more of these criteria: high blood glucose, low levels of HDL, high levels of triglycerides, large waist circumference, and high blood pressure, where several risk factors, including dyslipidemia, hypertension, and hyperglycemia, generally assemble coincidentally.[5] The impact of MetS includes remodeling in glucose and lipid homeostasis that induce insulin insensitivity, causing blood vessel damage. Blood vessel damage causes atherosclerotic disease and the development of hypertension. Also, hypertension negatively affects several body parts, increasing vascular resistance, causing peripheral vascular disease, left ventricular hypertrophy and cardiomyopathy, and renal impairment.[6]

The lipid dysregulation will trigger dyslipidemia condition that is correlated with signaling molecules that regulate the signaling pathways of insulin and inflammatory mediators. Adipose tissue lipolysis is correlated in the insulin-resistant condition directing to a persistent increase in free fatty acid (FFA) levels in the blood. Escalation of FFA circulation initiates a variety of metabolic defects, including reductions in insulin sensitivity and hyperinsulinemia.[6,7] Moreover, Paredes *et al.* (2019) found that several atherosclerotic lipoproteins remain elevated in metabolic syndrome even when the patients have optimal LDL-c levels. The other factors that cause increasing atherosclerotic are non-HDL-c, ApoB, and oxidized LDL-c. The study recommends these risks be included to identify therapeutic targets and stratify cardiovascular (CV) risk in these patients.[8]

MetS therapy is indicated for significant risk factors: high LDL-C, hypertension, and diabetes. Thus, proper treatment for the patient with diabetes, hypertension, and dyslipidemia must be strengthened to reduce their risk for Atherosclerotic Cardiovascular Disease (ASCVD).[9] An effective lifestyle modification is also prepared. These changes impact on reducing all metabolic risk factors.[10] The biggest challenge in treating chronic patients (hypertension, dyslipidemia, and diabetes) is maintaining therapy compliance and a healthy lifestyle. Compliance with treatment therapy is someone's behaviour to take medication, follow a diet, and make lifestyle changes based on healthcare recommendations. Without good compliance, therapy outcome is unattainable. In reality, forgetfulness is the most common barrier to achieving medication compliance.[11,12] Therefore, this study was conducted to examine how patient compliance influences the outcome of metabolic syndrome therapy.

Methods

The type of study is an observational analytic with a retrospective cohort design. This study investigates the influence of patient compliance on therapy outcomes. This research was carried out by taking medical records from patients at Bethesda Lempuyangwangi Hospital for one year of observation (April 2020–March 2021)

as the patient compliance parameters, while the outcome parameters consisted of blood tests and physical examinations. Subjects selected by purposive-sampling method with inclusion criteria including adult patients aged (>17 years), had an insurance *Badan Penyelenggara Jaminan Sosial* (BPJS), outpatient visit, and have undergone therapy with a single medicine or combination orally (anti-hypertensive, diabetes, or cholesterol), with at least three hospital visits in 1 year of observation. The exclusion criteria were that the medical history was incomplete or unwillingness to have blood drawn. The Ethics Commission of Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada-Dr. Sardjito General Hospital has approved this research (KE/FK/0520/EC/2021).

Patient selection was done under an internist's responsibility. Data were collected from each visit for one year, including demographic profile (gender, age, blood pressure, total cholesterol, HDL, LDL, HbA1c, and medication compliance), date of visit, primary and secondary diagnosis based on IC10 code or INA GBGs code, medicine (type, amount, and dosage rules), and hospitalization history. According to the selection criteria, patients were contacted by the research team to perform laboratory tests at the hospital, including total cholesterol, HDL, LDL, triglycerides, and HbA1c.

Therapeutic compliance was calculated using the medication possession ratio (MPR) parameter, obtained from the actual number of days the patient received the drug divided by the number of days the patient should receive the drugs and the number of days for last prescribing medicine.[13] The MPR score will be calculated based on the therapy. The MPR scores for subjects receiving more than one treatment were then averaged. Then, subjects were categorized as good compliance (MPR score ≥80%), medium compliance (MPR score 50–<80%), and poor compliance (MPR score <50%). Concerning these results, the MPR method was chosen as it indicates specific to identifying non-adherent patients, easy to use, inexpensive, and non-invasive (only use electronic databases) that make patients not aware that they are being monitored.[14]

$$\text{MPR} = \frac{\text{Days of getting the drug}}{\text{Days should get the drug} + \text{Last prescribing drug day}}$$

The MPR score for a year was calculated, and the outcomes were then analyzed. The therapy outcomes criteria of this study were defined based on several factors of metabolic syndrome. Controlled blood pressure was classified as <130/80 mmHg (age <65 years) and <140/90 mmHg (age >65 years).[15] The patient's lipid profile was determined to be uncontrolled if total cholesterol >200 mg/dL, LDL >130 mg/dL, HDL <40 mg/dL, triglycerides >150 mg/dL.[16] The patient's blood glucose profile was considered high if HbA1c >6.5% (non-diabetic patients) and HbA1c >7% (diabetic patients).[17]

The demographic profile will be displayed in descriptive statistics, namely the number or mean+SD. The compliance data were processed using statistics with computerized software with IBM SPSS 25 program. The mean difference based on patient compliance was analyzed using Anova (homogeneous data) or Kruskal-Wallis (not homogeneous data). The relationship between compliances and therapeutic outcomes (model 1) was analyzed using logistic bivariate. The confounding factors, including age and gender (model 2), were adjusted by multivariate logistic analysis. The logistic analysis shows the odds ratio for each test, and all the statistical tests use a p-value <0.05 to be considered significant statistically and a 95% Confidence Interval.

Results

In this study, 218 patients from internist suggestions were obtained, with 44 patients

Table 1 Characteristics of Respondents

Characteristics	n (%) / Mean+SD
Gender*	
Male	54 (31%)
Female	119 (68.4%)
Age (year)*	63.88+9.27
Systolic Blood Pressure (mmHg)*	136.43+18.96
Diastolic Blood Pressure (mmHg)*	75.89+10.55
Total Cholesterol (mg/dL)**	220.76+121.12
HDL (mg/dL)**	55.16+16.44
LDL (mg/dL)**	121.94+34.03
Triglycerides (mg/dL)**	192.31+156.63
HbA1c (%)**	7.23+1.67
Antihypertensive Treatment Compliance (n=123)	
Good compliance	66 (53.7)
Medium compliance	45 (36.5)
Poor compliance	12 (9.8)
Antidiabetic Treatment Compliance (n=82)	
Good compliance	41 (50.0)
Medium compliance	32 (39.0)
Poor compliance	9 (11.0)
Antidyslipidemic Treatment Compliance (n=54)	
Good compliance	38 (70.4)
Medium compliance	14 (25.9)
Poor compliance	2 (3.7)

*n = 174, **n = 151

being excluded due to incomplete medical records. Table 1 shows that 174 patient data were collected, with only 151 coming on the blood test day. The average systolic blood pressure, total cholesterol, triglyceride, and HbA1c levels increased above the normal threshold. A total of 123 patients received therapy for antihypertension, 82 received anti-diabetic, and 54 received anti-dyslipidemic. The results showed that compliance with taking dyslipidemic drugs had the largest percentage (70.4%), followed by antihypertensive drugs (53.7%) and oral anti-diabetic drugs (50%).

Patient characteristics based on total therapy of MPR classification are presented in Table 2. More than half of the respondents who had their blood checked had good compliance (80 respondents), followed by medium compliance (67 respondents) and poor compliance (13 respondents). The mean age, blood pressure, lipid profile, and HbA1c were not significantly different in the three compliance categories of high, medium, and low ($p>0.05$).

Bivariate analysis was conducted to determine the effect of medication compliance on blood pressure, HbA1c, and lipid profiles (Table 3). The results of this analysis (Model 1) showed that there was no significant relationship between the level of compliance on blood pressure, HbA1c, and lipid profiles ($p>0.05$). The researchers also adjusted the age and sex on compliance levels and studied their effects on blood pressure, HbA1c, and lipid profile (Model 2). The result showed that patients with low compliance had 2.08 times higher chance of having higher triglyceride levels than patients with high compliance ($p<0.05$, 95% CI=1.02–4.25).

Discussion

The results showed that majority of patients had uncontrolled blood pressure, high lipid profile, and high blood glucose, even though they received medicine as therapy. It becomes a consequential where most patients have a poor metabolic syndrome profile, and it can be assumed that the treatment is in vain because it does not achieve an outcome. The therapy can impact a false sense of security but will have fatal consequences someday. Failure to achieving the therapeutic outcome of metabolic syndrome in the long term can cause cardiovascular events.[18] Type II diabetes mellitus can lead to diastolic dysfunction without structural changes and systolic dysfunction in patients with well-controlled metabolic risk factors. Meanwhile, uncontrolled blood pressure can increase heart failure, stroke, kidney disease, and dementia in the long term. Furthermore, more uncontrolled metabolic risk factors were correlated with increasing progressive impairment of left ventricular (LV) structure and LV systolic (longitudinal) function event.[19,20]

Generally, monitoring of therapeutic outcomes only focuses on the diagnosis of the disease and the drugs taken by the patient. The BPJS patient cannot claim lab tests outside the diagnosis. BPJS Health of the Republic of Indonesia pays claims to secondary or above health facilities for service packages based on disease diagnosis groupings and procedures.[21] However, metabolic syndrome, consisting of hypertension, diabetes, and dyslipidemia, are interrelated. Diabetes can increase risks for developing hypertension. Insulin resistance in diabetes patients will cause hyperinsulinemia. Excessive insulin also disrupts vasodilation and increases oxidative stress and the inflammatory process in the vascular wall leading to vascular smooth muscle cell proliferation and raised vascular stiffness, a pioneer of hypertension.[22] Reducing insulin sensitivity will increase concentrations of free fatty acids and low-grade inflammation. This mechanism results in excessive production and decreased catabolism of intestinal and hepatic origin triglyceride-rich lipoproteins. These changes can be seen in a decrease in HDL and an increase in LDL in patients with diabetes.[23] Both hypertension and diabetes modify the endothelial cell structure and function. These alterations in the smooth muscle cells lead to atherosclerosis, which leads to Cardiovascular Disease.[24] Hypertension and high blood glucose levels also play a vital role as independent predictors of dyslipidemia in patients with metabolic syndrome.[25] These findings strengthen the recommendation for a comprehensive blood examination of patients with one of the disorders of metabolic syndrome.

The results showed no correlation between patient compliance and therapeutic outcomes, except for the relationship between therapy compliance and blood triglyceride levels after age and gender adjustment. Medication compliance to long-term treatments for chronic conditions remains a problematic issue. The poor attitude toward medication compliance is affected by many factors, including socio-demographic characteristics, patient-related factors, treatment-related factors, and health care services-related factors.[26] Socio-demographic elements can influence medication compliance. For example, female patients tended to have a poor habit of exercising regularly but were more likely to avoid tobacco and alcohol than male patients. Older patients were significantly more likely to have better compliance and self-monitoring, and patients with better-perceived health quality were substantially more likely to adhere to medication therapy. In addition, patients with a longer disease duration were found to adhere to self-monitoring and were significantly associated with patient compliance.[27]

A cohort study in Canada using medication possession ratios (MPR) methods showed

Table 2 Characteristics of Respondents Based on Medication Possession Ratio Classification Category

Characteristics	MPR Classification Category			p-value
	Good Compliance (n=93)	Medium Compliance (n=67)	Poor Compliance (n=14)	
Age (mean±SD)	63.03±9.43	65.24±8.76	63.00±10.44	0.31
Systolic blood pressure (mean±SD)	138.47±19.21	135.84±17.57	125.71±21.18	0.06
Diastolic blood pressure (mean±SD)	77.40±10.10	74.39±10.01	73.07±14.58	0.12
	Good Compliance (n=80)	Medium Compliance (n=58)	Poor Compliance (n=13)	
Total cholesterol (mean±SD)	209.52±37.89	238.43±188.31	211.01±55.04	0.37
HDL (mean±SD)	57.08±17.24	54.05±15.09	48.31±16.05	0.17
LDL (mean±SD)	125.00±32.60	120.29±35.52	110.46±35.53	0.33
Triglycerides (mean±SD)	158.13±72.64	221.28±196.42	273.46±263.92	0.06[a]
HbA1c (mean±SD)	7.20±1.82	7.25±1.49	7.32±1.52	0.96

[a]Kruskal-Wallis test

Table 3 Effect of Medication Compliance on Blood Pressure, HbA1c, and Lipid Profile (n=151)

Compliance	Uncontrolled Blood Pressure		Total Cholesterol (High)		HDL (Low)		LDL (High)		Triglycerides (High)		HbA1c (High)	
	OR (95% CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Model 1: Unadjusted												
Good compliance						1.00 (reference)						
Medium compliance	0.34 (1.01–1.13)	0.08	1.31 (0.39–4.35)	0.66	2.37 (0.55–10.24)	0.25	0.43 (0.11–1.67)	0.22	1.96 (0.59–6.50)	0.27	0.95 (0.29–3.07)	0.93
Poor compliance	0.76 (0.38–1.53)	0.76	0.88 (0.45–1.73)	0.70	1.85 (0.71–4.80)	0.21	0.64 (0.31–1.31)	0.22	1.86 (0.94–3.69)	0.08	1.36 (0.69–2.68)	0.37
Model 2: Adjusted (Age and Gender)												
Good compliance						1.00 (reference)						
Medium compliance	0.34 (0.10–1.13)	0.08	1.27 (0.38–4.24)	0.70	3.3 (0.69–15.71)	0.14	0.44 (0.11–1.71)	0.23	2.04 (0.59–7.02)	0.26	0.90 (0.27–2.99)	0.86
Poor compliance	0.78 (0.38–1.53)	0.44	0.93 (0.47–1.85)	0.84	1.87 (0.66–5.27)	0.24	0.66 (0.32–1.35)	0.26	2.08 (1.02–4.25)	0.04*	1.42 (0.71–2.86)	0.32

*p<0.05=significantly correlated

lesser variation in compliance rates and its closer association with mortality. The study used was a prescription-based MPR or MPRp. The study standard compliance threshold of 0.80 included the mean medication possession ratio. The MPRp (the same MPR methods that this study used) showed a statistically significant association between compliance and mortality that varied depending on the compliance threshold used.[28] There were four possible explanations for this poor-adherent group, including omitting to take medications (79.0%), being reckless at times about taking medication (29.3%), stopping medications when feeling better (21.1%), and stopping medications when feeling worse (24.1%). The next possible cause was inadequate education about metabolic syndrome. Higher educational level, knowledge, and attitude score related to metabolic syndrome positively increased compliance to lifestyle changes in patients at high risk of metabolic syndrome.[29,30] All respondents in this study were BPJS patients who received routine treatment, and the respondents were assumed to have no financial issues and had high compliance to redeeming the medicine. However, the results showed the contrary, possibly because most respondents are referred patients from first-level health facilities. Specifically, first-level and tertiary-level health facilities must carry out a referral system regarding the applicable laws and regulations in carrying out health services called a referral system.[31]

The BPJS health system also supports patient compliance. The improvement of BPJS has allowed health facilities to give prescribed drugs for 30 days, which was previously only allowed for seven days, according to medical indications for patients suffering from unstable chronic diseases.[32] However, if the patient does not come to have a routine check-up for more than 30 days, the patient will experience a treatment void until the patient returns to control. Other possible causes are fear of going to the hospital because of the Covid-19 pandemic, self-isolation due to exposure to Covid-19, transportation difficulties, and the unavailability of caretakers to get the medicines.[33] In addition, there is a possibility that the patient switches to undergoing herbal therapy because of fear of drug dependence, and they disbelieve that medicine can prevent them from being very ill.[34] A suitable education can reduce barriers inhibiting therapeutic outcomes by providing proper education by health workers. Appropriate education about lifestyle, the importance of control and treatment, false myths, and the effects of metabolic syndromes can improve patients' therapeutic outcomes and quality of life.[35,36]

Results of this study should help construct a more comprehensive outcome monitoring design for the patients with metabolic syndrome. As these syndromes (hypertension, dyslipidemia, and diabetes) are closely interrelated, any abnormalities in one of them can cause serious health problems someday. It is essential to periodically check for metabolic syndrome, even if the patient has only been diagnosed with one of these diseases, since patients need correct information about their medication to prevent misperceptions about the treatment. Furthermore, health professionals should educate the patients about the diseases and their appropriate treatments. Due to current challenges in secondary healthcare, future research is required to evaluate the patients in primary healthcare.

However, this study has some limitations; among others, the compliance level may be overestimated, as the researcher cannot confirm whether or not those patients take the medication properly. Furthermore, internal factors from the respondents affecting their compliance to treatment, i.e., bad experiences with drug side effects, forgetting to take medication, etc., are not examined in this study. The data obtained are also limited as it is only taken from secondary healthcare, while

most respondents receive their therapy from primary healthcare, which causes a bias in calculating patient compliance using the MPR method. Specifically, the MPR score for those who used a combined therapy becomes biased when high compliance to one medication may compensate for poor compliance to the other medications, leading to an acceptable average for the entire regimen. This measure has shown to be overestimated and underestimated compliance to a combination therapy. Furthermore, we did not provide the pseudo R square value. Thus, we cannot show how good the model is and how much the model can be explained by the factors included in the model.

Conclusions

The three levels of compliance have no significant relationship with blood pressure, HbA1c, and lipid profiles ($p>0.05$). The adjusted data for age and sex on compliance levels result in patients with low compliance, having a 2.08 times higher chance of having high triglyceride levels than patients with high compliance ($p<0.05$). The results show the urgency to determine other factors affecting patient compliance.

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Conflict of Interest

We declare no conflict of interest.

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