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Number of medications is associated with outcomes in the elderly patient with metabolic syndrome

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Abstract

Background The diagnosis of metabolic syndrome indicates a clustering of metabolic imbalances which in sum have been recognized as a major predictor of cardiovascular and all-cause mortality. The aim of this study was to assess the level of under-pharmacy and poly-pharmacy and its prognostic impact in elderly patients with metabolic syndrome. **Methods** Retrospective chart-review at a tertiary medical center, of 324 patients greater than 65 years of age who met the International Diabetes Foundation criteria for metabolic syndrome diagnosis [Body Mass Index (BMI) > 30 kg/m^2, diagnosis of type 2 diabetes, hypertension, and dyslipidemia]. **Results** There were 60 (18.5%) patients in the low (≤ 5) medication burden group, 159 (49.1%) in the medium (> 5 and ≤ 10) medication burden group, and 105 (32.4%) in the high (> 10) medication burden group. At baseline, the groups differed only by systolic blood pressure. At two years follow-up, the medium group had significantly better improvement in high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), HbA1c, and systolic blood pressure compared to the low medication burden group and significantly better improvement in triglycerides, Haemoglobin A1c (HbA1c) and systolic blood pressure compared to the high medication group. Decrease in HDL-C was the only variable associated with strokes. High medication burden predicted hospitalization burden. The number of anti-hypertensives, history of tobacco use, low and high medication burdens and decrease in HDL-C were all associated with death. **Conclusions** Both poly-pharmacy and under-pharmacy are associated with a decreased therapeutic benefit among patients with metabolic syndrome in terms of important laboratory measurements as well as clinical outcomes such as myocardial infarctions, hospitalization, and death.

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Keywords: Cardiovascular outcomes; Elderly patients; Poly-pharmacy; Metabolic syndrome; Diabetes; Mortality predictors

1 Introduction

Metabolic syndrome is a diagnosis indicative of a clustering of metabolic imbalances including hypertension, hyperglycemia, dyslipidemia, and central adiposity.[1–3] It has also become a major predictor of all-cause and cardiovascular mortality.[4–7] Moreover, the prevalence of the metabolic syndrome is correlated with age, with greater than 40% of those persons 60 over years of age having metabolic syndrome.[8] Recently, there has been much debate regarding the importance of a diagnosis of metabolic syndrome as well as the efficacy of its therapeutics in an elderly population.[9,10]

There has also been a great focus placed on the clinical effects of poly-pharmacy in the elderly population. Although the definition of poly-pharmacy varies with ranges from > 5[11] to > 10,[12,13] several studies have shown that negative consequences, such as adverse drug events, noncompliance, and hospitalizations are associated with an increase in number of medications.[14] However, studies continue to disagree about the degree of detrimental impacts of poly-pharmacy.[15–17] The concept of poly-pharmacy becomes even cloudier when discussing the therapy of metabolic syndrome and related diseases where strict adherence to guidelines quickly leads to the use of multiple medications. The high-risk nature of elderly cardiovascular patients and cardiovascular medications makes this specific group of patients especially difficult to treat adequately without incurring the effects of poly-pharmacy.[18] Additionally, a recent study has found that under-pharmacy, defined as lower than expected number of medications based on the number of diseases and indications for treatment with medication, was found in as much as 30%–43% of elderly patients with such high-risk cardiovascular diagnoses.[19] Nonetheless, the specific impact of poly-

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pharmacy on elderly patients with metabolic syndrome remains unknown.

The aim of this study was to assess the level of under-pharmacy and poly-pharmacy and its prognostic impact in elderly patients with metabolic syndrome. Additionally, we wished to identify variables associated with cardiovascular morbidity and mortality in relation to prescription drug burden. Our hypothesis was that under-pharmacy and poly-pharmacy would be associated with worse laboratory and clinical outcomes in older patients with metabolic syndrome.

2 Methods

This study was conducted at Saint Louis University Medical Center, a tertiary care academic center. Clinical and demographic data of older patients were recorded and maintained in an electronic health records (EHR) database. This database was used to identify all patients who were greater than 65 years of age and were seen in any of the internal medicine, geriatric medicine, or endocrine clinics between June 1, 2006 and June 1, 2007 (n = 1,291) (Figure 1). Of these, 378 (37.1%) met the diagnosis of metabolic syndrome as defined by the International Diabetes Foundation [Body Mass Index (BMI) > 30 kg/m^2, diagnosis of type 2 diabetes, hypertension, and dyslipidemia],[20] but 54 patients had incomplete data, leaving 324 patients for the analysis. There were no exclusion criteria to allow for a realistic community-based population.

Baseline data [age, gender, body mass index (BMI), alcohol use, tobacco use, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), trigylcerides, Haemoglobin A1c (HbA1C), systolic and diastolic blood pressures] was collected for these patients from up to one year prior to June 1, 2007. Data points for these variables were taken from the outpatient visit closest to June 1, 2007, except for systolic and diastolic blood pressures which were averaged over the previous year. A patient had to be on a medication for at least two consecutive months for it to be counted; thereafter the average number of medications each patient was on was recorded on a monthly basis and the average was taken for the two years of follow-up (From June 1, 2007 to June 1, 2009). This was used to determine the three groups of analysis: low medication burden (≤ 5 medications), medium medication burden (> 5 and ≤ 10 medications), and high medication burden (> 10 medications). The three groups of analysis were decided a priori based upon previous studies defining poly-pharmacy as being > 5 medications, and severe poly-pharmacy as > 10 medications.[21] The medications list for each patient was determined utilizing all medications profiled in the patient record.

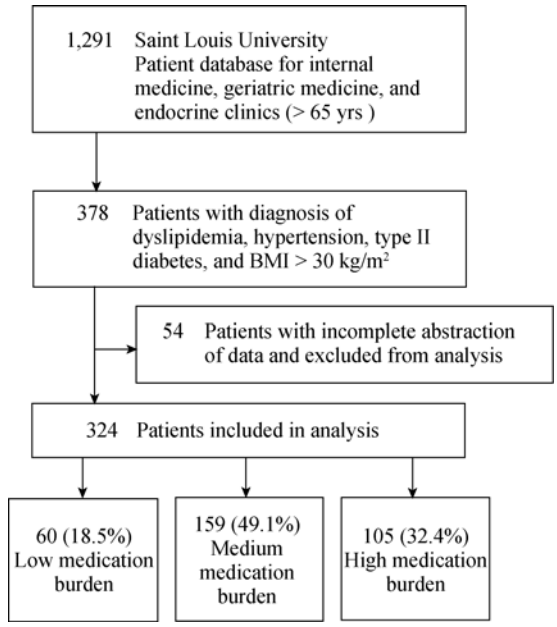

Figure 1. Flowchart of cohort assembly. BMI: body mass index.

Follow-up outcomes of blood pressures and laboratory measurements were taken from the outpatient visit closest to June 1, 2009. Through a thorough review of clinic notes and hospital electronic records, follow-up outcomes of stroke, hospitalization, and myocardial infarction (MI) were counted if they occurred any time during the two years. Follow-up outcome of death was taken from the social security death index between the dates of June 1, 2009 and June 1, 2010.

Approval by the institutional review board was obtained prior to the start of the study. Statistical analyses of the data were performed using SPSS version 17.0 (SPSS Inc., Illinois, USA). Chi square, 2-sided t-tests, and ANOVA where appropriate were used for comparisons between groups. Bivariate analysis and multivariate logistic regression was used to calculate odds ratios associated with the four clinical outcomes of MI, stroke, hospitalizations and death. For each of the clinical outcomes, a multivariate regression analysis was done adjusting for the following variables: age, gender, BMI, history of tobacco use, history of alcohol use, HDL-C, LDL-C, HbA1C, systolic and diastolic blood pressure, low medication group, medium medication group, high medication group, and type of medications. Statistical signify-cance was considered present when $P < 0.05$.

3 Results

There were 60 (18.5%) patients in the low medication burden group, 159 (49.1%) in the medium medication burden group, and 105 (32.4%) in the high medication burden group. A comparison of demographics and baseline lab values between groups is given in Table 1. At baseline, groups differed only in number of medications prescribed, as expected, and systolic blood pressure.

After the two-year follow-up, there were statistically significant differences amongst groups in all mean lab values and in mean systolic blood pressure, but not diastolic blood pressure (Table 2). In general, the medium medication burden group had better mean values for HDL-C, triglycerides, HbA1C and systolic blood pressure while the high medication group had lower mean LDL-C values. Additionally, there were differences amongst groups in clinical outcomes, including hospitalization, MI, and death but no difference for stroke.

Figure 2 depicts a more detailed snapshot using percent changes in lab values and blood pressure from baseline. The medium group had significantly better improvement in HDL-C, LDL-C, HbA1c, and systolic pressure in comparison to the low medication burden group. The medium group also had significantly better improvement in triglycerides, HbA1c and systolic pressure in comparison to the high medication burden group. The medium group showed no significant improvement in diastolic pressure over the other two groups. Overall, the high medication burden group had

Table 1. Demographics and baseline data of the studied population.

Characteristic	Low medication burden group < 5 medications, *n* = 60	Medium medication burden group 5-10 medications, *n* = 159	High medication burden group > 10 medications, *n* = 105	*P*-value
Age	74.1 ± 5.7	74.6 ± 5.6	75.4 ± 6.2	0.788
Gender (Female)	33 (55%)	104 (65%)	68 (65%)	0.336
Body mass index	38.7 ± 6.1	38.4 ± 6.0	40.1 ± 6.7	0.092
History of alcohol use	9 (15%)	25 (16%)	24 (23%)	0.271
History of tobacco use	3 (5%)	21 (13%)	13 (12%)	0.218
Total medications	4.7 ± 0.6	8.7 ± 1.2	13.2 ± 2.0	< 0.001
Aspirin	54 (90%)	156 (98%)	102 (97%)	0.015
Lipid modifying drugs	1.0 ± 0.7	1.9 ± 0.8	2.5 ± 1.0	< 0.001
Diabetes drugs	1.3 ± 0.7	1.8 ± 0.7	2.7 ± 1.1	< 0.001
Anti-hypertensives	1.1 ± 0.7	2.0 ± 0.8	2.3 ± 1.0	< 0.001
Other medications	0.4 ± 0.5	2.1 ± 1.1	4.8 ± 1.6	< 0.001
HDL-C	32 ± 9	34 ± 8	35 ± 8	0.135
LDL-C	121 ± 19	119 ± 19	115 ± 17	0.072
Triglycerides	230 ± 76	223 ± 61	229 ± 64	0.707
HbA1C	7.5 ± 1.0	7.5 ± 1.0	7.6 ± 1.2	0.491
Systolic pressure	136 ± 4	138 ± 6	139 ± 6	0.019
Diastolic pressure	91 ± 7	92 ± 7	93 ± 8	0.267

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.

Table 2. Predictors of clinical outcomes based on multivariate logistic regression analysis.

Primary outcomes	Independent variables	Adjusted odds ratio (95% CI)	*P*-value
Myocardial infarction	Low medication burden	1.096 (1.039–1.148)	0.037
	High medication burden	1.120 (1.085–1.164)	0.024
	Increase in triglycerides	1.007 (1.000–1.014)	0.036
	Increase in HDL-C	0.942 (0.865–0.998)	0.044
	History of tobacco use	3.375 (1.138–4.239)	0.011
	Female gender	0.269 (0.082–0.881)	0.03
Stroke	Increase in HDL-C	0.922 (0.853–0.997)	0.042
Hospitalization	High medication burden	1.837 (1.683–2.467)	0.017
Death	Low medication burden	1.134 (1.101–1.152)	0.041
	High medication burden	1.153 (1.123–1.182)	0.033
	Increase in HDL-C	0.964 (0.926–0.999)	0.046
	Anti-hypertensives	0.504 (0.299–0.850)	0.01
	History of tobacco use	3.834 (1.436–5.149)	0.008

Multivariate logistic regression analysis was done for each clinical outcome separately. The following variables were adjusted for: age (continuous), gender, BMI, history of tobacco use, history of alcohol use, HDL-C, LDL-C, HbA1C, systolic and diastolic blood pressure, low medication group, medium medication group, high medication group, and type of medications. HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.

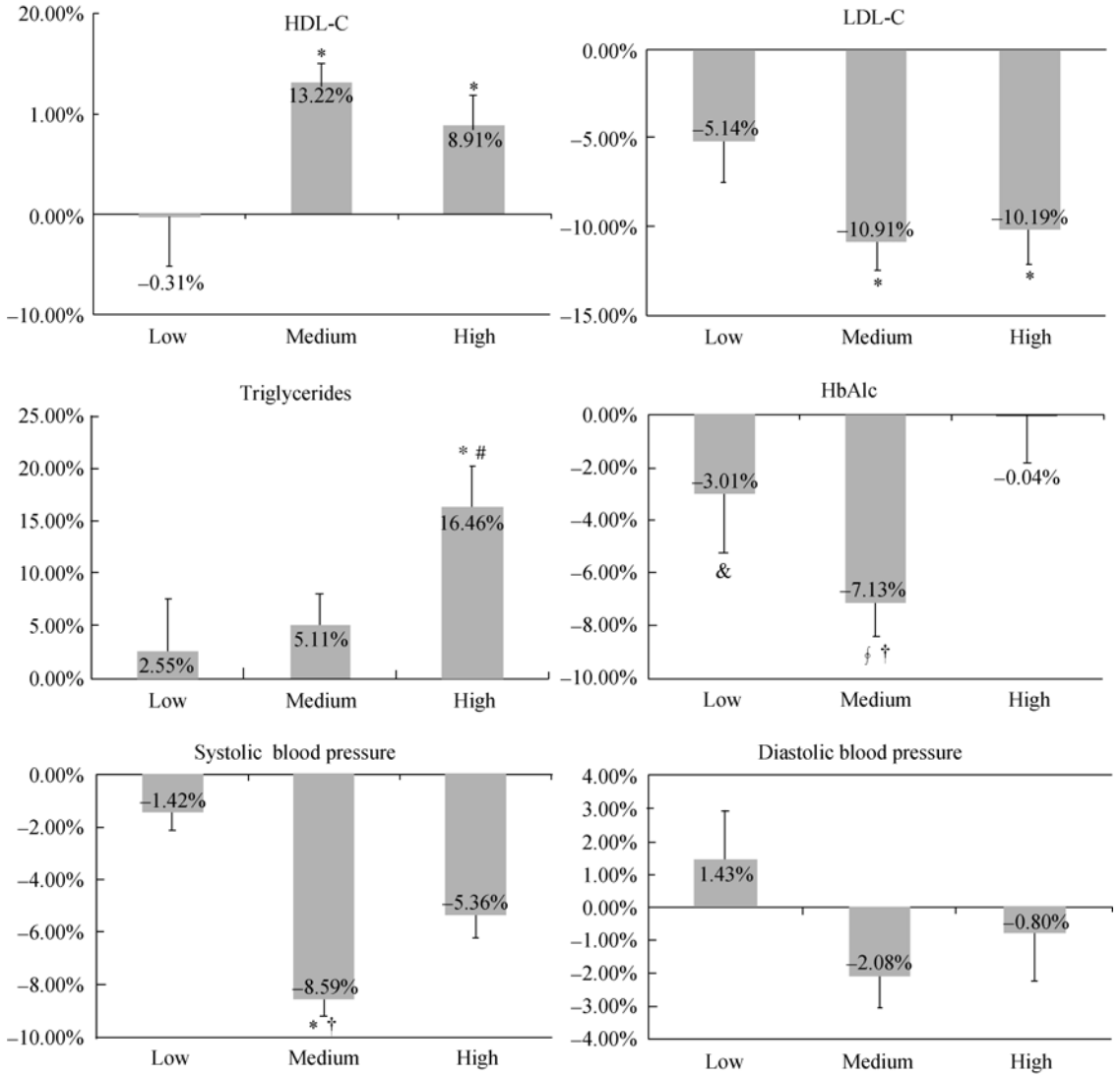

Figure 2. Comparison of percent change of laboratory measurements and blood pressure in two-year follow-up outcomes data between groups. The medium medication burden group had significantly better improvement in high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), HbA1c, and systolic blood pressure in comparison to the low medication burden group. The medium medication burden group also had significantly better improvement in triglycerides, HbA1c and systolic pressure in comparison to the high medication burden group. $^{*}P < 0.001$ compared with the low medication burden group; $^{\#}P < 0.001$ compared with the medium medication burden group; $^{\dagger}P < 0.001$ compared with the high medication burden group; $^{\S}P < 0.01$ compared with the low medication burden group; $^{\&}P < 0.01$ compared with the high medication burden group.

significantly better improvement in HDL-C, LDL-C in comparison to the low medication burden group but the low medication group had better improvement in triglycerides and HbA1c compared to the high medication group.

In terms of clinical outcomes, there were a total of 24 MI (7.4%), 12 stroke (3.7%), 60 hospitalization (18.5%) and 29 death (9.0%). Generally, the medium group had the lowest percent of MI, hospitalization, and death (Figure 3).

In the multivariate regression analysis for MI, the following variables were found to have significantly increased adjusted odds ratios (OR) with having an MI: increased triglycerides [1.007 (1.000–1.014); $P = 0.036$], history of tobacco use [3.375 (1.138–4.239); $P = 0.011$], low medication group [1.096 (1.039–1.148); $P = 0.037$], high medication group [1.120 (1.085–1.164); $P = 0.024$]. Female gender [0.269 (0.082–0.881); $P = 0.030$] and increase in HDL-C [0.942 (0.865–0.998); $P = 0.044$] were protective.

None of the variables was significantly associated with an increased OR of having a stroke but an increase in HDL-C was protective [0.922 (0.853–0.917); $P = 0.042$].

The only variable that was significantly associated with an increase OR of being hospitalized was high medication group [1.837 (1.683–2.467); $P = 0.017$].

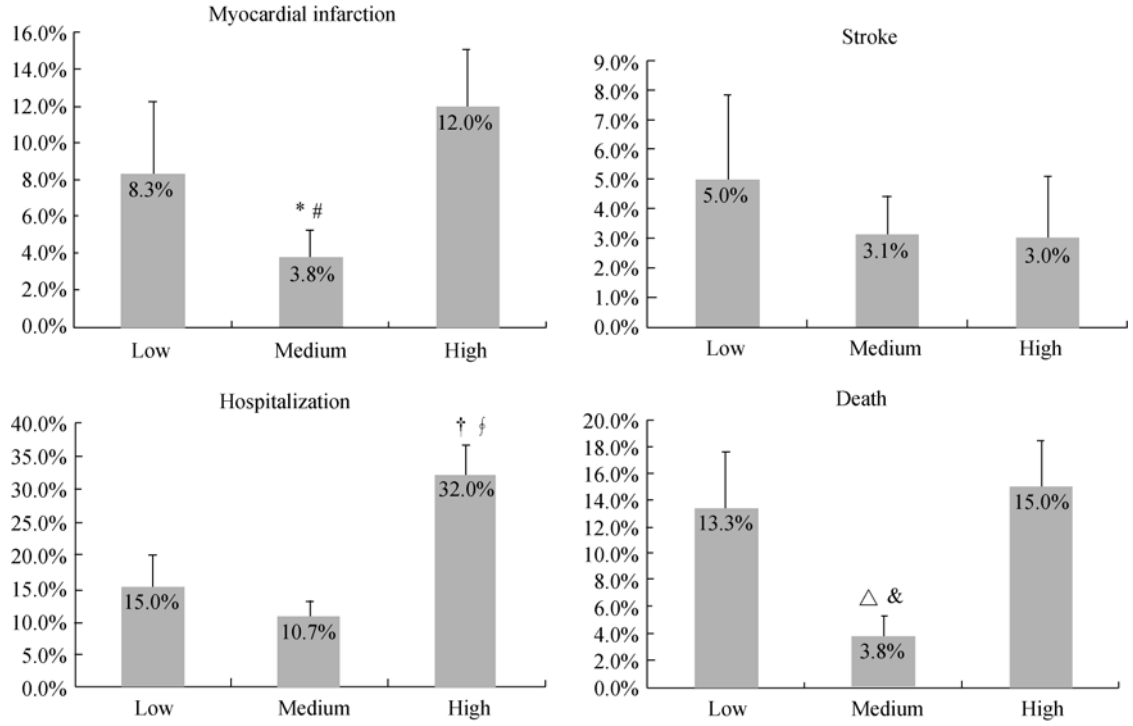

Figure 3. Comparison of percent incidence of clinical outcomes in two-year follow-up outcomes data between groups. There were a total of 24 myocardial infarction (MI) (7.4%), 12 strokes (3.7%), 60 hospitalizations (18.5%) and 29 deaths (9.0%). Generally, the medium medication burden group had the lowest percent of MI, hospitalizations, and death. $^{*}P = 0.072$ compared with the low medication burden group; $^{\#}P = 0.016$ compared with the high medication burden group; $^{\dagger}P = 0.021$ compared with the low medication burden group; $^{\S}P < 0.001$ compared with the medium medication burden group; $^{\triangle}P = 0.051$ compared with the low medication burden group; $^{\&}P = 0.005$ compared with the high medication burden group.

Three variables were significantly associated with an increased OR of death: history of tobacco use [3.834 (1.436–5.149); $P = 0.008$], low medication group [1.134 (1.001–1.152); $P = 0.041$], and high medication group [1.153 (1.123–1.182); $P = 0.033$]. An increase in HDL-C [0.964 (0.926–0.999); $P = 0.046$] and greater number of anti-hypertensives [0.504 (0.299–0.850); $P = 0.010$] were protective.

4 Discussion

Both poly-pharmacy and under-pharmacy are associated with a decreased therapeutic benefit among patients with metabolic syndrome in terms of important laboratory measurements as well as clinical outcomes such as MI, hospitalization, and death. However, while the poly-pharmacy may be explained by high disease burden, the under-pharmacy effect is most concerning, as it seems to be indicative of under-treatment.

Our results are supported by findings from previous studies where poly-pharmacy has been shown to result in greater rates of morbidity and mortality.[4,5] Additionally, our percentages of under-pharmacy (18.5%) and poly-pharmacy (32.4%) are similar to previous cross-sectional studies as is the prevalence of metabolic syndrome in our community-based population.[22] Our study also showed decreased therapeutic benefit of the additional medications in poly-pharmacy. Disturbingly, our study also showed that under-pharmacy is associated with similar negative outcomes.

Our study suggests that the number of medications elderly patients with metabolic syndrome take at any given time should be monitored to ensure that they do not fall out of the range of tolerance. Moreover, while physicians must be aware of the dangers of poly-pharmacy, this study suggests that they cannot be overly conservative in providing the appropriate and necessary medications due to a fear of poly-pharmacy because under-pharmacy is associated with similar or even worse outcomes simply due to under-treatment. These patients thus present clinicians with a challenge to target therapeutic interventions within the narrow range of tolerance.

Recently, Fitzgerald and Bean reported mathematical models questioning the therapeutic validity of single disease guidelines in both elderly patients as well as those with multiple chronic diseases.[23,24] They further reported a decreased cost/benefit ratio with increasing numbers of therapies

and interventions. In light of the results found in our study, it seems as if the elderly patient with multiple comorbidities indicative of metabolic syndrome, does gain benefit from the addition of therapies and such therapy should not be withheld when appropriate. Furthermore, care should be taken to not under-treat a patient with the belief that there is limited clinical benefit as the results of this study show otherwise. Clinical trials should be conducted to examine the validity of guidelines in the elderly patient with metabolic syndrome.

This study has several limitations. It was a retrospective study and thus we were unable to account for all possible confounders. Particularly, the regression models may over-control along the causal pathway, insofar as medication use effects biomarkers which in turn affects clinical outcomes. Additionally, since our data all comes from patient charts, it is possible that there may have been additional morbidity events that were not documented in the patient's charts. Nonetheless, our clinical lab value data adds strength to our clinical outcomes data. Furthermore, the strong similarity between all three groups at baseline further emphasizes the end points. Other limitations of the study include the size of the population and the length of follow-up time.

In conclusion, under-pharmacy is associated with decreased therapeutic benefit of medications as well as increased levels of morbidity and mortality in geriatric patients with metabolic syndrome. It is crucial, however, that the clinician takes special care to not under-treat a patient in the aim of simply avoiding poly-pharmacy or in the belief that there is limited clinical benefit. The total number of medications a geriatric patient with metabolic syndrome is prescribed should be given due attention in any assessment or therapeutic strategy.

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