

Optimal cut-off points for adherence measure among patients with type 2 diabetes in primary care clinics: a retrospective analysis

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Abstract:

Background: Medication adherence measures are often dichotomized to classify patients into those with good or poor adherence using a cut-off value $\geq 80\%$, but this cut-off may not be universal across diseases or medication classes. This study aimed to examine the cut-off value that optimally distinguish good and poor adherence by using the medication possession ratio (MPR) and proportion of days covered (PDC) as adherence measures and glycated hemoglobin (HbA1c) as outcome measure among type 2 diabetes mellitus (T2DM) patients.

Method: We used pharmacy dispensing data of 1461 eligible T2DM patients from public primary care clinics in Malaysia treated with oral antidiabetic drugs between January 2018 and May 2019. Adherence rates were calculated during the period preceding the HbA1c measurement. Adherence cut-off values for the following conditions were compared: adherence measure (MPR *versus* PDC), assessment period (90-day *versus* 180-day), and HbA1c target ($\leq 7.0\%$ *versus* $\leq 8.0\%$).

Results: The optimal adherence cut-offs for MPR and PDC in predicting HbA1c $\leq 7.0\%$ ranged between 86.1% and 98.3% across the two assessment periods. In predicting HbA1c $\leq 8.0\%$, the optimal adherence cut-offs ranged from 86.1% to 92.8%. The cut-off value was notably higher with PDC as the adherence measure, shorter assessment period, and a stricter HbA1c target ($\leq 7.0\%$) as outcome.

Conclusion: We found that optimal adherence cut-off appeared to be slightly higher than the conventional value of 80%. The adherence thresholds may vary depending on the length of assessment period and outcome definition but a reasonably wise cut-off to distinguish good *versus* poor medication adherence to be clinically meaningful should be at 90%.

Keywords: adherence measure, diabetes, glycated hemoglobin, medication adherence, optimal cut-off

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Introduction

Diabetes imposes a huge health and economic burden on patients and national healthcare systems worldwide. The number of adults living with diabetes is projected to rise from 463 million in 2019 to 700 million by 2045,¹ with a more rapid increase in the low- and middle-income countries, where about 79% of adults with

diabetes are currently located.^{1,2} Type 2 diabetes mellitus (T2DM) constitutes the majority of the diabetes cases and often requires pharmacologic therapy to keep blood sugar under control. Uncontrolled T2DM leads to an array of complications including coronary artery disease, stroke, nephropathy, neuropathy, retinopathy, and others.³

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Although a wide array of treatment options is currently available to manage T2DM, patient adherence to treatment can be less than optimal. Adherence rates to oral antidiabetic drugs (OADs), the first-line treatment of T2DM, has been reported to range from 36% to 93%.⁴ Poor adherence in T2DM is associated with poorer glycemic control, which leads to greater risk of diabetes-related complications, higher mortality rate, and higher health care costs.^{5,6} Given the high prevalence and health care cost associated with T2DM, improving medication adherence is crucial in improving health outcomes.

While numerous methods have been developed to measure medication adherence, the use of medication records to indirectly estimate adherence has gained prominence due to increasing availability of electronic medication records and administrative data.⁷ Two of the most widely used adherence measures that could be generated using medication records are the medication possession ratio (MPR) and proportion of days covered (PDC), which estimates the proportion of the time a patient has medication available.^{7,8} To define whether a patient is adherent to their medication using these measures, a threshold of $\geq 80\%$ is conventionally used regardless of the clinical contexts;⁹ however, the threshold may differ across medication therapeutic classes or disease condition.^{10,11} While there have been studies to estimate disease-specific adherence cut-offs, two major gaps remain. First, existing studies used healthcare utilization, for example, hospitalization, as the outcome marker¹⁰⁻¹² rather than clinical outcomes that reflect disease control. Clinical outcomes that reflect disease control, such as glycated hemoglobin (HbA1c) level for T2DM, would more accurately reflect medication adherence for patients with T2DM. Second, it is still unknown whether using outcomes with different stringency and for a different assessment period will give rise to different adherence cut-offs.

Our study addresses the gaps by examining optimal adherence cut-offs for MPR and PDC among patients with T2DM taking OAD using HbA1c as the gold standard. We further explored whether using different stringency of HbA1c values ($\leq 7.0\%$ versus $\leq 8.0\%$) from different assessment periods would yield different optimal cut-offs. Our findings will inform a more prudent use of MPR and PDC values in identifying patients with low medication adherence using readily available data such as medication dispensing records.

Methods

Study design and data source

This study was a retrospective analysis of data on patients with a recorded diagnosis of T2DM and prescribed with OADs identified from two sources:

1. T2DM patients were identified from a larger study titled “Evaluation of Enhanced Primary Health Care (EnPHC) interventions in public health clinics” (EnPHC-Eva: Facility). Briefly, the EnPHC-Eva: Facility was a quasi-experimental controlled study conducted between November 2016 and June 2019 which aimed to determine the effectiveness of a multifaceted intervention package at selected public primary care clinics in Malaysia. Patients were selected through systematic random sampling and their data were extracted from medical records in the clinics. The extracted data included demographics (age, gender, ethnicity), risk factors (comorbidities, duration of disease), and laboratory investigation (HbA1c).¹³
2. Medication data were obtained from the Pharmacy Information System (PhIS), an electronic medication management system implemented in the public primary care clinics. It contains medication order details [name of drug(s), dosage, frequency, duration] and records of medication dispensed to individual patients at the clinics.

For the present study, we linked data of patients in the EnPHC-Eva: Facility to the PhIS to identify matching dispensing records for OADs. All patient data were anonymized prior to analysis and this study received the approval of Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-17-267-34768).

Setting

Each public clinic in Malaysia has its own outpatient pharmacy that maintains records of prescription medicine usage. If a medicine is prescribed to a patient during the course of a doctor’s consultation, the medicine will be supplied by the clinic pharmacy. The medication order of a particular drug is considered valid for the duration prescribed and the maximum period of each

supply of any medication is limited to 1 month. Patients visit the clinic pharmacy directly for any prescription refills for up to the specified duration that will generally last until their next scheduled appointment with the doctor. For late refills, medication can still be dispensed if the medication order is still valid.

Study population

Patients with a recorded diagnosis of T2DM and treated with OADs between 1 January 2018 and 31 May 2019 were identified. Patients were included in the current study if they had at least two successive prescription fills for any of the following OADs: sulfonylureas, biguanides, thiazolidinediones, meglitinide analogues, glucosidase inhibitor, oral dipeptidyl peptidase-4 inhibitors, or combination therapy. Patients were required to have at least one HbA1c measurement during the study period. We further excluded patients who had (i) one or more prescriptions for insulin, (ii) no prescription for OAD prior to HbA1c measurement date.

Medication adherence measures

Adherence to OADs was calculated over (i) a 90-day period and (ii) a 180-day period preceding the latest HbA1c measurement available. Adherence was measured using MPR and PDC over a fixed time interval (90 days and 180 days) according to the following formula:

$$\text{MPR} = \frac{\text{Number of days' supply}}{\text{Assessment period}}$$

$$\text{PDC} = \frac{\text{Number of days "covered"}}{\text{Assessment period}}$$

MPR was defined as the sum of medicine days' supply divided by days of assessment period. MPR counts excess supply of a medication; hence, the MPR value may exceed 1.0 (100%) when patients have an early medication refill or oversupply of medications.^{14,15}

PDC was defined as the number of days covered with medication divided by days of assessment period. The formula is similar to MPR but PDC considers the days that are "covered" instead of adding the days supplied in a given period. If supply for the same medication overlapped, the

supply start date was adjusted to the day after the previous days' supply ended. PDC counts each day covered by a target medication only once; therefore, its maximum value is 1.0 (100%).^{15,16}

All OADs were considered interchangeable. For patients who are treated with more than one medication (polytherapy), both MPR and PDC were calculated considering adherence to any OADs within the assessment period.

Outcome measures

HbA1c measurement was used as the objective measure for glycemic control. For patients with multiple measurements of HbA1c during the study period, only the latest HbA1c measurement was used. In the present study, two HbA1c target values were used to define good glycemic control:

- (a) HbA1c \leq 7.0%;
- (b) HbA1c \leq 8.0%.

The values were selected based on guidelines recommendation of HbA1c target ranges for the general population and those with comorbid conditions.^{17,18}

Covariates

Data on baseline demographic characteristics and clinical characteristics were extracted and included in analysis. Demographic included age, gender, and ethnicity. Risk factors included obesity, comorbidity, and disease duration. Covariates were selected based on background clinical knowledge and data availability.^{19,20}

Statistical analysis

Descriptive statistics were used to summarize findings with mean and standard deviation (SD) values reported for continuous variables and frequencies and percentages for categorical variables. Patients were grouped into quartiles based on MPR and PDC to determine HbA1c at various level of adherence. For each adherence measure, the optimal adherence cut-off value was calculated using Liu's method.²¹ Based on Liu's method, the optimal cut-off value corresponds to the point associated with the maximum product of sensitivity and specificity. To estimate the predictive performance of the adherence measures at the optimal cut-off values, C-statistics were

reported. Associations of the adherence measures with HbA1c were determined with (i) univariate logistic regression and (ii) multiple logistic regression including all the covariates, taking into account clustering within clinics. Patients were clustered within clinics for analysis to account for hierarchical structure of the data where patients (level 1) were nested within clinics (level 2).²² Odds ratio (OR) and confidence interval (CI) were reported to determine whether good adherence based on the optimal cut-off values predicts good glycemic control. Cut-off values with C-statistic values closest to 1 and OR farthest from 1.0 were considered as the most ideal.^{21,23} Statistical significance was set at $p < 0.05$. All data were analyzed using Stata Version 15 (2017, Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX, USA).

Results

A total of 1461 patients met the inclusion and exclusion criteria and were included in analysis. These

patients had a mean age of 61.1 years (SD 10.6 years) with a range of 30–92 years (Table 1). The majority of them were women (64.1%), of Malay ethnicity (70.6%), and almost all had concomitant hypertension and hyperlipidemia. With a mean duration of diabetes of 6.6 years (SD 5.0), as many as 53.5% of them were on polytherapy with two or more OADs. The mean HbA1c was 7.7% (SD 1.8; median 7.2%; interquartile range 6.4, 8.6).

Overall, the PDC adherence estimates (mean 0.83) were similar to the equivalent MPR (mean 0.83; mean 0.84) estimates when calculated for the 90-day and 180-day assessment periods (Table 1). Medication oversupply (MPR > 1.0) was seen occasionally and it was more frequent during the 90-day interval (19.5%) compared with the 180-day interval (16.8%). Analysis was repeated to determine adherence estimates by antidiabetic drug classes. No important difference was observed across subgroups and the estimates are similar to the composite measures of adherence to any OADs (results not reported).

Table 1. Patient demographic data (N = 1461).

Characteristics	n (%) or mean (SD)
Age, years, mean (SD)	61.1 [10.6]
Gender, n (%)	
Male	525 [35.9]
Female	936 [64.1]
Ethnicity, n (%)	
Malay	1031 [70.6]
Chinese	281 [19.2]
Indian	137 [9.4]
Others	12 [0.8]
Location of primary care setting, n (%)	
Rural	634 [43.4]
Urban	827 [56.6]
BMI, kg/m ² , mean (SD), N = 1419*	28.1 [5.5]
Hypertension, n (%), N = 1302*	
Yes	1299 [99.8]
No	3 [0.2]

(Continued)

Table 1. (Continued)

Characteristics	<i>n</i> (%) or mean (SD)
Hyperlipidemia, <i>n</i> (%), <i>N</i> = 1135*	
Yes	1127 (99.3)
No	8 (0.7)
Duration of diabetes, years, mean (SD)	6.6 (5.0)
Duration of hypertension, years, mean (SD), <i>N</i> = 1302*	7.8 (6.4)
Duration of hyperlipidaemia, years, mean (SD), <i>N</i> = 1135*	4.5 (4.1)
Oral antidiabetic drug polytherapy, <i>n</i> (%)	
Yes	772 (53.5)
No	679 (46.5)
HbA1c, %, mean (SD)	7.7 (1.8)
Adherence measure	
90-day period	
MPR, mean (SD)	0.83 (0.26)
PDC, mean (SD)	0.83 (0.23)
180-day period	
MPR, mean (SD)	0.84 (0.22)
PDC, mean (SD)	0.83 (0.20)
MPR > 1.0	
90-day	285 (19.5)
180-day	245 (16.8)
*Denominator not equal to 1461 due to missing data. BMI, body mass index; HbA1c, glycated hemoglobin; MPR, medication possession ratio; PDC, proportion of days covered; SD, standard deviation.	

Table 2 describes HbA1c at various level of adherence. Patients in the lowest adherence quartile (<70%) had highest HbA1c and an inverse relationship was observed where HbA1c values appeared to be lower with increasing level of adherence. This observation was consistent for both 90-day and 180-day assessment periods.

Table 3 shows the computed optimal cut-off values of adherence in predicting glycemic control and its corresponding sensitivity and specificity. The values are presented for MPR and PDC by the different assessment periods (90-day and 180-day) and HbA1c upper limits ($\leq 7.0\%$ and

$\leq 8.0\%$). The optimal adherence cut-off values ranged from 0.86 to 0.95 for MPR and from 0.89 to 0.98 for PDC across these factors, in which a value of 1 indicates perfect adherence. The C-statistics and OR estimates for the univariable and multivariable logistic regression models using the computed adherence cut-off values in predicting HbA1c are presented in Table 3. The univariate C-statistics ranged from 0.53 to 0.56 and the C-statistics from multivariable models was higher as it ranged between 0.75 and 0.76. From the univariable analysis, adherence measured by MPR and PDC using the optimal cut-off values generated was independently associated with

Table 2. HbA1c values by the level of adherence for 90-day and 180-day assessment periods.

	Adherence level	HbA1c, %		
		n	Mean ± SD	Median (IQR)
90-day				
MPR	<70%	361	8.0 ± 2.0	7.4 (6.5, 8.9)
	70–<90%	309	7.8 ± 1.7	7.4 (6.6, 8.9)
	90–<100%	376	7.5 ± 1.7	7.1 (6.3, 8.4)
	≥100%	415	7.5 ± 1.7	7.0 (6.3, 8.4)
PDC	<70%	345	7.9 ± 2.0	7.4 (6.5, 9.0)
	70–<90%	281	7.8 ± 1.8	7.4 (6.5, 8.9)
	90–<100%	308	7.6 ± 1.8	7.2 (6.3, 8.4)
	≥100%	527	7.5 ± 1.6	7.0 (6.3, 8.4)
180-day				
MPR	<70%	334	8.1 ± 2.2	7.5 (6.5, 9.1)
	70–<90%	373	7.7 ± 1.6	7.3 (6.5, 8.5)
	90–<100%	422	7.6 ± 1.7	7.0 (6.3, 8.4)
	≥100%	332	7.4 ± 1.5	7.0 (6.3, 8.4)
PDC	<70%	326	8.1 ± 2.1	7.5 (6.5, 9.1)
	70–<90%	355	7.7 ± 1.6	7.3 (6.5, 8.7)
	90–<100%	452	7.6 ± 1.7	7.1 (6.3, 8.5)
	≥100%	328	7.4 ± 1.6	6.9 (6.2, 8.2)

IQR, interquartile range; MPR, medication possession ratio; PDC, proportion of days covered; SD, standard deviation.

higher odds of achieving good glycemic control (HbA1c ≤7.0%) across the two different assessment periods. However, when a higher (less strict) HbA1c value was used as the outcome (≤8.0%), there was no significant outcome association observed for the 180-day adherence estimates. In multivariable logistic regression analyses, good adherence (based on the optimal cut-off generated) was associated with increased odds of achieving HbA1c target ≤7.0%. However, the association was not statistically significant when HbA1c target was set at ≤8.0%, except for 90-day MPR (Table 3). Comparing all MPR estimates, the strength of association was stronger for 90-day adherence [adjusted OR (aOR) 1.89; 95%

CI 1.42, 2.33] than for 180-day adherence (aOR 1.61; 95% CI 1.23, 2.10). However, the association for PDC-measured adherence was similar for 90-day and 180-day adherence (aOR 1.75 versus 1.76).

Discussion

In this study, we derived the adherence thresholds to OADs that are linked to HbA1c level among T2DM patients using medication dispensing data. We compared the optimal cut-off for two objective measures of medication adherence (MPR versus PDC) at different assessment periods (90-day versus 180-day), using different

Table 3. Logistic regression analysis of cut -off points for adherence measures at different assessment periods in predicting glycemic control among type 2 diabetes mellitus patients.

HbA1c upper limit, %	Assessment period	Adherence measure	Optimal cut-off	Sensitivity	Specificity	Univariable analysis			Multivariable analysis*			
						C-statistic	OR (95% CI)	p-value	C-statistic	aOR (95% CI)	p-value	
7.0	90-day	MPR	0.950	0.506	0.610	0.558	1.60 (1.32, 1.93)	<0.001	0.750	1.89 (1.42, 2.33)	<0.001	
		PDC	0.983	0.462	0.646	0.554	1.56 (1.31, 1.87)	<0.001	0.750	1.75 (1.34, 2.28)	<0.001	
	180-day	MPR	0.861	0.635	0.451	0.543	1.43 (1.10, 1.85)	0.007	0.746	1.61 (1.23, 2.10)	<0.001	
		PDC	0.897	0.603	0.504	0.554	1.54 (1.18, 2.02)	0.002	0.750	1.76 (1.34, 2.30)	<0.001	
	8.0	90-day	MPR	0.861	0.627	0.464	0.546	1.46 (1.13, 1.88)	0.004	0.760	1.46 (1.04, 2.07)	0.030
			PDC	0.928	0.561	0.517	0.539	1.36 (1.04, 1.77)	0.021	0.759	1.24 (1.05, 1.71)	0.023
180-day	MPR	MPR	0.886	0.562	0.504	0.533	1.30 (0.99, 1.71)	0.056	0.756	1.26 (0.95, 1.66)	0.108	
		PDC	0.897	0.570	0.504	0.537	1.35 (1.00, 1.81)	0.05	0.757	1.30 (0.93, 1.81)	0.121	

*Adjusted for covariates age (years), gender (male/female), ethnicity (Malay/Chinese/Indian/others), hypertension (no/yes), hyperlipidemia (no/yes), body mass index, the location of primary care clinic (rural/urban), duration of diabetes (years), and polytherapy (no/yes).

aOR, adjusted odds ratio; CI, confidence interval; HbA1c, glycated hemoglobin; MPR, medication possession ratio; OR, odds ratio; PDC, proportion of days covered.

stringency of HbA1c target ($\leq 7.0\%$ versus $\leq 8.0\%$). We found that the optimal adherence cut-off most discriminative of good glycemic control ranged from 86% to 98%. When PDC was used as the adherence measure, the threshold values were higher than those obtained using MPR, albeit marginally. The adherence cut-offs were also dependent on the length of assessment period and HbA1c target used to define outcome. Our findings thus provide an empirical basis for selecting suitable thresholds to define adherence to medications in various circumstances.

Our results suggest that in predicting good glycemic control, the optimal cut-off value to group patients as adherent is higher than the commonly cited threshold of 80%. This finding was in line with a previous study in diabetes patients that had reported adherence thresholds $>80\%$ for reduction of hospitalization risk.¹⁰ Similarly, Lo-Ciganic and colleagues demonstrated that the adherence cut-off varies between 46% and 94% according to an individual's health status and complexity of treatment.¹¹ Although different outcome measure, study design, and population were used, these studies highlighted that the use of a historical threshold of 80% may not be adequate to assess the relationship between adherence to medication and attainment of the desired therapeutic response.

HbA1c is considered the gold standard to gauge glycemic control and monitor treatment effect in individuals with T2DM; therefore, it serves as an apt clinical endpoint to link with medication adherence. In the present study, we used two HbA1c upper limits to define glycemic control and compared the derived adherence thresholds. Our results indicate that for a more stringent HbA1c target, a relatively higher adherence threshold is needed to identify good and poor adherers. This was expected since many published studies have documented that higher adherence amplified the treatment effect and led to better glycemic control.^{24,25} We observed that the adherence thresholds varied according to the length of the assessment period in which a lower threshold to adherence could be considered when adherence is measured over a longer period. This was in line with prior studies that demonstrated the dependence of adherence on the length of assessment period.^{26,27} Taken together, these data suggest the need to orientate adherence threshold to time frame for estimating adherence as well as targeted clinical endpoint.

In this study, we used both MPR and PDC measures to strengthen the validity and reliability of the adherence estimates. These two measures are widely used in research and practice as they provide a robust estimate when calculating adherence from administrative data.^{16,28} We observed that adherence thresholds computed using MPR and PDC in the present study were fairly consistent. This suggests a stability of the optimal adherence threshold to adherence measure. Our results showed that the MPR and PDC values above the derived adherence thresholds were associated with higher odds of achieving targeted HbA1c values. For all derived adherence thresholds, the C-statistic values of around 0.6 were lower than expected (considering that a C-statistic of 0.5 represents random concordance while a value above 0.7 indicates a model with good predictive ability); however, the findings are comparable to those reported in a previous study which validate adherence threshold in a similar manner.¹⁰ Our findings indicate that adherence to medication, by itself, is a good predictor in achieving the targeted glycemic control. Nevertheless, glycemic status is known to be correlated with other elements, including lifestyle behaviors and diet, which are less likely to be adhered to as compared with medications.^{29,30} The relative contribution of these factors to disparities in adherence and the extent to which they are modifiable through health system intervention should be taken into consideration when addressing the issue of medication adherence.

The present study has several limitations to note. First, prescription filling may not reflect the actual consumption of medications by patients. Hence, the using of medication dispensing data may overestimate adherence to treatment for some patients. Second, we have more women than men in our data. Third, we measured adherence among patients on OADs. This may limit the generalizability as the findings may not be applicable to patients who are also on insulin therapy. Next, we measured adherence using objective measures based on medication refill data and we do not have data on self-report measure of adherence for comparison and a more detailed assessment. Last, only one HbA1c measurement was used for analysis and we were not able to control for baseline HbA1c for assessment of relationship with medication adherence. As such, the analysis might not reflect the actual duration of the optimal glucose control in patients. Nevertheless, we

used assessment periods that correspond to regular HbA1c monitoring interval of 3 to 6 months for measurement of the effect of medication adherence on HbA1c level. In this study, adherence was assessed using the MPR and PDC method, which is an objective measure that is reliable and depends on medication refill history. Moreover, we examined possible variation in adherence thresholds at different assessment periods and stringency of clinical outcome. By tying adherence cut-offs with a clinically relevant outcome, healthcare providers may be able to use adherence measures to target patients who would obtain clinical benefit when reaching a certain level of adherence.

Conclusion

In this study, we found that the optimal cut-off adherence values with MPR and PDC as adherence measures ranged between 86.1% and 98.3% in predicting HbA1c $\leq 7.0\%$ and ranged from 86.1% to 92.8% for HbA1c $\leq 8.0\%$. The adherence thresholds may vary depending on the length of assessment period and outcome definition, but a reasonably wise cut-off to distinguish good *versus* poor medication adherence to be clinically meaningful should be at 90%. Additionally, these adherence cut-offs can be used as screening tools to identify patients who are at higher risk of poor glycemic control and expedite medical making decision, especially in the leverage of target interventions that would clinically benefit patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics and informed consent

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia and complies with the Declaration of Helsinki. This included a waiver of informed consent. All medical records were reviewed retrospectively and data was anonymized before use in analysis.

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