Optimal Threshold Level of Fasting Blood Sugar and HbA1c to Detect Pre-Diabetes and Diabetes Based on 75 g OGTT Among At-Risk Filipino Subjects

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Background. The prevalence of pre-diabetes and diabetes mellitus type 2 (DMT2) among Filipinos exceeds 20%. Progressive loss of insulin sensitivity can occur with fasting blood sugar (FBS) ≥90 mg/dL. Studies among Asians with pre-diabetes show a higher prevalence of DMT2 diagnosed by 75 g oral glucose tolerance test (OGTT), the gold standard, which remains underutilized.

Objective. This prospective, observational, single-center study included adult patients admitted between January 2022 to August 2022 who were diagnosed with ARF type 1 and/or 2 and who were hooked to NIV as oxygen supplementation. Parameters of HACOR were collected and analyzed prior to initiation and 1 hour after hooking to NIV.

Methodology. This cross-sectional analysis was conducted in the outpatient departments of two hospitals in Cebu City. Ninety-five adult Filipino patients with FBS <126 mg/dL but with risk factors for DMT2 had HbA1c and 75 g OGTT taken. Test performance and receiver operating characteristic curves were computed for the optimal FBS and HbA1c threshold.

Results. Pre-diabetes or DMT2 was prevalent among 66% of participants. Using 75 g OGTT, 23% reached levels indicative of DMT2 but had normal or impaired fasting glucose, while this was found in 20% with pre-diabetic glycated hemoglobin (HbA1c) levels. HbA1c was more accurate than FBS.

Conclusion. Performing 75 g OGTT for high-risk Filipinos with FBS ≥94.2 mg/dL or HbA1c ≥5.6% is highly predictive of a change in glucose tolerance status to pre-diabetes, while an FBS ≥106 mg/dL or HbA1c ≥5.8% is predictive of DMT2. Lower cut-off levels promote earlier detection and intervention. Hypertension and age ≥35 years old were significantly associated with such conditions.

Keywords. *Diabetes mellitus, Prediabetic state, Glycated hemoglobin, Glucose tolerance test, Asian*

Introduction

One out of every five Filipinos could potentially have pre-diabetes or diabetes mellitus. The prevalence of diabetes mellitus type 2 (DMT2) in the Philippines reaches 20% after including pre-diabetes, which has a prevalence of 10.6%.[1] As of 2021, the country has a total of 4.3 million cases of diabetes, with deaths due to diabetes ranking fourth among the overall causes of mortality.[2,3]

In a study by Yoshida et al., patients who underwent endotracheal intubation had a significantly lower arterial

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pH. The study found that a respiratory rate of more than 25 breaths per minute after 1 hour of NIV, together with lower pH, were independent factors associated with the need for endotracheal intubation.[4]

Insulin resistance progressively worsens over time, in parallel with continuous decline in β-cell dysfunction.[4] With increasing fasting blood sugar (FBS) levels in the non-diabetic range, β-cell function also gradually diminishes; thus, individuals with normal FBS levels reaching 94 mg/dL (5.2 mmol/L), i.e., below the impaired fasting glucose (IFG) threshold of 100 mg/dL, still remain at an increased risk for developing diabetes.[4] Multiple studies have shown that insulin sensitivity was found to be 17% lower within the upper normal FPG range ≥90 mg/dL compared with FPG <90 mg/dL.[5]

FBS remains a useful tool for general screening due to its wide availability, reproducibility and lower cost. It has a high specificity of >90% but with a lower sensitivity ranging from 45% to 60%.[1] The 75 g oral glucose tolerance test (OGTT) is regarded as the gold standard for the diagnosis of DMT2 and pre-diabetes. Because it detects altered post-prandial metabolism, this 2-hour post-loading level would lead to greater detection at a sensitivity of 90% to 93% and specificity of 100%. Nevertheless, 75 g OGTT is not commonly used in clinical practice because it is time consuming and more costly to administer.[1] Patients with pre-diabetes ideally need a confirmatory 75 g OGTT.[6]

A reference study on Thai individuals with IFG showed that an additional 28.5% were diagnosed to have DMT2 using the 75 g OGTT. In addition, only 14.28% of those subjects were also diagnosed with DMT2 using the HbA1c criteria.[7] These results suggest that using the second-hour post-loading glucose (2h PG) level after OGTT was more effective than HbA1c. The discordance between the HbA1c and 75 g OGTT were similar to previous findings for Asian populations.[7-9] This study concluded that the optimal cut-off of FBS and HbA1c for IFG individuals in the prediction of DMT2 was ≥106 mg/dL or 6.0%, respectively; 75 g OGTT is recommended if such levels were reached to screen for DMT2.[7] Prior studies have also reported that Asians with IFG had a higher prevalence of DMT2 diagnosed by OGTT than Caucasians.[10,11] An increase in 2h PG levels after 75 g OGTT occurs before any increase in fasting plasma glucose (FPG) levels become apparent in older or Asian patients with pre-diabetes.[11] As glucose metabolism varies among ethnicities, it remains uncertain whether the recommended HbA1c and FBS cut-off levels in Asian studies can be applied to Filipino populations.

The American Diabetes Association (ADA) 2022 guidelines consider 75 g OGTT as an alternative to FBS and HbA1c in asymptomatic individuals, or as a confirmatory step in those with FBS 100 to 125 mg/dL (5.6 to 6.9 mmol/L).[6] The importance of detecting elevated 2h PG level is based on the DECODE study, which showed the strong correlation of the second-hour post-loading hyperglycemia in diabetic patients with all-cause mortality, cardiovascular disease, and stroke mortality.[12,13]

Primarily, this study promotes earlier and more intensive detection of pre-diabetes and DMT2 for at-risk Filipinos, with our country belonging to Southeast Asia which has the second-highest number of cases of diabetes among all International Diabetes Federation regions.[3]

This study aimed to determine the level of FBS and HbA1c highly predictive of pre-diabetes and DM Type 2 based on abnormal 75 g OGTT levels among high-risk Filipinos.

Specifically, its objectives are (1) to describe the demographics of the participants with risk factors for DMT2; (2) to determine the percentage of patients with normal FBS levels but with impaired glucose tolerance (IGT) or DMT2 based on 75 g OGTT threshold levels; (3) to determine the percentage of patients with normal HbA1c levels but with IGT or DMT2 based on 75 g OGTT levels; and (4) to determine the patient risk factors highly predictive of pre-diabetes and DMT2

Methodology

Study Design

This study was a cross-sectional analysis conducted at the outpatient departments of two hospitals in Cebu City, Philippines: Chong Hua Hospital and Cebu City Medical Center.

Participant Criteria

Adult patients ≥18 years old who came in for consult or follow-up under the Internal Medicine Outpatient Department of the two hospitals were screened daily. The participant should be of Filipino descent and previously undiagnosed with DMT2 (Figure 1). The criteria for inclusion of a high-risk patient is based on the ADA 2022 guidelines for screening of prediabetes or DMT2 in asymptomatic adults, specifically with at least one of the following:

1. Adults with overweight or obesity (body mass index [BMI] >23 kg/m2 in Asian category), who have one or more of the following risk factors: first-degree relative with DMT2; history of cerebrovascular disease; hypertension (≥140/90 mmHg or on maintenance therapy for hypertension); HDL cholesterol level <35 mg/dL or a triglyceride level >250 mg/dL or on maintenance therapy for dyslipidemia; women with polycystic ovary syndrome (PCOS); physical inactivity (defined as less than 150 minutes of moderate-intensity activity per week or equivalent based on the WHO definition)
2. Women who were diagnosed previously with gestational diabetes mellitus (GDM)
3. All adults ≥35 years old
4. Patients with pre-diabetes (HbA1C 5.7–6.4% or IFG 100–125 mg/dL or impaired glucose tolerance with 2-hour PG during 75 g OGTT of 140–199 mg/dL)

Exclusion criteria include any of the following, namely, subjects with known DMT2 at time of first contact (FBS ≥126 mg/dL, HbA1C ≥6.5%, 2h PG during 75 g OGTT ≥200 mg/dL), currently pregnant, subjects with liver cirrhosis, ongoing glucocorticoid therapy, currently on any hypoglycemic agent (including SGLT2-inhibitors, GLP-1 agonists), concomitant endocrinopathies that also cause hyperglycemia (Cushing's syndrome, acromegaly) and known defects of the exocrine pancreas (pancreatitis, cystic fibrosis).

Study Procedure

Basic demographics, risk factors, and BMI were collected via verbal interview and physical examination from the qualified patients. For screening, if without FBS for the last 3 months, subjects were instructed to have FBS sample taken. Fasting is defined as no caloric intake for 8 hours before the test. Those with FBS <126 mg/dL proceeded to have blood samples taken for HbA1c and 75 g OGTT. For HbA1c, National Glycohemoglobin Standardization Program–certified methods were used. Based on the standard protocol from the World Health Organization (WHO), 75 g OGTT was performed in the morning after an overnight fast of 8–14 hours. Each subject was asked to drink a 75 g glucose solution in 250 mL of water or a prepared glucose tolerance beverage (e.g., Trutol 75; Thermo Fisher Scientific) given orally to be consumed within 5 minutes, then post-loading glucose was extracted after 2 hours. From these results, the outcome variables were the glycemic status of the participants, in accordance with the ADA 2022 criteria:

1. Normal group – FBS <100 mg/dL, HbA1c <5.7%, and 2h PG after 75 g OGTT <140 mg/dL
2. Pre-diabetes – any of the following subtypes:
    2.1. IFG: FBS 100–125 mg/dL, HbA1c <5.7%, and 2h PG after 75 g OGTT <140 mg/dL
    2.2. IGT: FBS <100 mg/dL, HbA1c <5.7%, and 2h PG after 75 g OGTT 140–199 mg/dL
    2.3. Isolated elevated HbA1c: FBS <100 mg/dL, HbA1c ≥5.7%, and 2h PG after 75 g OGTT <140 mg/dL
    2.4. IFG and elevated HbA1c: FBS 100–125 mg/dL, HbA1c ≥5.7%, and 2h PG after 75 g OGTT <140 mg/dL
    2.5. IGT and elevated HbA1c: FBS <100 mg/dL, HbA1c ≥5.7%, and 2h PG after 75 g OGTT ≥140 mg/dL
    2.6. Combined IFG and IGT: FBS 100–125 mg/dL and 2h PG after 75 g OGTT 140–199 mg/dL
3. Newly diagnosed DMT2 group:
    3.1. Confirmed: HbA1c ≥6.5% and 2h PG after 75 g OGTT ≥200 mg/dL
    3.2. Presumptive: 2h PG after 75 g OGTT ≥200 mg/dL, with FBS <126mg/dL and HbA1c <6.5%

The primary outcome was the optimal threshold level of FBS and HbA1c to accurately detect pre-diabetes and DMT2 as confirmed with 75 g OGTT. Secondary outcomes included the sensitivity, specificity, accuracy, positive and negative predictive values (PPV, NPV) for each of the FBS and HbA1c levels. The risk factors with the strongest association for pre-diabetes and diabetes were also determined.

Sample Size Determination

The minimum sample size, based on the disease's national prevalence of 20%, was 50. This was calculated using the methods of both Kelsey and Fleiss, enabling a statistical power of 80%. Data collection commenced in August 2023 until January 2024. A total of 115 patients were enrolled and had blood samples taken. Cases were dropped from the analysis if they had any missing result (either FBS, HbA1C, or 75 g OGTT). Ninety-five participants were then included in the final analysis.

Statistical Analysis

Descriptive statistics summarized the clinical characteristics of the participants. Frequency and proportion were used for categorical variables (nominal/ordinal). For continuous variables, mean and standard deviation were used for normally distributed interval/ratio variables and median and interquartile range for non-normally distributed interval/ratio variables. Continuous variables were not converted to categorical, to maintain diagnostic accuracy. Kappa agreement analysis was used to determine the level of agreement between FBS and HbA1c in detecting pre-diabetes and DMT2. Receiver operating characteristic (ROC) curve was constructed to determine the optimal cut-off values of FBS and HbA1c in detecting pre-diabetes and DMT2. Youden's J index was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the best cut-off point. Diagnostic parameters such as sensitivity, specificity, PPV, NPV, positive likelihood ratio, negative likelihood ratio, and accuracy were used to determine the diagnostic performance of FBS and HbA1c, with 2h PG during 75 g OGTT as the gold standard. Odds ratios (ORs) and corresponding 95% confidence intervals from binary logistic regression were used to determine the association between risk factors and pre-diabetes in the cohort. Cochran-Armitage test was used to determine whether there was a significant trend in the proportion of patients with pre-diabetes or diabetes across the number of risk factors. Null hypothesis was rejected at 0.05 α-level of significance. Stata 15.0 (StataCorp, 2017) was used for data analysis.

Ethical Consideration

The Chong Hua Hospital Institutional Ethics Review Committee approved the study. Informed consent was obtained from all participants. Confidentiality was observed using a coding system. The principal investigator was responsible for the accuracy and integrity of the data presented. Data collection was compiled in a personal computer system and tabulated in Microsoft Excel format.

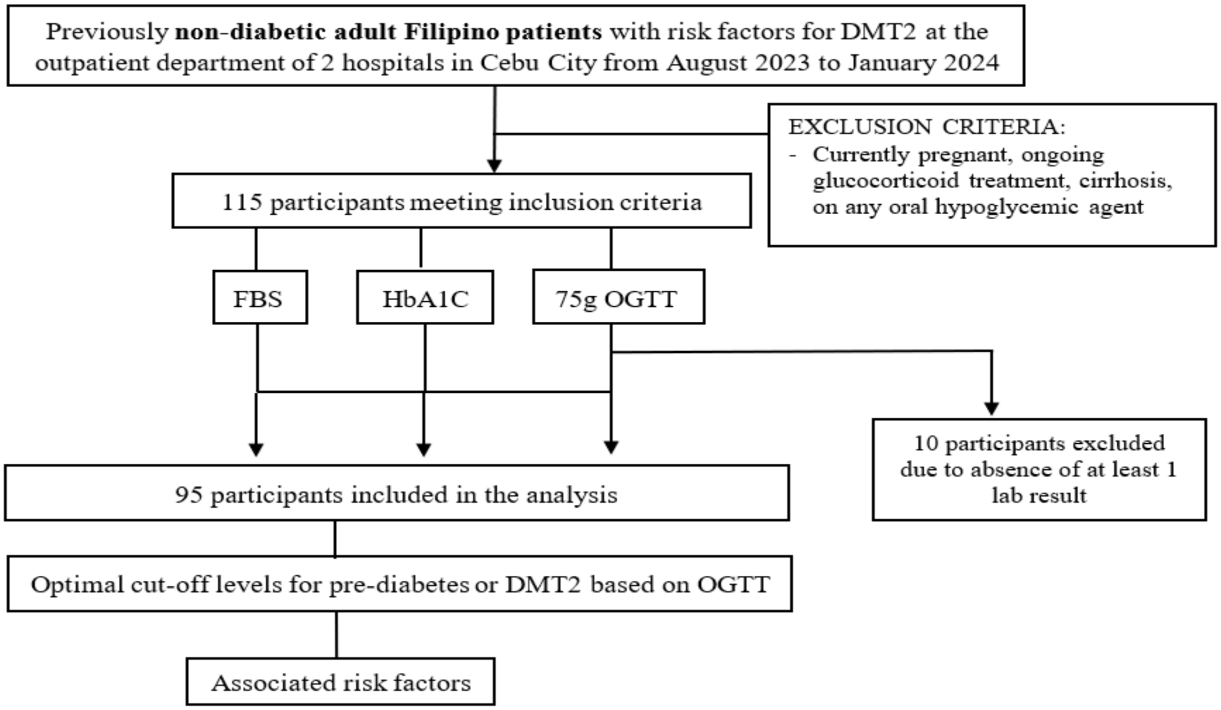


Figure 1. Schematic diagram of study design

Results

In the analysis of 95 at-risk Filipino patients, Table 1 shows that the average age was 48.92 years (±14.45), indicating a middle-aged cohort, predominantly female. A significant portion (77.89%) had a BMI beyond the normal cut-off for Asians at 23 kg/m², majority of whom were obese. Notably, 43% reported having a first-degree relative with diabetes. Chronic cardiac disease was present in 41% of patients, with hypertension being the most prevalent. Dyslipidemia was noted in almost 30% of patients. Among the female subgroup (n=68), PCOS was reported in one case, and GDM history in 11.76%. Physical inactivity, defined as <150 minutes of moderate-intensity activity per week according to WHO guidelines, was alarmingly observed in 66% of the participants. Finally, the study identified that approximately 32% of the patients had history of pre-diabetes, characterized either by elevated HbA1C levels (5.7–6.4%), IGT, or IFG.

Table 1. Demographic and Clinical Profile of patients

	Participants (n=95)
Age, years	48.14±14.67
Sex, n (%)	
Male	27 (28.42)
Female	68 (71.58)
Height, cm, median (IQR)	155 (152–162)
Weight, kg, median (IQR)	65 (55–75)
Body mass index, kg/m^2, mean ± SD	26.93±4.97
Normal, n (%)	21 (22.11)
Overweight (≥23 kg/m^2), n (%)	13 (13.68)
Obese class I (≥25 kg/m^2), n (%)	38 (40)
Obese class II (≥30 kg/m^2), n (%)	23 (24.21)
First-degree relative with diabetes, n (%)	41 (43.16)
History of smoking, n (%)	
None	77 (81.05)
Previous	14 (14.74)
Current	4 (4.21)

History of smoking, n (%)	
None	77 (81.05)
Previous	14 (14.74)
Current	4 (4.21)
Comorbidities, n (%)	
Chronic cardiac disease	39 (41.05)
- Hypertension	38 (97.44)
- Coronary artery disease	2 (5.13)
Cerebrovascular disease	3 (3.16)
Acute or chronic renal insufficiency	0
Dyslipidemia	28 (29.47)
Polycystic ovarian syndrome [N=71]	1 (1.47)
History of gestational diabetes mellitus [N=71], n (%)	8 (11.76)
History of pre-diabetes (HbA1C 5.7-6.4%, IGT with 2h glucose during 75 g OGTT of 140-199 mg/dL; or IFG 100-125 mg/dL), n (%)	30 (31.58)
Physical inactivity (<150 minutes of moderate-intensity activity per week or equivalent), n (%)	63 (66.32)

Table 2. Glycemic status categories based on ADA 2022 criteria

	Frequency (%)
Normal	32 (33.68)
Pre-diabetes	53 (55.79)
- Impaired fasting glucose (IFG)	7 (13.21)
- Impaired glucose tolerance (IGT)	8 (15.09)
-	
- IFG and IGT	24 (45.28)
- IFG and elevated HbA1c	8 (15.09)
- IGT and elevated HbA1c	12 (22.64)
- Elevated HbA1c	2 (3.77)
Newly diagnosed DMT2	10 (10.53)

Using the 2022 ADA criteria to classify glycemic status (Table 2), more than half (56%) were classified to have pre-diabetes, with combined IFG and IGT (45.28%) in the highest frequency. Additionally, 10.53% were categorized as having newly diagnosed DMT2.

Tables 3A and 3B show the distribution of the cohort based on the combination of FBS, HbA1c, and 75 g OGTT levels. Among the patients with normal FBS, a combined 42% were re-classified as pre-diabetes or DMT2 based on HbA1c and OGTT levels, with 20% more patients detected on 75 g OGTT alone (14.5% IGT, 5.45% with 2hr PG ≥200 mg/dL). Almost 18% of patients exhibited IFG levels but had presumptive DMT2 based solely on OGTT.
Among patients with normal HbA1c (Table 3B), a cumulative 41% were identified to have different subtypes of pre-diabetes based on FBS and OGTT levels; specifically 15.52% were identified based on OGTT alone. Among those with pre-diabetic levels of HbA1c, almost 20% had presumptive DMT2 based on 2hr PG result of ≥200 mg/dL.

Table 3A. FBS compared with combination of HbA1c and 75 g OGTT

	Normal HbA1c and OGTT	**Pre-diabetes**			**DMT2, newly diagnosed**
		Pre-diabetic HbA1c with normal OGTT	**IGT** With normal HbA1c	**Pre-diabetic HbA1c *and* IGT**	
	Frequency (%)				
Normal FBS n=55	32 (58.18)	2 (3.64)	8 (14.55)	10 (18.18)	3 (5.45)*
IFG n=40	7 (17.50)	2 (5)	9 (22.5)	15 (37.5)	7 (17.5)†

*Presumptive DMT2: second-hour post-loading glucose after 75 g OGTT ≥200 mg/dL, with FBS <126 mg/dL and HbA1c <6.5%.
†Only one participant (2.5%) with confirmed DMT2 based on HbA1c ≥6.5% and 75 g OGTT ≥200 mg/dL.

Table 3B. Hba1c compared with combination of FBS and 75 g OGTT

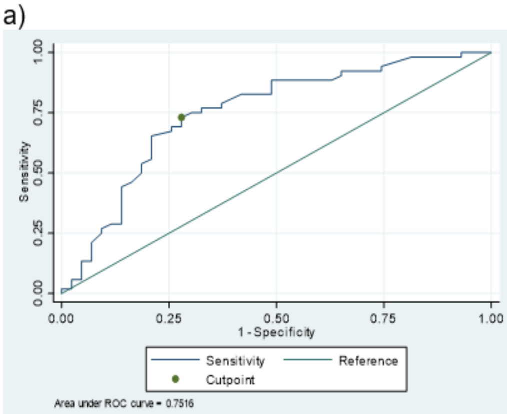
	Normal HbA1c and OGTT	Pre-diabetes			DMT2, newly diagnosed
		Pre-diabetic HbA1c with normal OGTT	**IGT** With normal HbA1c	**Pre-diabetic HbA1c *and* IGT**	
	Frequency (%)				
Normal HbA1c n=58	32 (55.17)	0	9 (15.52)	15 (25.86)	2 (3.45)*
Pre-diabetic HbA1c [n=36]	2 (5.56)	2 (5.56)	15 (41.26)	10 (27.78)	7 (19.84)*

*Presumptive DMT2: second-hour post-loading glucose after 75 g OGTT ≥200 mg/dL, with FBS <126 mg/dL and HbA1c <6.5%.

Figures 2 and 3 illustrate the ROC curves for FBS and HbA1c, which demonstrate their predictive capacity for pre-diabetes and DMT2. For pre-diabetes, the area under the ROC curve (AUROC) was calculated to be 0.7516 for FBS, indicating a good predictive ability. In comparison, the AUROC for HbA1c was higher, at 0.8378, suggesting a superior overall diagnostic effectiveness in identifying pre-diabetes. The empirical optimal cut-off values for FBS and HbA1c are 94.2 mg/dL and 5.6%, respectively. For DMT2, AUROC for HbA1c was still superior (0.83) compared to FBS (0.7) in this population. The optimal cut-off values for FBS and HbA1c are 106 mg/dL and 5.8%, respectively.

Figure 2. Receiver operating characteristic curve depicting the performance of FBS and HbA1c in detecting pre-diabetes and diabetes among at-risk Filipino patients. (a) FBS; (b) HbA1c.

a)



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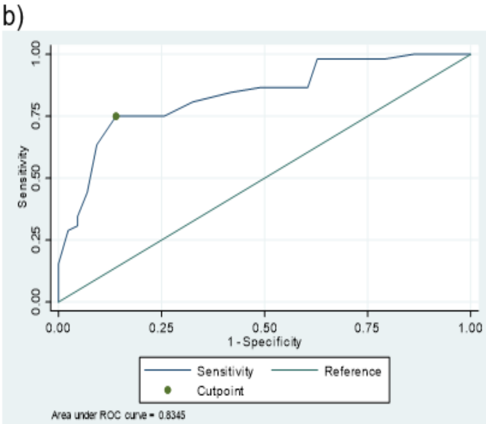
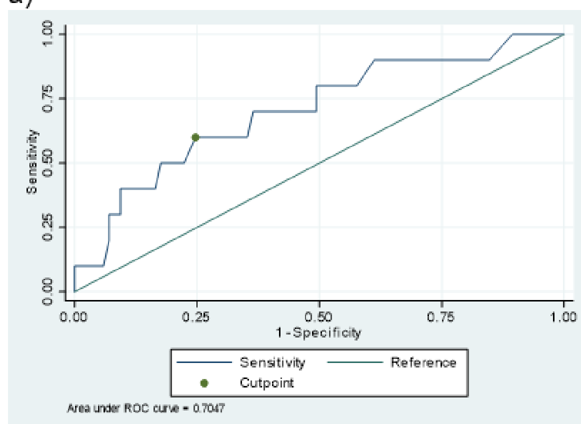


Figure 3. Receiver operating characteristic curve depicting the performance of FBS and HbA1c in detecting diabetes among at-risk Filipino patients. (a) FBS; (b) HbA1c.

a)



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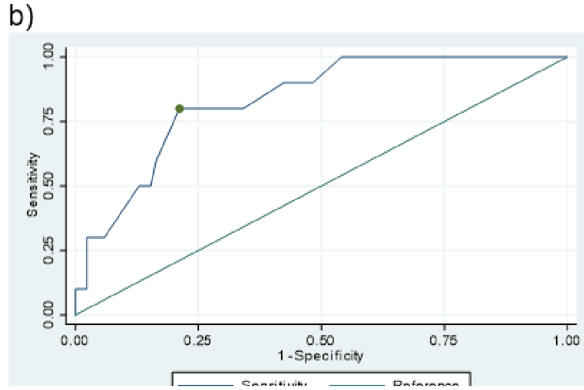

Table 4 evaluates the diagnostic performance of FBS and HbA1c in detecting pre-diabetes and DMT2, using the 2h PG after 75 g OGTT as the gold standard. For pre-diabetes FBS threshold of ≥94.2 mg/dL, the sensitivity was 73.1%, indicating a good capacity to correctly identify pre-diabetes in about three-quarters of the cases, while specificity was 72.1%, showing a fair accuracy in ruling out patients without the condition. For HbA1c cut-off of ≥5.6%, the sensitivity (75%) and specificity (86%) were higher, showing a stronger ability to correctly identify patients without the condition. The accuracy of HbA1c was higher (80%) compared to FBS (72.6%).

For DMT2 (Table 4), with FBS threshold of ≥106 mg/dL, it had a lower sensitivity (60%) but higher specificity (78.8%), showing good accuracy in ruling out these conditions in patients without the disease. Although the PPV was lower (22.2%) than the FBS pre-diabetes level, the high NPV (94.1%) reflected a high proportion of true negatives. For HbA1c cut-off set at ≥5.8%, both the sensitivity (80%) and specificity (78.8%) were higher than FBS, indicating a stronger capacity to accurately identify non-diabetic individuals. Similar to the FBS cut-off, the PPV (30.8%) was also lower than the pre-diabetic threshold, but with high NPV (97.1%). The diagnostic accuracy for both FBS and HbA1c cut-offs were considered high (73.7% and 79.0%, respectively)

FBS threshold of ≥ 94.2 mg/dL and ≥ 106 mg/dL for pre-diabetes and DMT2, respectively, showed a good balance between sensitivity and specificity, indicating its usefulness as a screening tool. However, the presence of false negatives and positives suggested that FBS should ideally be used in conjunction with the other diagnostic tests. HbA1c thresholds ≥5.6% and ≥5.8% both demonstrate higher sensitivity and specificity, making HbA1c more effective at ruling out non-diabetic patients. However, neither test alone is definitive, especially for ruling out dysglycemia. The overall accuracy of both tests and their threshold levels for both pre-diabetes and DMT2 are high (FBS at 72.6% and 73.7%; HbA1c at 80% and 79%, respectively), indicating their value in clinical settings. Nonetheless, reliance on a single test could be misleading, highlighting the need for clinical evaluation and combination with 75 g OGTT for certain populations for more accurate diagnosis.

Table 4. Diagnostic performance of the FBS and HbA1c thresholds in predicting pre-diabetes and DM type 2 with second-hour plasma glucose during 75 g OGTT as gold standard (n=95)

	Pre-diabetes threshold levels	
	FBS ≥94.2 mg/dL	**HbA1c ≥5.6%**
	Estimate (95% CI)	
Sensitivity, %	73.1 (59.0–84.4)	75.0 (61.1–86.0)
Specificity, %	72.1 (56.3–84.7)	86.0 (72.1–94.1)
Positive predictive value, %	76.0 (61.8–86.9)	86.7 (73.2–94.9)
Negative predictive value, %	68.9 (53.4–81.8)	74.0 (59.7–85.2)
Positive likelihood ratio	2.62 (1.58–4.35)	5.38 (2.52–11.5)
Negative likelihood ratio	0.37 (0.23–0.61)	0.29 (0.18–0.47)
Accuracy, %	72.6 (62.5–81.3)	80.0 (70.5–87.5)
	DM type 2 threshold levels	
	FBS ≥106 mg/dL	**HbA1c ≥5.8%**
	Estimate (95% CI)	
Sensitivity, %	60.0 (26.2–87.8)	80.0 (44.4–97.5)
Specificity, %	75.3 (64.7–84.0)	78.8 (68.6–86.9)
Positive predictive value, %	22.2 (8.6–42.3)	30.8 (14.3–51.8)
Negative predictive value, %	94.1 (85.6–98.4)	97.1 (89.9–99.6)
Positive likelihood ratio	2.43 (1.30–4.55)	3.78 (2.26–6.32)
Negative likelihood ratio	0.53 (0.25–1.15)	0.25 (0.07–0.88)
Accuracy, %	73.7 (63.7–82.2)	79.0 (69.4–86.6)

On crude analysis (Table 5), hypertension and age of at least 35 years were significantly associated with pre-diabetes in this population. The crude OR for hypertension was 2.96, indicating that patients with hypertension are three times more likely to develop pre-diabetes than their non-hypertensive counterparts. This finding suggests a potential link between blood pressure regulation and glucose metabolism, highlighting the need for routine diabetes screening in hypertensive individuals. Additionally, the crude OR for patients aged ≥35 years was significantly higher (3.81), underscoring the heightened risk of pre-diabetes with increasing age, likely due to age-related physiological changes affecting insulin sensitivity and metabolism. These results advocate for more aggressive screening in older adults to mitigate the risk of developing diabetes. In contrast, other factors such as BMI ≥23 kg/m^2, family history of diabetes, dyslipidemia, and physical inactivity did not show a significant association with pre-diabetes in this study. This observation suggests that while these factors are recognized risk factors for diabetes, their direct association with pre-diabetes may not be as strong as age and hypertension in this specific population or that we had insufficient evidence to demonstrate such association.

Table 5. Association of patient characteristics with pre-diabetes and diabetes (N=95)

	Crude odds ratio (95% CI)	p-value
BMI ≥23 kg/m^2	1.44 (0.56–3.70)	.446
First-degree relative with diabetes	1.46 (0.57–3.76)	.428
Hypertension (BP ≥140/90 mmHg or on maintenance therapy for hypertension)	**2.96 (1.12-7.87)**	**.029**
HDL cholesterol level <35 mg/dL (0.9 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) or on maintenance therapy for dyslipidemia	2.43 (0.85–6.91)	.097
Physical inactivity (less than 150 minutes of moderate-intensity activity per week or equivalent – WHO definition)	0.94 (0.23–3.83)	.928
Women who were diagnosed previously with gestational diabetes mellitus	0.94 (0.21–4.09)	.929
Age ≥35 years old	**3.81 (1.39-10.44)**	**.009**

In Figure 4, we analyzed the correlation between the number of risk factors for pre-diabetes/diabetes and the actual glycemic status of the patients. Every patient in the cohort had a minimum of two risk factors. A patient with only two risk factors exhibited a normal glycemic status, while a significant increase in the prevalence of pre-diabetes or DMT2 was noted as the number of risk factors rose. Among the patients with the highest number, i.e., seven risk factors, 75% were found to have abnormal glycemic levels. This discernible upward trend in the prevalence of pre-diabetes/diabetes with an increasing number of risk factors was statistically validated by the Cochran-Armitage test for trend, which yielded a significant p-value of <.001. This significant finding confirms the cumulative impact that multiple risk factors have on an individual's glycemic status.

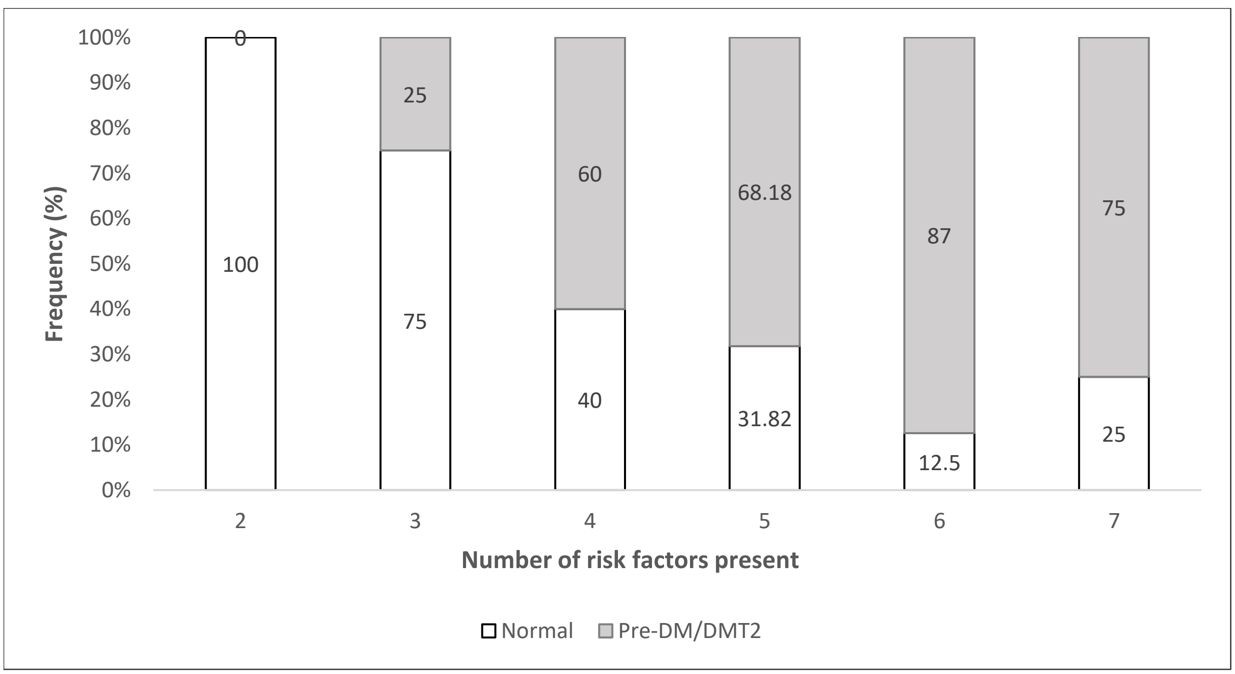

Figure 4: Glycemic status in relation to the number of risk factors present

Discussion

The present study emphasized the use of the 75 g OGTT for earlier and more intensive diagnosis of dysglycemia among at-risk adult Filipinos, with a lower threshold level for FBS and HbA1c inferred based on 75 g OGTT, as done in studies among other Asian populations. The study demonstrated that a significant portion of the participants were overweight or obese, based on Asia-Pacific criteria, prevalent in 78%. This correlates with >60% of the participants who were classified as pre-diabetes (56%) and newly diagnosed DMT2 (10.5%). BMI has a strong and consistent association with DMT2 and insulin resistance. The family history of diabetes was notable, with over half having a first-degree relative with the condition. Hypertension and dyslipidemia were also prevalent. These findings reiterate the ADA's recommendations on targeted public health interventions focusing on weight management, familial risk assessments, and routine monitoring for cardiovascular risk factors in similar populations.

The study shows that among patients with normal FBS (<100 mg/dL), a cumulative 42% were re-classified as pre-diabetes or DMT2 based on HbA1c and/or OGTT levels, with 20% more patients detected with 75 g OGTT alone. For both normal FBS and IFG, 23% had levels indicative of DMT2 based on a 2h PG of ≥200 mg/dL after OGTT. This percentage is close to the value reported in the study among Thai individuals with IFG, showing that 28.5% were diagnosed to have diabetes using the 75 g OGTT.[7] An increase in second-hour post-prandial glucose levels after 75 g OGTT occurs before any increase in FPG levels become apparent in older population and Asians with pre-diabetes.[7,11]

This study also observed that 45% of those with normal HbA1c levels had abnormal FBS and/or OGTT results. Those with pre-diabetic levels of HbA1c often had corresponding OGTT results, while 20% had levels indicative of DMT2, based on OGTT. This pattern supports prior studies showing that OGTT is a more sensitive indicator of early glucose intolerance, particularly of benefit in patients with normal or falsely low HbA1c levels.[1,7] The discordance between the HbA1c and 75 g OGTT were similar to previous findings for Asian populations and underscores the importance of screening using multiple tests to improve early detection in clinical practice.[7-9] The HbA1c may be affected by conditions that affect red blood cell turnover (hemolytic and other anemias, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, etc.), resulting in discrepancies between the A1C and the patient's true mean glycemic levels.[6]

This study showed that the optimal threshold level for FBS and HbA1c to detect pre-diabetes based on 75 g OGTT are ≥94.2 mg/dL (sensitivity, 73.1%; specificity, 72.1%) and ≥5.6% (sensitivity, 75%; specificity, 86%), respectively. For DMT2, the corresponding threshold for FBS and HbA1c are ≥106 mg/dL, (sensitivity, 60%; specificity, 78.8%) and ≥5.8% (sensitivity, 80%; specificity, 78.8%), respectively. HbA1c threshold overall had a higher diagnostic accuracy (80%) compared to FBS (73%). This study has demonstrated that performing 75 g OGTT for high-risk Filipinos with FBS ≥94.2 mg/dL or HbA1c ≥5.6% is highly predictive of a change in glucose tolerance status to pre-diabetes, while an FBS ≥106 mg/dL or HbA1c ≥5.8% is predictive of DMT2.

Comparing the results with prior studies among Asian populations, the HbA1c cutoff is close to a study among high-risk Chinese people aged >45 years old, where HbA1c of 5.4% and 5.8% were proposed for predicting pre-diabetes and diabetes, respectively.[14] Specifically in Southeast Asia, a study involving >3,000 adult Malaysians showed that an HbA1c cut-off of 6.3% gave the optimal sensitivity and specificity for predicting DMT2 based on 75 g OGTT.[15] A decline in the first phase of the insulin response to glucose is a key feature of deteriorating glucose homeostasis, and this may commence at levels of glycemia well within conventional normal limits. This has been confirmed in a study by Godsland et al., which showed progressive loss of first-phase insulin response to occur with FBS levels between 90 and 97 mg/dL and late-phase insulin responses declining at levels above 108 mg/dL.[4] Likewise, a study done among 30,000 Japanese individuals with normal FBS showed that the risk of DMT2 among subjects having FBS of 90–99 mg/dL is progressively higher with increasing level of fasting glucose.[16] Our study showed an FBS cutoff of 106 mg/dL to predict diabetes, which is congruent with studies among pre-diabetic Korean and Thai participants, which showed a cut-off of 104.5 and 106 mg/dL, respectively, to predict DMT2.[7,15] Among the risk factors, the significant association of hypertension and older age (≥35 years) with dysglycemia reinforces the need for focused screening in these groups. The increasing prevalence of pre-diabetes or DMT2 with more risk factors highlights the cumulative effect of these factors, recommending that individuals with multiple risk factors be prioritized for intervention.

Limitations of the Study

To the investigator's knowledge, this is the first study in the Philippines to determine the optimal threshold of FBS and HbA1c levels to predict pre-diabetes or DMT2. The present study has some limitations. Recall bias was a limitation during interview, with possibly inadequate information supplied by the informant at the time of interview. For laboratory testing, 75 g OGTT was only performed once. Screening guidelines require that, in otherwise asymptomatic patients, a single result in the diabetes range (FBS, HbA1c, or 75 g OGTT) should ideally have a repeat confirmatory test within 2 weeks.[6] The OGTT results with 2h PG ≥200 mg/dL were in the context of patients with multiple risk factors and IFG levels, decreasing the likelihood of false positives. Lastly, results of the study is applicable only to high-risk Filipino subjects, and the FBS and HbA1c threshold to be used in the general population may be different.

Recommendation

The presence of anemia as confounding factor for the sensitivity of HbA1c test should be investigated. Further studies on high-risk Filipinos, with larger sample sizes and more male participants, are recommended. Lastly, cost-effectiveness analysis in future studies is advised, to evaluate both the costs and outcomes of adding 75 g OGTT to high-risk Filipinos who reach the threshold.

Conclusion

Among high-risk adult Filipinos in this study, 66% had levels indicative of pre-diabetes or DMT2. Among those with FBS <100 mg/dL, 20% were reclassified as pre-diabetes or DMT2, based on 75 g OGTT, and this increases to 40% when abnormal HbA1c was also accounted for. Among those with FBS <126 mg/dL, 23% were re-classified as DMT2, based on 75 g OGTT. On the other hand, among patients with normal HbA1c, 45% were re-classified as pre-diabetes and/or DMT2, based on 75 g OGTT. Among patients with pre-diabetic levels of HbA1c, 20% had presumptive DMT2, based on OGTT.

HbA1c is more accurate than FBS for the prediction of pre-diabetes or DMT2, but a combination of tests with OGTT are recommended to improve diagnostic accuracy. Hypertension and age ≥35 years are the risk factors with the strongest association to dysglycemia.

This study concludes that performing 75 g OGTT for high-risk Filipinos with FBS ≥94.2 mg/dL or HbA1c ≥5.6% is highly predictive of a change in glucose tolerance status to pre-diabetes, while an FBS ≥106 mg/dL or HbA1c ≥5.8% is predictive of DMT2. Lower cut-off levels signal earlier preventive measures against diabetes.

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