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ORIGINAL RESEARCH

Optimal Glycated Hemoglobin Cutoff for Diagnosis of Diabetes and Prediabetes in Chinese Breast Cancer Women

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Purpose: Glycated hemoglobin (HbA1c) is widely used in diabetes management and now recommended for diagnosis and risk assessment. Our research focused on investigating the optimal cutoff points of HbA1c for diagnosis of diabetes and prediabetes in Chinese breast cancer women, aiming to enhance early detection and tailor treatment strategies.

Patients and Methods: This study involved 309 breast cancer women without diabetes history in China. Patients were categorized into groups of newly diagnosed diabetes, prediabetes, and normal glucose tolerance using oral glucose tolerance test (OGTT) according to the 2010 ADA criteria. HbA1c data were collected from all patients. Receiver operating characteristic (ROC) curve analysis was used to assess the effectiveness of the HbA1c screening.

Results: Among the 309 breast cancer women without diabetes history, 96 (31.0%) were identified with diabetes and 130 (42.1%) had prediabetes according to OGTT, and the incidence of normal glucose tolerance was only 26.9% (83). ROC curve analysis, using OGTT as a reference, revealed that the area under the curve of 0.903 (P<0.001, 95% CI, 0.867–0.938) for HbA1c alone, indicating high accuracy. The optimal HbA1c cutoff for identifying diabetes was determined to be 6.0%, with a sensitivity of 78.1% and specificity of 86.4%. For prediabetes, the ROC curve for HbA1c alone showed that the area under the ROC curve of 0.703 (P<0.001, 95% CI, 0.632–0.774), with an optimal cutoff of 5.5% (sensitivity of 76.9% and specificity of 51.8%).

Conclusion: The prevalence of undiagnosed diabetes is very high in breast cancer women without diabetes history in China. The optimal cutoff points of HbA1c for identifying diabetes and prediabetes are 6.0% and 5.5% in Chinese breast cancer women, respectively.

Keywords: breast cancer, diabetes, HbA1c, prediabetes

Introduction

Globally, the prevalence of diabetes and breast cancer is rising significantly, especially in China.[1,2] Currently, female breast cancer has become the most diagnosed cancer worldwide, accounting for 11.7% of all new cancer diagnoses.[1] From 1980 to 2018, China experienced a significant shift in its health profile, with diabetes rates escalating sharply from just below 1% to 12.4%.[2] However, more than 61.9% of adults in China remain unaware of their diabetes condition. In the US, over 85% of individuals with prediabetes are also unaware of their condition.[2,3] Notably, as many as 50% of newly diagnosed type 2 diabetes patients had early indications of microvascular or macrovascular complications. A significant number of individuals with type 2 diabetes are frequently undiagnosed for several years, emphasizing the crucial role of early detection and timely intervention.[4] Prediabetes is an intermediate stage between normal glucose tolerance and diabetes. The International Diabetes Federation (IDF) emphasizes that prediabetes is a global concern. An

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epidemiological study in China showed that the prevalence of prediabetes was 38.1% in 2018.[2] Numerous studies have demonstrated that individuals with prediabetes are at a high risk of developing diabetes and experiencing higher rates of cardiovascular disease and mortality compared to the general population.

With the increasing co-occurrence of diabetes and breast cancer becomes more common, there is a growing number of undiagnosed cases of diabetes and prediabetes are being observed among breast cancer patients.[5,6] This situation can substantially heighten both the financial burden and psychological distress, potentially resulting in higher mortality rates for these patients.[7–9] Consequently, the prompt and accurate diagnosis of diabetes and prediabetes in breast cancer patients is becoming critically essential.

The American Diabetes Association (ADA) recommended the use of the fasting plasma glucose (FPG) value or the 2-h plasma glucose value during a 75-g oral glucose tolerance test (OGTT), or the glycated hemoglobin (HbA1c) criteria for the diagnosis of diabetes, which is also relevant for identifying disorders in glucose metabolism among patients with breast cancer.[10] While the OGTT is recognized as the gold standard for diagnosing diabetes with highly sensitive and specific, its usage is limited in clinical settings due to being time-consuming, requiring overnight fasting and multiple hours at a healthcare facility. This approach is particularly relevant for breast cancer patients, who are already burdened by extensive oncological treatments. HbA1c is a blood marker indicating average blood glucose concentrations over a period of 2–3 months and is vital for diabetes detection and management without requiring fasting. The ADA recommends HbA1c levels of 5.7% for prediabetes and 6.5% for diabetes diagnosis, emphasizing its role in identifying retinal complications and managing diabetes-related risks.[11] However, the use of HbA1c for diabetes diagnosis has not been fully elucidated, particularly in terms of defining appropriate cutoff points for various ethnic and population groups. A Chinese study showed that the optimal HbA1c thresholds for diagnosing newly diagnosed diabetes (NDD) and prediabetes in the population were 6.0% and 5.6% respectively, in Shanghai, China.[12] Another study recommended that an HbA1c threshold of 6.3% could be used to detect diabetes in Chinese adults with high specificity.[13] It is important to note that HbA1c levels can be affected by factors such as age, pregnancy, tumors and unique hematologic conditions, suggesting that standard threshold values might not be suitable for every individual.[10]

To our knowledge, there are no studies have explored the optimal cutoff points of HbA1c for diagnosing diabetes and prediabetes, specifically in Chinese breast cancer women.

Hence, our objective was to perform a cross-sectional study to investigate the efficacy of HbA1c in diagnosing diabetes and prediabetes specifically in Chinese breast cancer women and to determine the cutoff points for HbA1c by receiver operating characteristic (ROC) curve analysis.

Methods

Study Design and Population

This cross-sectional study was conducted on breast cancer patients at the First Affiliated Hospital of Chongqing Medical University, between June 2015 and December 2020. For all breast cancer patients initially diagnosed through the Department of Pathology of Chongqing Medical University, the exclusion criteria included male sex, age younger than 18 years, distant metastasis of breast cancer, history of diabetes, history of other cancers, treatment for HIV/AIDS, pregnancy status, and lack of OGTT and HbA1c data. Finally, a total of 309 participants met these criteria and were included in the final analysis, and their data collected included physical examinations such as weight, height, and blood pressure (BP), including systolic blood pressure (SBP) and diastolic blood pressure (DBP). The personal medical history (hypertension, coronary heart disease) and family medical history (diabetes, malignant tumors) of the participants were collected from the electronic records of the First Affiliated Hospital of Chongqing Medical University. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. We defined generalized underweight as a BMI (kg/m^2) of less than 18.5; normal weight, 18.5 to 23.9; overweight, 24 to 27.9, and obese, at least 28, based on the Chinese national standard.[14] According to the WHO BMI classification,[15] underweight was <18.5 kg/m^2, normal weight was 18.5 to <25 kg/m^2, overweight was 25 to <30 kg/m^2, and obesity was ≥30 kg/m^2.

Data Collection

Blood samples were collected from all participants after at least a 10-hour overnight fast. The 309 participants without diabetes history underwent HbA1c testing and a standard 75-g glucose solution during the OGTT, 270 of them underwent insulin releasing test (IRT). During the OGTT and IRT, blood samples were taken at intervals of 0, 30, 60, and 120 minutes post-glucose administration to assess glucose and insulin levels. Plasma glucose, plasma insulin, HbA1c, and serum lipids such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), all of which were analyzed using an automatic biochemical analyzer (Roche c701, Basel, Switzerland). This study received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Informed consent was not obtained as this was a retrospective study.

Outcomes and Data Collection

In this study, we aimed to evaluate the accuracy of HbA1c in identifying NDD and prediabetes, using the ADA glucose criteria. Based on ADA criteria, participants were categorized into three groups: NDD is diagnosed with FPG ≥ 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or 2-h PG ≥ 200 mg/dL; prediabetes is diagnosed with FPG 100 to 125 mg/dL and 2-h PG 140 to 199 mg/dL; normal glucose tolerance (NGT) is diagnosed with FPG < 100 mg/dL, and 2-h PG < 140 mg/dL.

The homeostasis model assessment of insulin resistance (HOMA-IR), is widely used in both clinical and epidemiologic studies and estimates insulin sensitivity during an OGTT. It calculated as (fasting insulin μU/mL) × (fasting glucose mg/dL) / 405.[16] The homeostasis model assessment of β-cell function (HOMA-β), an index of insulin secretory function, was calculated as (fasting insulin μU/mL) × 360/(fasting glucose mg/dL-63). Moreover, the Matsuda index is an insulin sensitivity index that reflects a composite estimate of hepatic and muscle insulin sensitivity determined from OGTT data. ISI (Matsuda) =10,000/[(fasting glucose mg/ dL×fasting insulin μU/mL) $^{1/2}$ (mean fasting glucose mg/dL×mean fasting insulin μU/mL)$^{1/2}$], where fasting glucose and insulin data were taken from time 0 of the OGTT and the mean data represent the average glucose and insulin values obtained throughout the OGTT period. The early insulin response during an OGTT was estimated as the insulinogenic index (IGI), [Δinsulin (30–0 min)/Δglucose (30–0 min)], and the disposition index (DI) of the early phase during an OGTT, [Δinsulin (30–0 min)/Δglucose (30–0 min)]/HOMA-IR.[17] Patients were divided into two groups based on the time of peak insulin secretion during an IRT at baseline: the InsP30+InsP60 group, with a peak at 30 or 60 min; the InsP120 group, with a peak at 120 min. In addition, if two equal peaks occurred, the earlier time was defined as the peak during the IRT.

We stratified the study sample into different subgroups based on age and BMI to explore the cutoff points of HbA1c for diagnosing diabetes and prediabetes within each subgroup.

Statistical Analysis

The statistical analysis was performed using R Studio version 4.3.1, while other analyses were performed using SPSS 26. All continuous variables were tested for normality and are described be means ± standard deviations (SD), and categorical data are presented as proportions. Categorical data were analyzed using Pearson's chi-square test or Fisher's test. For parametric data, we employed the sample *t*-test or two-way ANOVA with repeated measures and Bonferroni's adjustment for multiple comparisons. Kappa coefficients were used to evaluate the consistency between blood glucose test results obtained from the HbA1c and glucose criteria. The diagnostic accuracy of HbA1c for diagnosing diabetes and prediabetes, using the OGTT as the reference standard, was evaluated across four dimensions: sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. Additionally, ROC curves were used to calculate the area under the curve (AUC) of HbA1c to diagnose diabetes and prediabetes and were calculated using the GraphPad prism version 9.00. The optimal cutoff point was established using the Youden's index, calculated as the sum of the sensitivity and specificity minus 1. A 2-sided $P<0.05$ was used to determine statistical significance.

Results

Demographic and Clinical Characteristics

From June 2015 to December 2020, a total of 309 breast cancer women without diabetes history were enrolled in the study (Figure 1). Table 1 presents the baseline demographic characteristics of patients. The average age was 53.4±11.8 years and the average BMI was 24.1±3.5 kg/m^2, with 28.4% of the patients were older than 60 years, 14.9% had a BMI of 28.0 kg/m^2 or higher, and 19.7% were diagnosed with hypertension.

In this study, based on the ADA glycemic criteria, there were 96 (31.1%) patients had NDD, 130 (42.1%) patients had prediabetes, and only 83 (26.9%) had NGT, of which 11.4% showed a delay in insulin peak time. More than 70% of patients presented hyperglycemia. Furthermore, we found significant differences among the three groups, patients with NDD and prediabetes were older, more likely to be obese, and more likely to have hypertension than patients with NGT. The average HbA1c level was higher in patients with NDD (7.0±1.5%) and prediabetes (5.7±0.3%) than NGT (5.4 ±0.4%), P<0.001. Moreover, levels of SBP, DBP, TG, and HOMA-IR were significantly higher in patients with NDD and prediabetes compared to NGT, while HDL-C, Matsuda, IGI and DI were higher in NGT (all P<0.001). Levels of LDL-C and TC were higher in patients with NDD than NGT, but no significant differences were observed between patients with prediabetes and NGT. Notably, OGTT plasma glucose concentrations at all time points, plasma insulin concentrations at fasting, 30 and 120 minutes were significantly different in each group (Figure 2A). However, fasting plasma insulin levels remained within the normal range in three groups. Patients with NDD and prediabetes exhibited peak insulin secretion at 120 minutes, whereas patients with NGT showed peak insulin secretion at 30 minutes (Figure 2B).

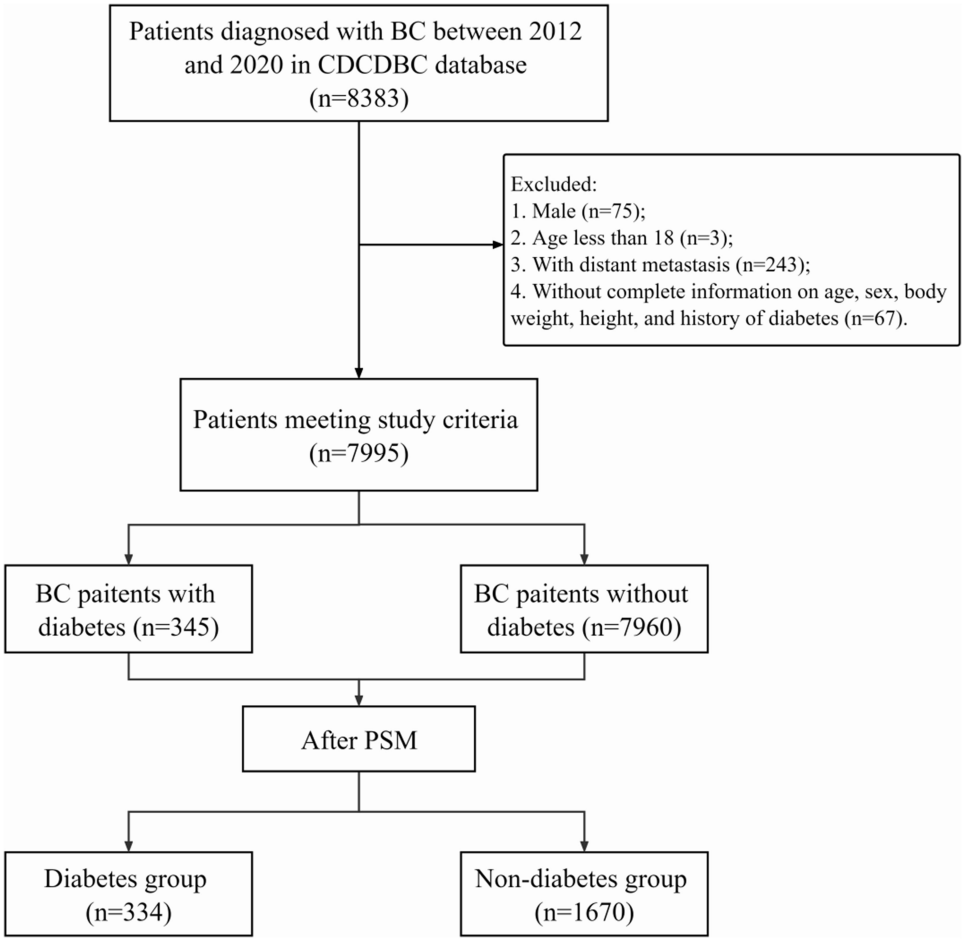

Figure 1 Flowchart shows participants in this study.

Table 1 Characteristics of Chinese Breast Cancer Patients

	Whole N=309	NGT N=83	Prediabetes N=130	Diabetes N=96	P
Age (years)	53.4(11.8)	46.7(11.1)	52.6(10.9)[a]	60.2(9.8)[ab]	<0.001
Age group (years)					<0.001
<50	114(36.9)	49(59)	55(42.3)	10(10.4)	
50–59	107(34.6)	25(30.1)	44(33.8)	38(39.6)	
60–69	57(18.4)	7(8.4)	22(16.9)	28(29.2)	
≥70	31(10.0)	2(2.4)	9(6.9)	20(20.8)	
Weight(kg)	59.3(9.0)	57(7.3)	59.5(10.1)	61.2(8.2)[a]	0.007
Height(cm)	157.0(5.2)	156.4(4.2)	157.8(5.5)	156.3(5.5)[b]	0.058
BMI(kg/m^2)	24.1(3.5)	23.3(3.1)	23.9(4)	25(3.1)[ab]	0.004
Based on Chinese BMI standard					0.002
Underweight (<18.5)	8(2.6)	2(2.4)	4(3.1)	2(2.1)	
Normal (18.5–23.9)	160(51.8)	52(62.7)	75(57.7)	33(34.4)	
Overweight (24–27.9)	95(30.7)	19(22.9)	32(24.6)	44(45.8)	
Obese (≥28)	46(14.9)	10(12)	19(14.6)	17(17.7)	
Hypertension	61(19.7)	3(3.6)	22(16.9)[a]	36(37.5)[ab]	<0.001
Coronary heart disease	6(1.9)	0(0)	4(3.1)	2(2.1)	0.336
Family history of malignancy	32(10.4)	10(12)	13(10)	9(9.4)	0.830
Family history of diabetes	14(4.5)	3(3.6)	5(3.8)	6(6.2)	0.652
Laboratory findings					
SBP(mmHg)	126.7(18.7)	118.2(13.9)	123.8(17.2)[a]	137.9(19.1)[ab]	<0.001
DBP(mmHg)	77.4(10.9)	73.1(9.6)	77.0(11.0)[a]	81.6(10.5)[ab]	<0.001
HbA1c(%)	6.0(1.1)	5.4(0.4)	5.7(0.3)[a]	7.0(1.5)[ab]	<0.001
LDL-C(mg/dL)	112.1(30.9)	112.1(38.7)	108.3(27.1)	119.9(30.9)[b]	0.023
HDL-C(mg/dL)	54.1(11.6)	58(11.6)	54.1(11.6)	46.4(15.5)[ab]	<0.001
TG(mg/dL)	141.8(132.9)	97.5(53.2)	115.2(88.6)	194.9(194.9)[ab]	<0.001
TC(mg/dL)	177.9(30.9)	177.9(42.5)	174(30.9)	189.5(30.9)[b]	0.002
HOMA-IR	1.7(1.0)	1.2(0.5)	1.5(0.7)[a]	2.3(1.2)[ab]	<0.001
HOMA-β	56.0(29.9)	59.1(25.9)	57.2(32)	51.8(30.2)	0.221
Matsuda	6.2(3.0)	8.2(3.2)	6.1(2.5)[a]	4.2(2.1)[ab]	<0.001
IGI	0.6(0.4)	0.8(0.5)	0.6(0.4)[a]	0.4(0.3)[ab]	<0.001
DI	0.5(0.4)	0.8(0.6)	0.4(0.3)[a]	0.2(0.3)[ab]	<0.001
Fasting plasma glucose(mg/dL)	109.9(28.8)	91.9(7.2)	102.7(9.0)[a]	133.3(41.4)[ab]	<0.001
0.5-h Plasma glucose(mg/dL)	191.0(46.8)	155.0(21.6)	182.0(25.2)[a]	234.2(48.6)[ab]	<0.001
1-h Plasma glucose(mg/dL)	205.4(72.1)	140.5(30.6)	187.4(36.0)[a]	284.7(59.5)[ab]	<0.001
2-h Plasma glucose(mg/dL)	189.2(82.9)	118.9(12.6)	158.6(21.6)[a]	291.9(75.7)[ab]	<0.001
Fasting plasma insulin(μU/mL)	6.2(3.4)	4.9(2.2)	6.0(3.0)[a]	7.9(4.2)[ab]	<0.001
0.5-h Plasma insulin(μU/mL)	46.1(28.7)	52.5(27.3)	48.5(30.8)	36.3(24.4)[ab]	0.001
1-h Plasma insulin(μU/mL)	52.0(30.5)	46.7(26.2)	54.9(28.4)	53.0(36.7)	0.174
2-h Plasma insulin(μU/mL)	59.8(45.9)	37.8(18.8)	62.2(46.4)[a]	78.5(54.9)[ab]	<0.001

Notes: Data are presented as mean ± SD or numbers (percentages); [a]Compared to patients with NGT: $P<0.05$; [b]Compared to patients with Prediabetes: $P<0.05$.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DI, disposition index; HbA1c, Glycated Hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cellfunction; IGI, insulinogenic index; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

As shown in Table 2, a subgroup analysis was performed based on the time of peak insulin secretion during an IRT, and patients were divided into InsP30+InsP60 and InsP120 groups. A total of There are 11.4%, 57.4% and 82.1% of the patients were categorized as InsP120 in the NGT, prediabetes, and NDD groups, respectively. The 2 hour plasma insulin levels in the Insp120 group were greater than those in the Insp30+60 group across all three groups (Figure 2C and D).

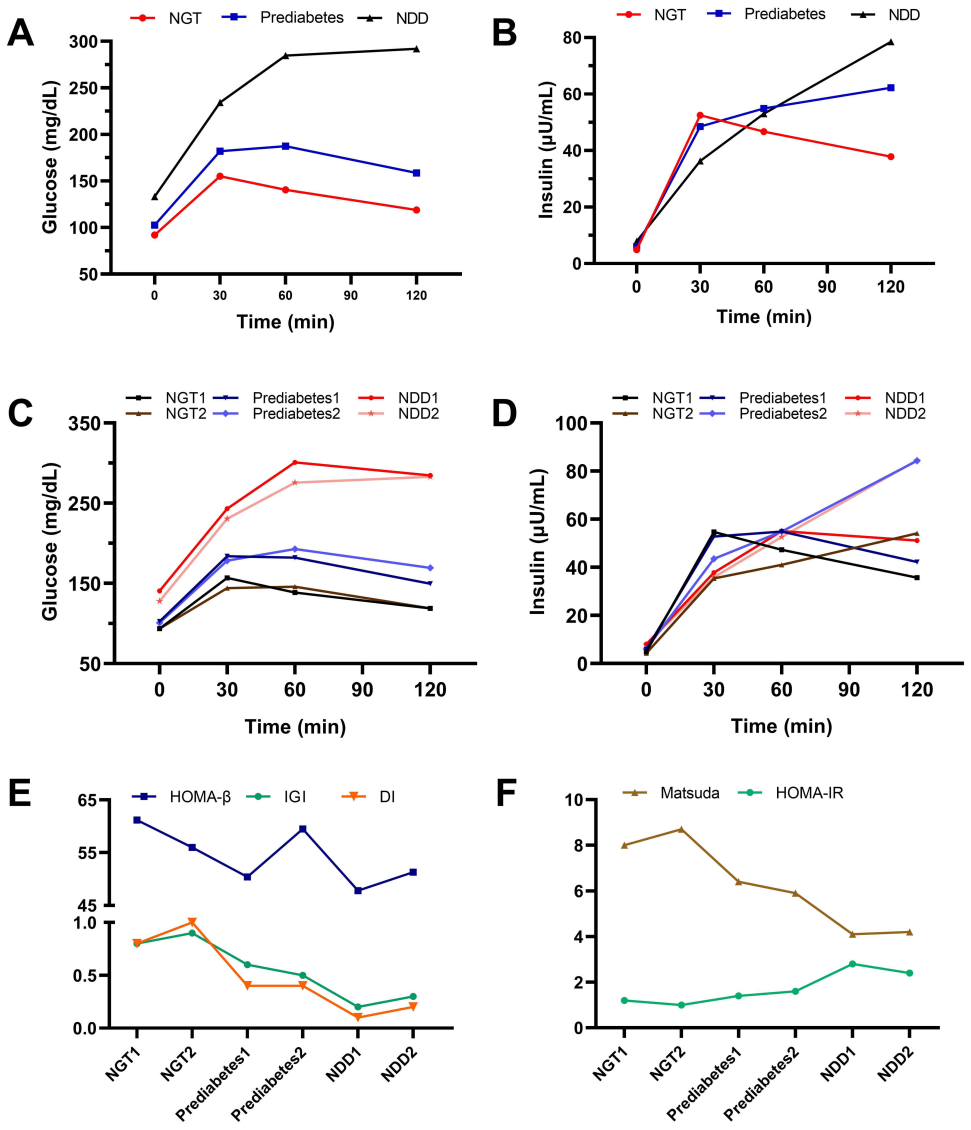

Figure 2 Changes in plasma glucose (**A**) and insulin (**B**) concentrations during the OGTT and IRT in Chinese breast cancer women with NGT (red), prediabetes (blue) and NDD (black), respectively. Plasma glucose (**C**) and insulin (**D**) concentrations for different insulin patterns in the NGT, prediabetes, and NDD groups, respectively. Indices for β-cell function (**E**) and insulin sensitivity (**F**) during the OGTT in Chinese breast cancer women with NGT, prediabetes and NDD, respectively. NGT1: NGT patients with a peak of insulin during an IRT at 30 or 60 min; NGT2: NGT patients with peak of insulin at 120 min; Prediabetes1: prediabetes patients with peak of insulin at 30 or 60 min; Prediabetes2: prediabetes patients with peak of insulin at 120 min; NDD1: NDD patients with peak of insulin at 30 or 60 min; NDD2: NDD patients with peak of insulin at 120 min.

However, no significant differences were observed in the levels of HbA1c, FPG, indices of β-cell function and insulin sensitivity (Figure 2E and F), fasting plasma insulin and lipid profile between the Insp30+60 and Insp120 groups.

The Cutoff Points for HbA_{1c} in Diagnosing Diabetes and Prediabetes

The performance of HbA1c in predicting diabetes and prediabetes, as defined by OGTT, was evaluated in a cross-sectional setting using ROC curve analysis (Figure 3). Tables 3 and 4 show the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and Youden's index for detecting diabetes and prediabetes at HbA1c cutoff points ranging from 5.6% to 6.6% and 5.2% to 6.1%, respectively. As the cutoff points increased, the sensitivity decreased, while the specificity for diagnosing of diabetes and prediabetes increased. As shown in Figure 3A, the AUC was 0.903 ($P<0.001$, 95% CI, 0.867–0.938) for diagnosing diabetes using HbA1c. As shown in Table 4, the cutoff point of HbA1c of 6.0% had the largest Youden's index for diagnosing diabetes in women with breast

Table 2 Characteristics of Chinese Breast Cancer Patients Stratified by the Time of Peak Insulin Secretion

	NGT				Prediabetes				Diabetes			
	Whole	InsP30 +InsP60	InsP120	p	Whole	InsP30 +InsP60	InsP120	p	Whole	InsP30+InsP60	InsP120	p
	N=79	N=70	N=9		N=114	N=60	N=54		N=78	N=14	N=64	
Age (years)	46.7 (11.2)	47.3 (11.0)	42.3 (12.5)	0.284	53.1 (11.1)	53.5 (11.8)	52.6 (10.4)	0.645	60.9 (9.8)	53.7 (6.5)	62.5 (9.7)	<0.001
Age group (years)				0.895				0.201				0.005
<50	46 (58.2)	41 (58.6)	5 (55.6)		47 (41.2)	29 (48.3)	18 (33.3)		6 (7.7)	3 (21.4)	3 (4.7)	
50–59	25 (31.6)	22 (31.4)	3 (33.3)		37 (32.5)	15 (25.0)	22 (40.7)		31 (39.7)	9 (64.3)	22 (34.4)	
60–69	6 (7.6)	5 (7.1)	1 (11.1)		21 (18.4)	10 (16.7)	11 (20.4)		24 (30.8)	2 (14.3)	22 (34.4)	
≥70	2 (2.5)	2 (2.9)	0 (0.0)		9 (7.9)	6 (10.0)	3 (5.6)		17 (21.8)	0 (0.0)	17 (26.6)	
Weight(kg)	56.8 (7.3)	57.2 (7.4)	53.7 (5.6)	0.109	58.7 (8.4)	59.7 (9.3)	57.5 (7.2)	0.16	60.7 (8.2)	60.8 (6.5)	60.7 (8.5)	0.936
Height(cm)	156.5 (4.2)	156.3 (4.3)	157.3 (3.6)	0.465	157.5 (5.3)	157.3 (5.8)	157.8 (4.7)	0.618	156.3 (5.7)	156.5 (4.1)	156.3 (6.0)	0.855
Body mass index (kg/m2)	23.2 (3.1)	23.4 (3.1)	21.7 (1.8)	0.023	23.7 (3.4)	24.2 (3.9)	23.1 (2.8)	0.09	24.8 (3.1)	24.9 (3.0)	24.8 (3.1)	0.962
Based on Chinese BMI standard				0.495				0.128				0.936
Underweight (<18.5)	2 (2.5)	2 (2.9)	0 (0.0)		4 (3.5)	2 (3.3)	2 (3.7)		1 (1.3)	0 (0.0)	1 (1.6)	
Normal (18.5–23.9)	50 (63.3)	42 (60.0)	8 (88.9)		66 (57.9)	33 (55.0)	33 (61.1)		31 (39.7)	5 (35.7)	26 (40.6)	
Overweight (24–27.9)	18 (22.8)	17 (24.3)	1 (11.1)		29 (25.4)	13 (21.7)	16 (29.6)		34 (43.6)	7 (50.0)	27 (42.2)	
Obese (≥28)	9 (11.4)	9 (12.9)	0 (0.0)		15 (13.2)	12 (20.0)	3 (5.6)		12 (15.4)	2 (14.3)	10 (15.6)	
Based on WHO BMI standard				0.801				0.055				0.728
Underweight (<18.5)	2 (2.5)	2 (2.9)	0 (0.0)		4 (3.5)	2 (3.3)	2 (3.7)		1 (1.3)	0 (0.0)	1 (1.6)	
Normal (18.5–24.9)	58 (73.4)	50 (71.4)	8 (88.9)		72 (63.2)	36 (60.0)	36 (66.7)		40 (51.3)	9 (64.3)	31 (48.4)	
Overweight (25–29.9)	17 (21.5)	16 (22.9)	1 (11.1)		31 (27.2)	15 (25.0)	16 (29.6)		31 (39.7)	4 (28.6)	27 (42.2)	
Obesity (≥30)	2 (2.5)	2 (2.9)	0 (0.0)		7 (6.1)	7 (11.7)	0 (0.0)		6 (7.7)	1 (7.1)	5 (7.8)	
Hypertension	3(3.8)	3 (4.3)	0 (0.0)	1	19 (16.7)	11 (18.3)	8 (14.8)	0.801	30 (38.5)	4 (28.6)	26 (40.6)	0.592
Coronary heart disease	0 (0)	0 (0)	0 (0)	–	4(3.5)	4 (6.7)	0 (0.0)	0.12	2(2.6)	0 (0.0)	2 (3.1)	1
Family history of malignancy	10 (12.7)	9 (12.9)	1 (11.1)	1	11 (9.6)	3 (5.0)	8 (14.8)	0.146	6(7.7)	0 (0.0)	6 (9.4)	0.584
Family history of diabetes	3(3.8)	3 (4.3)	0 (0.0)	1	3 (2.6)	1 (1.7)	2 (3.7)	0.603	5(6.4)	1 (7.1)	4 (6.2)	1
Laboratory findings												
SBP(mmHg)	118 (14)	118 (14)	115 (11)	0.466	124 (18)	124 (19)	123 (17)	0.863	139 (20	130 (11)	141 (20)	0.008
DBP(mmHg)	73 (10)	74 (10)	70 (7)	0.213	77 (11)	75 (12)	77 (10)	0.357	82 (10)	79 (7)	82 (11)	0.257
HbA1c(%)	5.4 (0.3)	5.4 (0.4)	5.3 (0.2)	0.117	5.7 (0.3)	5.7 (0.3)	5.7 (0.3)	0.942	6.9 (1.5)	7.0 (1.5)	6.8 (1.5)	0.751
LDL-C(mg/dL)	112.1 (30.9)	112.1 (30.9)	100.5 (30.9)	0.262	104.4 (27.1)	108.3 (27.1)	104.4 (27.1)	0.747	119.9 (30.9)	119.9 (30.9)	119.9 (34.8)	0.432
HDL-C(mg/dL)	58.0 (11.6)	58.0 (11.6)	58.0 (15.5)	0.725	50.3 (11.6)	50.3 (15.5)	54.1 (11.6)	0.701	50.3 (15.5)	50.3 (15.5)	46.4 (11.6)	0.629
TG(mg/dL)	97.5 (53.2)	97.5 (53.2)	106.3 (62.0)	0.802	124.0 (88.6)	132.9 (106.3)	106.3 (53.2)	0.073	186.1 (159.5)	186.1 (159.5)	177.2 (159.5)	0.514
TC(mg/dL)	177.9 (30.9)	177.9 (34.8)	170.1 (30.9)	0.46	170.1 (30.9)	174 (34.8)	166.3 (30.9)	0.356	189.5 (30.9)	189.5 (30.9)	185.6 (34.8)	0.118
HOMA-IR	1.1 (0.5)	1.1 (0.5)	1.0 (0.3)	0.325	1.5 (0.8)	1.5 (0.6)	1.5 (0.9)	0.825	2.5 (1.3)	2.6 (1.4)	2.4 (1.3)	0.629
HOMA-β	59.6 (26.6)	60.1 (27.8)	52.3 (13.4)	0.174	57.4 (34.3)	54.5 (23.1)	60.6 (43.3)	0.359	50.8 (33.4)	47.6 (32.3)	51.5 (33.9)	0.694

(*Continued*)

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Table 2 (Continued).

	NGT				Prediabetes				Diabetes			
	Whole	InsP30 +InsP60	InsP120	p	Whole	InsP30 +InsP60	InsP120	p	Whole	InsP30+InsP60	InsP120	p
	N=79	N=70	N=9		N=114	N=60	N=54		N=78	N=14	N=64	
Matsuda	8.2 (3.2)	8.2 (3.3)	8.0 (2.7)	0.814	6.1 (2.5)	6.2 (2.6)	6.0 (2.5)	0.662	4.2 (2.1)	4.3 (2.1)	4.1 (2.1)	0.77
IGI	0.8 (0.5)	0.9 (0.5)	0.8 (0.5)	0.678	0.6 (0.4)	0.6 (0.4)	0.5 (0.3)	0.059	0.3 (0.3)	0.3 (0.4)	0.3 (0.2)	0.724
DI	0.8 (0.6)	0.8 (0.6)	0.9 (0.7)	0.819	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.251	0.2 (0.3)	0.3 (0.6)	0.1 (0.1)	0.485
Fasting plasma glucose(mg/dL)	93.7 (3.6)	93.7 (3.6)	93.7 (5.4)	0.851	102.7 (9.0)	102.7 (9.0)	100.9 (9.0)	0.303	131.5 (36.0)	140.5 (52.3)	127.9 (32.4)	0.429
0.5-h Plasma glucose(mg/dL)	155.0 (21.6)	156.8 (19.8)	144.1 (23.4)	0.152	182.0 (23.4)	183.8 (25.2)	178.4 (21.6)	0.363	232.4 (46.8)	243.2 (63.1)	230.6 (43.2)	0.472
1-h Plasma glucose(mg/dL)	140.5 (30.6)	138.7 (30.6)	145.9 (28.8)	0.525	187.4 (36.0)	182.0 (41.4)	192.8 (28.8)	0.11	279.3 (57.7)	300.9 (75.7)	275.7 (54.1)	0.261
2-h Plasma glucose(mg/dL)	118.9 (12.6)	118.9 (12.6)	118.9 (12.6)	0.906	158.6 (23.4)	149.5 (23.4)	169.4 (16.2)	<0.001	282.9 (73.9)	284.7 (79.3)	282.9 (72.1)	0.952
Fasting plasma insulin(μU/mL)	4.9 (2.2)	4.9 (2.3)	4.3 (1.4)	0.277	6.0 (3.0)	5.9 (2.3)	6.1 (3.7)	0.696	7.9 (4.2)	8.0 (4.9)	7.9 (4.1)	0.907
0.5-h Plasma insulin(μU/mL)	52.9 (27.3)	54.7 (28.0)	35.4 (11.4)	0.001	48.4 (30.8)	52.8 (30.5)	43.5 (30.5)	0.106	36.3 (24.4)	37.8 (25.9)	35.9 (24.3)	0.807
1-h Plasma insulin(μU/mL)	46.7 (26.2)	47.3 (27.3)	41.0 (13.2)	0.282	54.9 (28.4)	54.9 (26.1)	54.9 (31.0)	0.992	53.0 (36.7)	55.0 (35.8)	52.6 (37.1)	0.818
2-h Plasma insulin(μU/mL)	37.8 (18.9)	35.7 (17.8)	54.1 (19.8)	0.024	62.2 (46.4)	42.2 (21.8)	84.3 (55.8)	<0.001	78.5 (54.9)	51.1 (31.2)	84.5 (57.3)	0.004

Note: Data are presented as mean ± SD or numbers (percentages).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DI, disposition index; HbA1c, Glycated Hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cellfunction; IGI, insulinogenic index; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

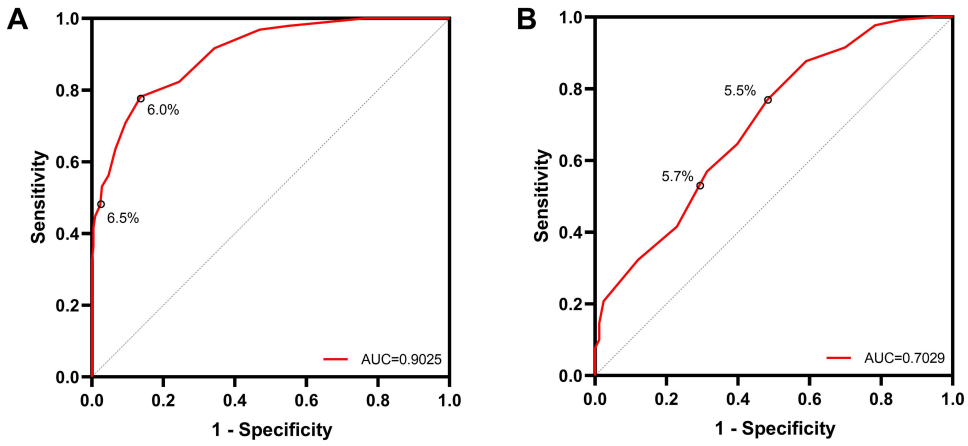

Figure 3 (**A**) ROC curve analysis of the performance of HbA1c in predicting diabetes in Chinese women with breast cancer. The AUC was 0.903 (P<0.001, 95% CI, 0.867–0.938). For cutoff point of HbA1c≥6.0%, the sensitivity was 78.1%, and the specificity was 76.9%. (**B**) ROC curve analysis of the performance of HbA1c in predicting prediabetes in Chinese women with breast cancer. The AUC was 0.703 (P<0.001, 95% CI, 0.632–0.774). For cutoff point of HbA1c≥5.5%, the sensitivity was 76.9%, and the specificity was 51.8%. 5.5%: HbA1c cutoff point for prediabetes found in this study. 5.7%: HbA1c cutoff point for prediabetes recommended by ADA. 6.0%: HbA1c cutoff point for diabetes found in this study. 6.5%: HbA1c cutoff point for diabetes recommended by the ADA.

Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; CI, confidence interval; HbA1c, glycated hemoglobin; ROC, receiver operating characteristic.

cancer, with corresponding sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of 78.1%, 86.4%, 72.1%, 89.8%, 7.04, and 0.31, respectively. An HbA1c cutoff point of 6.5%, as recommended by the ADA and World Health Organization (WHO), showed a lower sensitivity (47.9% vs 78.1%) compared to a 6.0% cutoff, but with a higher specificity (97.7% vs 86.4%). Figure 3A shows the positions of 6.0% and 6.5% of the HbA1c levels on the diabetes ROC curve.

For prediabetes, the AUC was 0.703 [P<0.001, 95% confidence interval (CI), 0.632–0.774]. An HbA1c cutoff point of 5.5% showed a moderate sensitivity of 76.9%, and a specificity of 51.8%, achieving the largest Youden's index. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for diagnosing prediabetes in breast cancer women of 76.9%, 51.8%, 71.4%, 58.9%, 1.60, and 0.45, respectively. Using the ADA and WHO recommended that an HbA1c cutoff point of 5.7% resulted in decreased sensitivity (56.9% vs 76.9%) compared to the 5.5% cutoff, but increased specificity (68.7% vs 51.8%). Figure 3B shows the positions of 5.5% and 5.7% HbA1c on the diabetes ROC curve.

The Concordance Between the OGTT and the HbA1c Criteria

Table 5 shows the concordance between the OGTT and the HbA1c criteria based on the ADA criteria. Among 309 patients, 96 were diagnosed with diabetes based on the ADA glycemic criteria, while only 50 were diagnosed with diabetes by the ADA HbA1c criteria. Only 46 (47.9%) patients were diagnosed with diabetes by both criteria. Furthermore, 50 (52.1%) patients were underdiagnosed and 5 patients were overdiagnosed as diabetes according to the ADA HbA1c criteria. The agreement between the classifications of diabetes and prediabetes between the criteria of the OGTT and HbA1c, with kappa value of 0.523 (95% CI 0.419–0.627) and 0.240 (95% CI 0.115–0.365), respectively.

Using the HbA1c cutoff points for diagnosing diabetes and prediabetes established in our research, 75 (78.1%) patients were diagnosed with diabetes according to both criteria. Additionally, only 21 (21.8%) patients were underdiagnosed and 29 patients were overdiagnosed with diabetes. The agreement between the diabetes and prediabetes classifications using the OGTT and HbA1c criteria was reflected in kappa values of 0.631 (95% CI 0.539–0.723) and 0.294 (95% CI 0.163–0.365), respectively.

Table 3 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood Ratio, Negative Likelihood Ratio, and Youden's Index of HbA1c Cutoff Values for Diabetes

HbA1c Cutoff (%)	Number of Diabetes cases/Total Number of Patients(%)		Sensitivity(%)	Specificity(%)	Positive Predictive Value(%)	Negative Predictive Value(%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Youden's Index
	Below the Cutoff	Above the Cutoff							
5.5	1/74(1.4)	95/235(40.4)	99.0(94.3–100)	34.3(27.9–41.1)	40.4(34.1–47.0)	98.6(92.7–100)	1.51(1.36–1.66)	0.03(0.00–0.22)	0.3323
5.6	2/98(2.0)	94/211(44.5)	97.9(92.7–99.6)	45.1(38.5–51.8)	44.5(38.3–52.0)	98.0(92.8–100)	1.78(1.57–2.02)	0.05(0.01–0.18)	0.4299
5.7	3/116(2.6)	93/193(48.2)	96.9(91.2–99.2)	53.1(46.4–59.6)	48.2(41.0–55.5)	97.4(92.6–99.5)	2.06(1.78–2.39)	0.06(0.02–0.18)	0.4993
5.8	8/148(5.4)	88/161(54.7)	91.7(84.4–95.7)	65.7(59.1–71.8)	54.7(46.6–62.5)	94.6(89.6–97.6)	2.67(2.20–3.25)	0.13(0.06–0.25)	0.574
5.9	17/178(9.6)	79/131(60.3)	82.3(73.5–88.6)	75.6(69.4–80.9)	60.3(51.4–68.7)	90.4(85.1–94.3)	6.31(3.93–10.13)	0.44(0.35–0.54)	0.5788
6.0	21/205(10.2)	75/104(72.1)	78.1(68.9–85.2)	86.4(81.1–90.4)	72.1(62.5–80.5)	89.8(84.8–93.5)	7.04(4.61–10.74)	0.31(0.23–0.42)	0.6451
6.1	28/221(12.7)	68/88(77.3)	70.8(61.1–79.0)	90.6(85.9–93.8)	77.3(67.1–85.5)	87.3(82.2–91.4)	7.54(4.88–11.67)	0.32(0.23–0.44)	0.6144
6.2	35/234(15.0)	61/75(81.3)	63.5(53.6–72.5)	93.4(89.3–96.0)	81.3(70.7–89.4)	85.0(79.8–89.4)	9.67(5.70–16.40)	0.39(0.30–0.51)	0.5697
6.3	42/245(17.1)	54/64(84.4)	56.3(46.3–65.7)	95.3(91.6–97.4)	84.4(73.1–92.2)	82.9(77.5–87.4)	11.98(6.38–22.50)	0.46(0.37–0.58)	0.5156
6.4	45/252(17.9)	51/57(89.5)	53.1(43.2–62.8)	97.2(94.0–98.7)	89.5(78.5–96.0)	82.1(76.8–86.7)	18.86(8.38–42.43)	0.48(0.39–0.60)	0.5031
6.5	50/258(19.4)	46/51(90.2)	47.9(38.2–57.8)	97.7(94.6–99.0)	90.2(78.6–96.7)	80.6(75.3–85.3)	20.41(8.37–49.75)	0.53(0.44–0.65)	0.4557
6.6	53/264(20.1)	43/45(95.6)	44.8(35.2–54.8)	99.1(96.6–99.8)	95.6(84.9–99.5)	79.9(74.6–84.6)	47.70(11.80–192.89)	0.56(0.47–0.67)	0.4385

Table 4 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood Ratio, Negative Likelihood Ratio, and Youden's Index of HbA1c Cutoff Values for Prediabetes

HbA1c Cutoff (%)	Number of Prediabetes Cases/ Total Number of Patients (%)		Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Youden's Index
	Below the Cutoff	Above the Cutoff							
5.2	3/21 (14.3)	127/192 (66.1)	97.7 (93.4–99.4)	21.7 (14.2–31.7)	66.1 (59.0–72.8)	85.7 (63.7–97.0)	1.25 (1.11–1.40)	0.11 (0.03–0.35)	0.1938
5.3	11/36 (30.6)	119/177 (67.2)	91.5 (85.5–95.2)	30.1 (21.3–40.7)	67.2 (59.8–74.1)	69.4 (51.9–83.7)	1.31 (1.13–1.52)	0.28 (0.15–0.54)	0.2166
5.4	16/50 (32.0)	114/163 (69.9)	87.7 (80.9–92.3)	41.0 (31.0–51.7)	69.9 (62.3–76.9)	68.0 (53.3–80.5)	1.49 (1.23–1.80)	0.30 (0.18–0.51)	0.2865
5.5	30/73 (41.1)	100/140 (71.4)	76.9 (69.0–83.3)	51.8 (41.2–62.2)	71.4 (63.2–78.7)	58.9 (46.8–70.3)	1.60 (1.25–2.03)	0.45 (0.31–0.65)	0.2873
5.6	46/96 (47.9)	84/117 (71.8)	64.6 (56.1–72.3)	60.2 (49.5–70.1)	71.8 (62.7–79.7)	52.1 (41.6–62.4)	1.63 (1.21–2.18)	0.59 (0.44–0.79)	0.2486
5.7	56/113 (49.6)	74/100 (74.0)	56.9 (48.3–65.1)	68.7 (58.1–77.6)	74.0 (64.3–82.3)	50.4 (40.9–60.0)	1.82 (1.28–2.58)	0.63 (0.49–0.80)	0.2559
5.8	76/140 (54.3)	54/73 (74.0)	41.5 (33.4–50.1)	77.1 (67.0–84.8)	74.0 (62.4–83.5)	45.7 (37.3–54.3)	1.82 (1.16–2.83)	0.76 (0.63–0.91)	0.1865
5.9	88/161 (54.7)	42/52 (80.8)	32.3 (24.9–40.8)	88.0 (79.2–93.3)	80.8 (67.5–90.4)	45.3 (37.5–53.4)	2.68 (1.43–5.05)	0.77 (0.67–0.89)	0.2026
6.0	103/184 (56.0)	27/29 (93.1)	20.8 (14.7–28.5)	97.6 (91.6–99.6)	93.1 (77.2–99.2)	44.0 (36.7–51.5)	8.62 (2.11–35.29)	0.81 (0.74–0.89)	0.1836
6.1	111/193 (57.5)	19/20 (95.0)	14.6 (9.6–21.7)	98.8 (93.5–99.9)	95.0 (75.1–99.9)	42.5 (35.4–49.8)	12.13 (1.66–88.92)	0.86 (0.80–0.93)	0.1342

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Table 5 Agreement Between HbA1c and Glucose Criteria by ADA and Our Research

		HbA1c(%)			Total(N)	Kappa Coefficient (95 CI)	HbA1c(%)			Total(N)	Kappa Coefficient (95 CI)
Overall		<5.7	5.7–6.4	≥6.5			<5.5	5.5–5.9	≥6.0		
	NGT	57(68.7)	26(31.3)	0(0)	83		44(51.8)	38(45.8)	2(2.4)	83	
	Prediabetes	56(43.1)	69(53.1)	5(3.8)	130	0.240 (0.115, 0.365)	30(23.1)	73(56.2)	27(20.8)	130	0.294 (0.163, 0.365)
	Diabetes	3(3.1)	47(49.0)	46(47.9)	96	0.523 (0.419, 0.627)	1(1.0)	20(20.8)	75(78.1)	96	0.631 (0.539, 0.723)

Table 6 The Cutoff Points of HbA1c for Diagnosing Diabetes and Prediabetes in Different Subgroups

	Age (Year)				BMI (kg/m^2)			
	< 60		≥ 60		< 25		≥ 25	
	Diabetes	Prediabetes	Diabetes	Prediabetes	Diabetes	Prediabetes	Diabetes	Prediabetes
HbA1c cutoff point (%)	5.8	5.4	6.1	5.7	6.0	5.4	6.0	5.7
Sensitivity (%)	89.6	85.9	75.0	83.3	75.6	81.4	80.4	70.5
Specificity (%)	72.8	46.4	80.0	33.3	90.6	42.9	76.6	75.0
Area under the curve	0.914	0.698	0.845	0.652	0.906	0.646	0.875	0.818
P	< 0.001	< 0.001	< 0.001	0.17	< 0.001	0.002	< 0.001	< 0.001

Subgroup Analysis

In our analysis, we performed subgroup analyses of the study sample for age and BMI. Table 6 shows the HbA1c cutoff points, sensitivity, specificity and AUC for diagnosing diabetes and prediabetes, based on ROC curve. These findings align closely with the cutoff points which we determined for the all of breast cancer women.

Discussion

In our research, we discovered that a significant number of undiagnosed diabetes (NDD) and prediabetes cases exist, among Chinese breast cancer women without diabetes history. Specifically, we found that 11.4% of the NGT patients had a delayed time of peak insulin concentration after an oral glucose load. This highlights the significant incidence of glucose intolerance in breast cancer women, underscoring that prompt detection and management of these glucose anomalies are crucial.

According to the current WHO and ADA criteria, diabetes may be diagnosed based on plasma glucose criteria, either the FPG value or the 2hPG value during a 75-g OGTT, or the HbA1c criteria.[11,18] There are several limitations of the use of FPG and OGTT in the diagnosis of this disease, including the requirements for blood sampling in the fasting state and some special requirements for the OGTT. In recent years, the useful and reliable tools for diabetes screening and diagnosis have been need to develop, which will allow effective early detection. HbA1c is convenient and easy to measure, does not require patients to fast overnight or for 2 hours after the administration of oral glucose and has less sample instability and the significant biological variability than glucose measurements.[19]

The ADA established an HbA1c≥ 6.5% for diagnosing diabetes, and the levels in the range of 5.7–6.4% could be considered to identify individuals with prediabetes. However, previous studies have shown that the an HbA1c≥6.5% may miss 70% of the individuals with diabetes identified collectively using HbA1c, FPG, or 2hPG, according to National Health and Nutrition Examination Survey (NHANES) data.[20] Despite the implementation of this criterion, debates continue regarding the appropriateness of using HbA1c as a diagnostic tool for diabetes, particularly concerning the determination of specific HbA1c cutoff points for various ethnic and racial groups. However, there has been no research specifically on the HbA1c cutoff point for breast cancer patients. Therefore, we calculated the cutoff points for HbA1c in the assessment of diabetes and prediabetes in Chinese breast cancer women, which was defined based on plasma glucose

measurements during the OGTT. In our study, an HbA1c level of 6.5% resulted in a sensitivity of 47.9% (95% CI: 38.2, 57.8) and a specificity of 97.7% (95% CI: 94.6, 99.0) for diabetes diagnosis. This finding indicates that nearly 52.1% of diabetes cases were not identified using HbA1c. Furthermore, for prediabetes, an HbA1c level of 5.7% proved to be an inadequate predictor, with a sensitivity of 56.9% (95% CI: 48.3, 65.1) and specificity of 68.7% (95% CI: 58.1, 77.6). The HbA1c level recommended by the ADA for breast cancer patients is insufficient for accurately diagnosing diabetes or prediabetes. Our study revealed that an HbA1c cutoff point of 6.0% is highly specific for detecting undiagnosed diabetes in Chinese breast cancer women, showing a higher AUC and indicating greater diagnostic accuracy, and a cutoff point of 5.5% was showed a moderate sensitivity and a specificity for detecting undiagnosed prediabetes, these values were lower than the ADA criteria.

Different studies have shown significant variations in HbA1c thresholds for diagnosing diabetes. The 1999–2004 NHANES found that an HbA1c value of 5.8% or higher was the optimal cutoff point for detecting diabetes among the American population, defined as an FPG≥126 mg/dL.[21] A study in the United States, participating in early diabetes intervention programs, identified HbA1c ≥ 6.1% as the optimal cutoff point for detecting diabetes.[22] Another meta-analysis, including multiple countries, also recommended an HbA1c cutoff point of 6.1% as the best predictor of diabetes.[23] A Japanese study suggested that the optimal cutoff points of HbA1c for diagnosing diabetes and undiagnosed prediabetes were 6.1% (sensitivity 86%, specificity 92%) and 5.5% (sensitivity 71%, specificity 64%), respectively.[24] These results are all slightly higher than ours. The optimal cutoff points of HbA1c for diabetes in the Chinese population has been inconsistent across different studies, which ranges from 5.7 to 6.4%.[12,13,25–31] In the population of Chinese adults aged 40 years or older, it was found that an HbA1c level of ≥6.0% could be used to diagnose diabetes, which is comparable with our findings and many studies in China, such as Wang et al, Zhou et al and so on.[12,13,28,31] A study recommended the HbA1c cutoff value of 6.3% in Chinese adults and the sensitivity and specificity were 62.8% and 96.1%, respectively.[25] An HbA1c≥6.1% was associated with a sensitivity of 77.5% and a specificity of 78.8% in the Hong Kong Chinese population with known risk factors for glucose intolerance.[32]

Additionally, the lack of clarity in the guidelines for prediabetes criteria may present certain challenges. The optimal cutoff point of HbA1c for prediabetes defined by the WHO criteria in the Chinese population has been inconsistent across different studies, ranging from 5.6 to 6.1%.[12,13,27–29,31] However, based on the ADA glycemic criteria, we found that an HbA1c cutoff point of 5.5% was weakly valuable for detecting prediabetes. Overall, the poor outcome of prediabetes diagnosed using HbA1c, based on the AUC slightly above 0.7, which is similar to other studies.

Therefore, many studies have used a combination of HbA1c and FPG for detecting diabetes and prediabetes. This approach merges FPG's sensitivity to short-term blood sugar variations with HbA1c's ability to indicate long-term glycemic trends, thereby enhancing the accuracy and reliability of diabetes and prediabetes diagnosis.[30] In summary, the results of numerous studies suggest that the HbA1c cutoff points for diagnosing diabetes and prediabetes are lower than the ADA standards. There are several potential explanations for the lower HbA1c cutoff point in breast cancer patients in the present study. First, metabolic changes and poor nutritional status may impact red blood cell production and clearance in cancer patients, potentially altering HbA1c measurements.[33] Second, the treatments of cancer such as chemotherapy and radiation might disrupt glucose regulation mechanisms, which could affect the accuracy of HbA1c measurements.[34,35] Variations outcomes between studies could have resulted from different study designs, populations, diabetes diagnostic criteria, and HbA1c measurement methods. Therefore, it is advisable to use tailored cutoff points for detecting undiagnosed diabetes and prediabetes in cancer patients. Evaluating the optimal HbA1c cutoff points for diabetes and prediabetes in Chinese breast cancer women requires substantial cohorts with long-term follow-up data, encompassing a diverse age range. Some research indicates that defects in pancreatic β-cell function can be present even in individuals with NGT.[36] The deficiencies in pancreatic β-cell secretion and insulin sensitivity are pivotal in the pathophysiology of diabetes and glycemic metabolism.[37,38] Among the general population, hyperinsulinemia and impaired glucose metabolism are associated with an increased risk of breast cancer and may increase the likelihood of poor prognosis.[9,39] In our study, there was still a delay in the insulin peak time among some patients with NGT, which predicts a high risk of prediabetes or diabetes.[40] Additionally, regular monitoring and lifestyle modifications are

beneficial for individuals with prediabetes or diabetes, as well as those who have NGT but exhibit delayed insulin peaks, to help reduce their risk of developing diabetes.

Previous research has examined the HbA1c cutoff points in healthy populations. Our study is the first to investigate optimal HbA1c cutoff points in breast cancer women, aiming to facilitate early detection and intervention of diabetes and prediabetes. However, there are some limitations to the current research. Firstly, this was a cross-sectional and retrospective study for patients diagnosed with breast cancer initially, these patients have not undergone treatment of cancer and without long-term follow-up. Hence, the results require further research with larger sample sizes for validation. Secondly, while the influence of AIDS and pregnancy in breast cancer women was excluded, other conditions, including hemoglobinopathy or other factors affecting the HbA1c level, were not considered and might impact HbA1c test results. Thirdly, we did not perform a repeat measurement in patients with abnormal glucose levels over time, which may have been misclassified of diabetes and it is unclear how frequently this occurred and miss patients with diabetes of less than 3 months duration. Thus, despite controversies in its practical implementation, HbA1c seems to be a dependable tool for identifying diabetes and prediabetes. In Chinese breast cancer women, a 6.0% HbA1c cutoff point is very valuable for detecting diabetes, while a 5.5% cutoff point has relatively weaker value for detecting prediabetes.

Conclusion

The prevalence of undiagnosed diabetes is very high in Chinese breast cancer women without diabetes history. We found that the HbA1c cutoff points of 6.0% and 5.5% have enhanced the accuracy in identifying potential diabetes and prediabetes in Chinese breast cancer women. Future research could further explore and determine optimal HbA1c cutoff points by conducting larger cohort studies of breast cancer populations and long-term follow-up.

Abbreviations

ADA, American Diabetes Association; AUC, area under the curve; BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; DI, disposition index; FPG, fasting plasma glucose; HbA1c, Glycated Hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cellfunction; IDF, International Diabetes Federation; IGI, insulinogenic index; LDL-C, low-density lipoprotein cholesterol; NDD, newly diagnosed diabetes; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; SBP, systolic blood pressure; SD, standard deviations; TC, total cholesterol; TG, triglycerides; WHO, World Health Organization.

Data Sharing Statement

The datasets used in this study are available on request from the corresponding author.

Ethics Approval and Informed Consent

This study was approved by the ethical review committee of the First Affiliated Hospital of Chongqing Medical University in accordance with the principles of the Helsinki Declaration (approval no.2014-1-6). In this retrospective study, all data remained anonymous, and the requirement for written informed consent from patients was waived. Written informed consent from participants was not required in accordance with local/national guidelines.

Author Contributions

All authors made a significant contributions to the research, whether through conception, study design, data acquisition, analysis and interpretation, or in all these areas. All authors have drafted, written, substantially revised, or critically reviewed the article, and agreed on the journal for submission. Additionally, All authors have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

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