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Cardiovascular Risk Stratification in Pregnant Women with Gestational Diabetes: A Comparative Analysis of Predictive Models in Padang, Indonesia

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A B S T R A C T

Introduction: Gestational diabetes mellitus (GDM) significantly increases the risk of both short-term and long-term cardiovascular disease (CVD) in women. Effective risk stratification during pregnancy is crucial for targeted interventions. This study aimed to compare the performance of established cardiovascular risk prediction models in a cohort of pregnant women with GDM in Padang, Indonesia. **Methods:** A prospective cohort study was conducted involving 350 pregnant women diagnosed with GDM at two major hospitals in Padang, Indonesia, between January 2022 and June 2023. Baseline demographic, clinical, and laboratory data were collected. Three established CVD risk prediction models – the Framingham Risk Score (FRS), the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations (PCE), and a modified version of the PCE adapted for GDM (PCE-GDM) – were applied to calculate individual 10-year CVD risk scores. The primary outcome was the development of any major adverse cardiovascular event (MACE), defined as myocardial infarction, stroke, or cardiovascular death, or new-onset hypertension requiring medication, within one year postpartum. Model performance was assessed using discrimination (c-statistic) and calibration (Hosmer-Lemeshow goodness-of-fit test). **Results:** The mean age of participants was 32.4 ± 5.1 years. The prevalence of pre-existing hypertension was 8.6%, and the mean pre-pregnancy BMI was 28.5 ± 4.7 kg/m². During the one-year follow-up, 25 (7.1%) women experienced a MACE. The PCE-GDM model demonstrated the best discrimination (c-statistic = 0.82, 95% CI 0.76-0.88), followed by the PCE (c-statistic = 0.75, 95% CI 0.68-0.82), and the FRS (c-statistic = 0.68, 95% CI 0.60-0.76). The PCE-GDM also showed good calibration (x^2 = 8.3, p = 0.41), while the FRS and PCE tended to underestimate risk (x^2 = 18.5, p = 0.02 and x^2 = 15.2, p = 0.06, respectively). **Conclusion:** The PCE-GDM model, specifically adapted for GDM, showed superior performance in predicting short-term cardiovascular risk compared to traditional models in this Indonesian cohort. These findings highlight the need for GDM-specific risk stratification tools to improve cardiovascular risk management in this vulnerable population.

1. Introduction

Gestational diabetes mellitus (GDM), characterized by glucose intolerance first recognized during pregnancy, presents a significant global health challenge, affecting a substantial proportion of pregnancies worldwide. The prevalence of GDM varies considerably across populations and diagnostic criteria, underscoring the complex interplay of genetic, environmental, and lifestyle factors in its development. In Indonesia, a country with a diverse population and

a rising prevalence of obesity and metabolic syndrome, the estimated prevalence of GDM ranges from 6% to 18%, depending on the region and diagnostic criteria used. This wide range highlights the need for comprehensive epidemiological studies to accurately assess the burden of GDM in specific regions and populations within Indonesia. While GDM poses immediate risks to both mother and infant during pregnancy, such as macrosomia, preeclampsia, and cesarean delivery, its implications extend far beyond the perinatal period. GDM is now recognized as a potent risk factor for future cardiovascular disease (CVD), a leading cause of morbidity and mortality worldwide. Women with a history of GDM have a substantially increased risk of developing type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia, all of which are major contributors to CVD. This increased risk persists even in women who revert to normoglycemia after delivery, suggesting that GDM may unmask a pre-existing metabolic vulnerability or induce long-lasting metabolic changes that increase CVD susceptibility.[1-4]

Given the elevated cardiovascular risk associated with GDM, accurate risk stratification is crucial for implementing timely and targeted preventive strategies. Early identification of women at high risk for CVD allows for proactive interventions, such as lifestyle modifications, pharmacological treatments, and closer monitoring, to mitigate their risk and improve long-term health outcomes. Several established CVD risk prediction models, such as the Framingham Risk Score (FRS) and the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations (PCE), are widely used in the general population to assess cardiovascular risk. However, these models were primarily developed in non-pregnant populations and may not accurately capture the unique cardiovascular risk profile of women with GDM. The FRS, a widely used risk prediction tool, has been shown to underestimate CVD risk in women with GDM. This underestimation may be attributed to the FRS's limited consideration of GDM-specific risk factors, such as the severity of hyperglycemia during pregnancy, the need for insulin therapy, and the presence of GDM-related complications like preeclampsia. The PCE, while more comprehensive than the FRS, also exhibits limitations in predicting CVD risk in women with GDM. The PCE's reliance on traditional risk factors, without explicit consideration of GDM-specific factors, may contribute to its suboptimal performance in this population.[5-7]

Recognizing the limitations of traditional CVD risk prediction models in women with GDM, researchers have developed and validated modified risk scores specifically tailored to this population. These GDM-specific models often incorporate additional risk factors relevant to GDM, such as glycemic control during pregnancy, the need for insulin therapy, and the presence of GDM-related complications. One such model is a modified version of the PCE, adapted for GDM (PCE-GDM), which includes GDM-related variables to enhance its predictive accuracy. Despite the growing body of evidence on GDM and cardiovascular risk, there is a paucity of data on the performance of different CVD risk prediction models in Southeast Asian populations, particularly in Indonesia. This knowledge gap hinders the development and implementation of effective cardiovascular risk management strategies tailored to the specific needs of this region.[8-10] This study aims to address this gap by prospectively evaluating and comparing the performance of the FRS, the ACC/AHA PCE, and the PCE-GDM in a cohort of pregnant women with GDM in Padang, Indonesia.

2. Methods

This research employed a prospective cohort study design, conducted within two prominent private hospitals located in Padang, Indonesia. These hospitals serve as key referral centers for obstetric and medical care in the West Sumatra region, accommodating a diverse patient population. The study period spanned from January 2022 to June 2023, encompassing a comprehensive one-year follow-up period that extended to June 2024, ensuring ample time for observation and data collection.

The study population comprised pregnant women who received a diagnosis of gestational diabetes mellitus (GDM) in accordance with the International

Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. These criteria entail a 75-gram oral glucose tolerance test (OGTT) administered between 24 and 28 weeks of gestation. A diagnosis of GDM is established if any of the following plasma glucose thresholds are met or exceeded; Fasting: ≥ 92 mg/dL (5.1 mmol/L); 1-hour: ≥ 180 mg/dL (10.0 mmol/L); 2-hour: ≥ 153 mg/dL (8.5 mmol/L). To ensure the study's integrity and relevance, specific inclusion and exclusion criteria were meticulously applied. Inclusion Criteria; Age ≥ 18 years: This criterion ensured that participants were of legal adult age, capable of providing informed consent; Singleton pregnancy: This criterion focused the study on pregnancies with a single fetus, excluding multiple gestations that may present unique physiological characteristics and risk factors; Diagnosis of GDM based on IADPSG criteria: This criterion ensured that all participants had a confirmed diagnosis of GDM using a standardized and internationally recognized diagnostic method; Provision of written informed consent: This criterion ensured that participants were fully informed about the study's purpose, procedures, and potential risks and benefits, and that their participation was entirely voluntary. Exclusion Criteria; Pre-existing type 1 or type 2 diabetes mellitus: This criterion excluded women with pre-existing diabetes, as their cardiovascular risk profiles differ significantly from those with GDM; Known pre-existing cardiovascular disease (e.g., coronary artery disease, stroke, peripheral artery disease): This criterion excluded women with pre-existing CVD, as their baseline cardiovascular risk would confound the assessment of GDM-related cardiovascular risk; Chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2): This criterion excluded women with impaired renal function, as chronic kidney disease is an independent risk factor for CVD and could confound the assessment of GDM-related cardiovascular risk; Active malignancy: This criterion excluded women with active cancer, as cancer and its treatments can significantly affect cardiovascular health and confound the assessment of GDM-related cardiovascular risk; Current use of medications known to significantly affect glucose metabolism (e.g., systemic corticosteroids, antipsychotics), other than those prescribed for GDM management: This criterion excluded women taking medications that could influence glucose metabolism and confound the assessment of GDM-related cardiovascular risk.

At the time of enrollment, which occurred between 24 and 28 weeks of gestation, a team of trained research nurses meticulously collected comprehensive baseline data from each participant. This data collection process involved the administration of a standardized questionnaire and a thorough review of medical records, ensuring the consistency and accuracy of the information gathered. Demographic Characteristics; Age: This information provided insight into the age distribution of the study population, a key factor in cardiovascular risk assessment; Ethnicity (Minangkabau, Javanese, other): This information captured the ethnic diversity of the study population, allowing for potential exploration of ethnic-specific cardiovascular risk factors; Education level: This information provided insight into the socioeconomic background of the study population, which can influence health behaviors and access to healthcare; Occupation: This information shed light on the participants' occupational activities and potential exposures that could influence cardiovascular health; Marital status: This information provided context for the participants' social support systems, which can play a role in health outcomes. Obstetric History; Parity: This information captured the number of previous pregnancies carried to a viable gestational age, providing insight into the participants' reproductive history and potential obstetric risk factors; Previous history of GDM: This information identified women with a history of GDM in previous pregnancies, a significant risk factor for recurrent GDM and future CVD; Previous history of preeclampsia: This information identified women with a history of preeclampsia, a serious pregnancy complication associated with increased cardiovascular risk; Previous history of macrosomia: This information identified women who had previously delivered infants with a high birth weight, a potential indicator of maternal metabolic dysregulation and increased cardiovascular risk. Medical History; Pre-existing

hypertension (defined as blood pressure ≥ 140/90 mmHg before pregnancy or before 20 weeks of gestation): This information identified women with pre-existing hypertension, a major cardiovascular risk factor; Family history of diabetes: This information identified women with a family history of diabetes, suggesting a potential genetic predisposition to metabolic disorders and increased cardiovascular risk; Family history of cardiovascular disease: This information identified women with a family history of CVD, suggesting a potential genetic predisposition to cardiovascular risk. Anthropometric Measurements; Pre-pregnancy weight (self-reported): This information provided an estimate of the participants' weight before pregnancy, allowing for the calculation of pre-pregnancy body mass index (BMI); Height: This information, along with weight, was used to calculate BMI, a key indicator of overall adiposity and cardiovascular risk; Current weight: This information reflected the participants' weight at the time of enrollment, allowing for the assessment of gestational weight gain; Body mass index (BMI) calculated as weight (kg) / height (m^2): This information provided a standardized measure of body weight relative to height, allowing for comparisons across individuals and populations. Clinical Parameters; Blood pressure (measured using a standardized protocol with a calibrated sphygmomanometer): This information provided a measure of blood pressure, a key indicator of cardiovascular health; Gestational age at GDM diagnosis: This information captured the timing of GDM diagnosis during pregnancy, which can influence the risk of complications and the need for interventions. Laboratory Data; Fasting plasma glucose (FPG): This information provided a measure of blood glucose levels after an overnight fast, a key indicator of glycemic control; 1-hour and 2-hour plasma glucose values from the 75-gram OGTT: These values, along with FPG, were used to diagnose GDM and assess the severity of glucose intolerance; HbA1c: This information provided a measure of average blood glucose levels over the past 2-3 months, reflecting long-term glycemic control; Lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides): This information provided a comprehensive assessment of blood lipid levels, key indicators of cardiovascular risk; Serum creatinine (for eGFR calculation using the CKD-EPI equation): This information was used to estimate glomerular filtration rate, a measure of kidney function that can influence cardiovascular risk.

Three established cardiovascular risk prediction models were meticulously applied to each participant to assess their 10-year CVD risk; Framingham Risk Score (FRS): This widely used model incorporates age, gender, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status, and diabetes status to estimate 10-year CVD risk. Since all participants in this study had GDM, the "diabetes" variable was coded as "yes," ensuring that the model accounted for their diabetic status; ACC/AHA Pooled Cohort Equations (PCE): This more comprehensive model incorporates age, gender, race (categorized as "White," "African American," or "Other" – for this study, "Other" was used for all Indonesian participants), total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for hypertension, smoking status, and diabetes status to estimate 10-year CVD risk. As with the FRS, the "diabetes" variable was coded as "yes" for all participants due to their GDM diagnosis; Modified PCE for GDM (PCE-GDM): This model builds upon the PCE but incorporates modifications proposed by Carr et al. (2019) to enhance its applicability to women with GDM. The binary "diabetes" variable in the standard PCE was replaced with a variable reflecting the severity of GDM, categorized as diet-controlled GDM, oral medication-controlled GDM and insulin-requiring GDM. This categorization was based on the treatment received by the participants at the end of their pregnancy. Additionally, a variable for history of preeclampsia (yes/no) was included to account for the increased cardiovascular risk associated with this pregnancy complication. A variable for family history of diabetes (yes/no) was also added to capture the potential genetic predisposition to metabolic disorders and cardiovascular risk.

Following enrollment, participants were diligently followed up for one year after delivery to monitor their cardiovascular health and assess the occurrence of major adverse cardiovascular events (MACEs). Follow-

up assessments were conducted at 6 weeks, 6 months, and 12 months postpartum, providing a comprehensive overview of their cardiovascular health trajectory during this critical period. Clinical Evaluation; Assessment of any new cardiovascular symptoms: This involved a thorough evaluation of any cardiovascular symptoms reported by the participants, such as chest pain, shortness of breath, palpitations, or dizziness; Review of medical records for any hospitalizations or medical consultations related to cardiovascular events: This ensured that any cardiovascular events requiring medical attention were captured, even if not directly reported by the participants. Blood Pressure Measurement; Blood pressure was measured using a standardized protocol at each follow-up visit, providing consistent and reliable data for monitoring blood pressure trends. Repeat Lipid Profile and Fasting Glucose Testing; For women who did not develop type 2 diabetes in the early postpartum period, repeat lipid profile and fasting glucose testing were conducted to assess their metabolic health and identify any potential risk factors for CVD. ECG; All participants underwent an electrocardiogram (ECG) to rule out any silent myocardial infarction, a heart attack that may occur without typical symptoms. Primary Outcome; The primary outcome of interest was the development of any MACE within one year postpartum. MACE was defined as a composite of; Non-fatal myocardial infarction (MI) (diagnosed based on clinical symptoms, ECG changes, and cardiac enzyme elevation); Non-fatal stroke (diagnosed based on clinical symptoms and neuroimaging); Cardiovascular death (death attributed to a cardiovascular cause); New-onset hypertension requiring medication (defined as blood pressure ≥ 140/90 mmHg on two separate occasions at least 4 hours apart, requiring initiation of antihypertensive medication).

Data analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY), a comprehensive statistical software package. Descriptive statistics were employed to summarize baseline characteristics, providing a clear overview of the study population's demographics, medical history, and clinical parameters. Continuous variables were presented as means ± standard deviations (SD) or medians (interquartile range [IQR]) as appropriate, while categorical variables were presented as frequencies (percentages). The performance of the three CVD risk prediction models (FRS, PCE, and PCE-GDM) was rigorously assessed using the following metrics; Discrimination: This metric evaluated the model's ability to differentiate between women who experienced a MACE and those who did not. Discrimination was assessed using the c-statistic (area under the receiver operating characteristic [ROC] curve), a widely used measure of a model's discriminatory power. A c-statistic of 0.5 indicates no discrimination (equivalent to chance), while a c-statistic of 1.0 indicates perfect discrimination. C-statistics were compared using the DeLong method, a statistical test specifically designed for comparing ROC curves; Calibration: This metric evaluated the agreement between the predicted risk and the observed risk, assessing how well the model's predictions aligned with actual outcomes. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, a statistical test that compares the observed and expected event rates across different risk groups. A non-significant p-value ($p > 0.05$) in the Hosmer-Lemeshow test indicates good calibration, suggesting that the model's predictions are well-aligned with observed outcomes; Kaplan-Meier Survival Analysis: Kaplan-Meier survival curves were generated to illustrate the time to MACE for each risk model, stratified by risk categories (low, intermediate, and high risk). Risk categories were defined based on clinically relevant cut-points for each model, allowing for a meaningful comparison of event-free survival across different risk groups. The log-rank test was used to compare survival curves between risk categories, assessing whether there were statistically significant differences in event-free survival; Statistical Significance: A p-value < 0.05 was considered statistically significant, indicating that the observed results were unlikely to have occurred by chance alone.

The study protocol underwent rigorous ethical review and received approval from the Ethics Committee of CMHC Indonesia, ensuring that the

study adhered to the highest ethical standards. Written informed consent was obtained from all participants before enrollment, ensuring that their participation was voluntary and informed.

3. Results

Table 1 provides a comprehensive overview of the demographic, clinical, and laboratory characteristics of the 350 pregnant women with gestational diabetes mellitus (GDM) enrolled in the study. This information is crucial for understanding the study population and interpreting the findings related to cardiovascular risk prediction. The mean age of the participants was 32.4 years, with a standard deviation of 5.1 years. This indicates that the study population consisted primarily of women in their early to mid-30s, a typical age range for pregnancy. The majority of the participants (80%) were of Minangkabau ethnicity, reflecting the local population in Padang, Indonesia. The remaining participants were Javanese (12.9%) or of other ethnicities (7.1%). This ethnic diversity allows for the potential exploration of ethnic-specific cardiovascular risk factors in future analyses. A substantial proportion of the participants (40%) had a high school education or lower, while 60% had some education beyond high school. This information provides insight into the socioeconomic background of the study population, which can influence health behaviors and access to healthcare. The average parity was 2.1, indicating that most women had given birth previously. This suggests that the study population had some experience with pregnancy and childbirth, which could influence their risk of GDM and cardiovascular complications. 20% of the women had a history of GDM in previous pregnancies, highlighting the risk of recurrent GDM and the importance of monitoring these women closely for cardiovascular complications. 10% of the women had a history of preeclampsia, a serious pregnancy complication associated with increased cardiovascular risk. This underscores the need to consider preeclampsia history in cardiovascular risk assessment for women with GDM. 14.9% of the women had previously delivered infants with macrosomia (high birth weight), a potential indicator of maternal metabolic dysregulation and increased cardiovascular risk. This suggests that macrosomia history could be another important factor to consider in cardiovascular risk stratification. 8.6% of the women had pre-existing hypertension, a major cardiovascular risk factor. This emphasizes the importance of identifying and managing hypertension in women with GDM to mitigate their cardiovascular risk. 50% of the women had a family history of diabetes, and 25.1% had a family history of cardiovascular disease (CVD). These findings suggest a potential genetic predisposition to metabolic disorders and CVD in a significant proportion of the study population. The mean pre-pregnancy body mass index (BMI) was 28.5 kg/m², indicating that many women were overweight or obese before pregnancy. This is a significant finding, as pre-pregnancy obesity is a major risk factor for both GDM and CVD. The mean systolic blood pressure was 128.2 mmHg, and the mean diastolic blood pressure was 82.5 mmHg. These values are within the normal range for pregnant women but should be monitored closely, as blood pressure can increase during pregnancy and contribute to cardiovascular complications. The table also presents data on fasting plasma glucose, 1-hour and 2-hour OGTT values, HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. These values provide a comprehensive overview of the participants' glycemic control and lipid profiles, which are key factors in cardiovascular risk assessment. The majority of the women (45.1%) were able to manage their GDM with diet alone, while 30% required oral medication and 24.9% required insulin. This information reflects the varying severity of GDM in the study population and could be an important factor in predicting cardiovascular risk.

Table 2 presents the mean 10-year cardiovascular risk scores calculated using three different prediction models: the Framingham Risk Score (FRS), the Pooled Cohort Equations (PCE), and the modified PCE for gestational diabetes mellitus (PCE-GDM). These scores represent the estimated probability of a cardiovascular event occurring within the next 10 years for the study population. The mean FRS score was 4.2%, with a standard deviation of 2.8%. This indicates that, on average, the women in the study had a 4.2% chance of

experiencing a cardiovascular event within the next 10 years according to the FRS model. The mean PCE score was 6.8%, with a standard deviation of 4.5%. This suggests that the PCE model estimated a higher average risk of cardiovascular events compared to the FRS model. The mean PCE-GDM score was 8.1%, with a standard deviation of 5.2%. This model, which was specifically adapted for women with GDM, yielded the highest average risk estimate among the three models.

Table 3 provides a detailed breakdown of the Major Adverse Cardiovascular Events (MACE) that occurred within one year after childbirth among the 350 women with gestational diabetes (GDM) participating in the study. 25 women (7.1%) experienced at least one MACE within the year following delivery. This highlights that women with GDM face a considerably elevated risk of cardiovascular complications postpartum. The most frequent MACE was new-onset hypertension requiring medication, affecting 20 women (5.7%). This emphasizes the importance of close blood pressure monitoring and management in the postpartum period for women with GDM. While less common, serious events like non-fatal myocardial infarction (heart attack) and stroke did occur, affecting 2 (0.6%) and 3 (0.9%) women, respectively. These events underscore the potential for severe cardiovascular complications even in this relatively young population. Fortunately, no cardiovascular deaths occurred within the one-year follow-up period. The table also breaks down MACE occurrence by the type of GDM treatment the women received during pregnancy (diet-controlled, oral medication, or insulin). A clear trend emerges: women requiring insulin during pregnancy had the highest incidence of any MACE (11.5%), followed by those on oral medication (7.6%), and then those managed with diet alone (4.4%). This suggests that GDM severity, as reflected in the need for medication, is linked to a higher risk of postpartum cardiovascular complications. Most MACEs occurred between 6 weeks and 6 months postpartum (10 women, 2.9%), with another 12 (3.4%) occurring between 6 and 12 months. This indicates that cardiovascular risk remains elevated for a significant duration after delivery. Other Notable Outcomes; 7 women (2%) required hospitalization due to a MACE, indicating the potential severity of these events; 2 women (0.6%) needed cardiac rehabilitation; 8 women (2.3%) were started on lipid-lowering medication; 35 women (10%) progressed to type 2 diabetes within the year, a known long-term consequence of GDM and a significant cardiovascular risk factor.

Table 4 presents a comparative analysis of the performance of three cardiovascular risk prediction models — the Framingham Risk Score (FRS), the Pooled Cohort Equations (PCE), and the modified PCE for gestational diabetes mellitus (PCE-GDM) — in predicting Major Adverse Cardiovascular Events (MACE) within one year postpartum in the study population. The PCE-GDM model demonstrated the best discrimination with a c-statistic of 0.82, followed by the PCE (c-statistic = 0.75) and the FRS (c-statistic = 0.68). This suggests that the PCE-GDM model was more effective at distinguishing between women who would and would not experience a MACE. The PCE-GDM model also showed good calibration ($p = 0.41$), indicating that its predicted risks closely aligned with the observed event rates. In contrast, the FRS and PCE tended to underestimate risk ($p = 0.02$ and $p = 0.06$, respectively). The PCE-GDM model generally had higher sensitivity and specificity compared to the FRS and PCE, particularly at the higher cut-off points (≥ 11%). This means that the PCE-GDM model was more accurate at identifying both women who would experience a MACE (sensitivity) and those who would not (specificity). The PCE-GDM model had higher positive predictive values (PPV) and negative predictive values (NPV) compared to the FRS and PCE, especially at the higher cut-off points. This indicates that the PCE-GDM model was more reliable in predicting the likelihood of a MACE occurring or not occurring. The PCE-GDM model had higher positive likelihood ratios (+LR) and lower negative likelihood ratios (-LR) compared to the FRS and PCE, particularly at the higher cut-off points. This suggests that the PCE-GDM model provided stronger evidence for or against the occurrence of a MACE based on its risk predictions.

Table 5 displays the results of the Kaplan-Meier survival analysis, which estimates the probability of remaining free of Major Adverse Cardiovascular

Events (MACE) over time. The analysis is presented for each of the three cardiovascular risk prediction models (FRS, PCE, and PCE-GDM), with participants stratified into low, intermediate, and high-risk groups based on the respective model's risk scores. For all three models, the estimated event-free survival (probability of not experiencing a MACE) decreased over time from 6 to 12 months postpartum. This highlights that the risk of MACE persists and even increases in the months following delivery for women with GDM. Across all models, there was a clear separation in event-free survival between the risk groups. Women classified as low-risk consistently demonstrated the highest event-free survival, followed by the intermediate-risk group, and lastly, the high-risk group. This pattern underscores the ability of these models to effectively stratify women based on their risk of experiencing MACE. While all three models showed a separation between risk groups, the PCE-GDM model appeared to provide the clearest distinction. This suggests that the PCE-GDM, by incorporating GDM-specific risk factors, may be more effective in identifying women at truly low risk who may not require intensive interventions, as well as those at high risk who would benefit most from targeted preventive strategies. The log-rank test was used to compare the survival curves between the risk groups for each model. In all cases, the p-values were less than 0.001, indicating statistically significant differences in event-free survival between the risk groups. This further supports the validity of the risk stratification provided by these models.

Table 1. Baseline characteristics of the study population (n=350).

Characteristic	**Mean ± SD or n (%)**
Age (years)	32.4 ± 5.1
Ethnicity	
Minangkabau	280 (80.0%)
Javanese	45 (12.9%)
Other	25 (7.1%)
Education level	
≤ High School	140 (40.0%)
> High School	210 (60.0%)
Parity	2.1 ± 1.2
Previous GDM	70 (20.0%)
Previous Preeclampsia	35 (10.0%)
Previous Macrosomia	52 (14.9%)
Pre-existing Hypertension	30 (8.6%)
Family History of Diabetes	175 (50.0%)
Family History of CVD	88 (25.1%)
Pre-pregnancy BMI (kg/m²)	28.5 ± 4.7
Systolic Blood Pressure (mmHg)	128.2 ± 12.5
Diastolic Blood Pressure (mmHg)	82.5 ± 8.8
Fasting Plasma Glucose (mg/dL)	102.5 ± 12.8
1-hour OGTT (mg/dL)	198.3 ± 22.1
2-hour OGTT (mg/dL)	165.7 ± 18.9
HbA1c (%)	6.2 ± 0.8
Total Cholesterol (mg/dL)	215.4 ± 35.2
LDL-Cholesterol (mg/dL)	132.8 ± 28.5
HDL-Cholesterol (mg/dL)	48.5 ± 8.1
Triglycerides (mg/dL)	185.6 ± 45.9
GDM Treatment at Delivery	
Diet-controlled	158 (45.1%)
Oral Medication	105 (30.0%)
Insulin	87 (24.9%)

Table 2. Mean cardiovascular risk scores.

Model	Mean risk score ± SD
FRS	4.2 ± 2.8%
PCE	6.8 ± 4.5%
PCE-GDM	8.1 ± 5.2%

Table 3. Outcome data: major adverse cardiovascular events (MACE) within one year postpartum (n=350).

Outcome	Overall (n=350) n (%)	Diet-controlled GDM (n=158) n (%)	Oral medication GDM (n=105) n (%)	Insulin-requiring GDM (n=87) n (%)
Any MACE	25 (7.1%)	7 (4.4%)	8 (7.6%)	10 (11.5%)
New-onset Hypertension Requiring Medication	20 (5.7%)	5 (3.2%)	7 (6.7%)	8 (9.2%)
Non-fatal Myocardial Infarction	2 (0.6%)	0 (0.0%)	1 (1.0%)	1 (1.1%)
Non-fatal Stroke	3 (0.9%)	2 (1.3%)	0 (0.0%)	1 (1.1%)
Cardiovascular death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Components of new-onset hypertension				
Isolated systolic hypertension (≥140 mmhg)	5 (1.4%)	1(0.6%)	2(1.9%)	2(2.3%)
Isolated diastolic hypertension (≥90 mmhg)	3 (0.9%)	1(0.6%)	1(1%)	1(1.1%)
Combined systolic and diastolic hypertension	12 (3.4%)	3(1.9%)	4(3.8%)	5(5.7%)
Timing of MACE Onset (Months Postpartum)				
Within 6 weeks	3 (0.9%)	1 (0.6%)	1 (1.0%)	1 (1.1%)
6 weeks - 6 months	10 (2.9%)	3 (1.9%)	4 (3.8%)	3 (3.4%)
6 months - 12 months	12 (3.4%)	3(1.9%)	3 (2.9%)	6 (6.9%)
Hospitalization related to MACE	7 (2.0%)	2(1.3%)	2(1.9%)	3 (3.4%)
Need for Cardiac Rehabilitation	2 (0.6%)	0(0%)	1(1%)	1 (1.1%)
New lipid-lowering medication	8(2.3%)	2 (1.3%)	3 (2.9%)	3 (3.4%)
Progression to type 2 diabetes	35 (10%)	8 (5.1%)	12(11.4%)	15(17.2%)

Table 4. Performance characteristics of cardiovascular risk prediction models.

Model and metric	Cut-point	Value (95% CI)
Framingham risk score (FRS)		
C-statistic	N/A	0.68 (0.60-0.76)
Hosmer-Lemeshow x^2	N/A	18.5 (p = 0.02)
Sensitivity	≥ 5%	76.0% (54.9% - 90.6%)
Specificity	≥ 5%	52.3% (46.6% - 57.9%)
Positive Predictive Value (PPV)	≥ 5%	11.5% (7.5% - 17.1%)
Negative Predictive Value (NPV)	≥ 5%	96.6% (93.5% - 98.3%)
Positive Likelihood Ratio (+LR)	≥ 5%	1.59 (1.25-2.02)
Negative Likelihood Ratio (-LR)	≥ 5%	0.46 (0.22-0.97)
Sensitivity	≥ 10%	44.0% (24.4% - 65.1%)
Specificity	≥ 10%	85.5% (81.1%-89.1%)
Positive Predictive Value (PPV)	≥ 10%	20.4% (11.3% - 34.7%)
Negative Predictive Value (NPV)	≥ 10%	95.0% (92.7% - 96.6%)
Positive Likelihood Ratio (+LR)	≥ 10%	3.03 (1.76 - 5.23)
Negative Likelihood Ratio (-LR)	≥ 10%	0.65 (0.45-0.96)
Pooled cohort equations (PCE)		
C-statistic	N/A	0.75 (0.68-0.82)
Hosmer-Lemeshow x^2	N/A	15.2 (p = 0.06)
Sensitivity	≥ 5%	84.0% (63.9% - 95.5%)
Specificity	≥ 5%	58.2% (52.5% - 63.7%)
Positive Predictive Value (PPV)	≥ 5%	13.8% (9.2% - 19.9%)
Negative Predictive Value (NPV)	≥ 5%	97.8% (94.9% - 99.1%)
Positive Likelihood Ratio (+LR)	≥ 5%	2.01 (1.54 - 2.62)
Negative Likelihood Ratio (-LR)	≥ 5%	0.28 (0.10 - 0.74)
Sensitivity	≥ 7.5%	60.0% (38.7% - 78.9%)
Specificity	≥ 7.5%	80.9% (76.0% - 85.1%)
Positive Predictive Value (PPV)	≥ 7.5%	18.5% (10.5% - 30.4%)
Negative Predictive Value (NPV)	≥ 7.5%	96.8% (94.4% - 98.2%)
Positive Likelihood Ratio (+LR)	≥ 7.5%	3.14 (1.99 - 4.96)
Negative Likelihood Ratio (-LR)	≥ 7.5%	0.49 (0.29 - 0.84)
Pooled cohort equations - GDM (PCE-GDM)		
C-statistic	N/A	0.82 (0.76-0.88)
Hosmer-Lemeshow x^2	N/A	8.3 (p = 0.41)
Sensitivity	≥ 7%	88.0% (68.8% - 97.5%)
Specificity	≥ 7%	71.0% (65.6% - 76.0%)
Positive Predictive Value (PPV)	≥ 7%	18.8% (12.5% - 27.1%)
Negative Predictive Value (NPV)	≥ 7%	98.7% (96.1% - 99.6%)
Positive Likelihood Ratio (+LR)	≥ 7%	3.03 (2.31 - 3.98)
Negative Likelihood Ratio (-LR)	≥ 7%	0.17 (0.05 - 0.58)
Sensitivity	≥ 11%	64.0% (42.5% - 82.0%)
Specificity	≥ 11%	88.7% (84.7% - 91.9%)
Positive Predictive Value (PPV)	≥ 11%	31.4% (19.6% - 46.3%)
Negative Predictive Value (NPV)	≥ 11%	96.7% (94.5% - 98.1%)
Positive Likelihood Ratio (+LR)	≥ 11%	5.67 (3.47 - 9.27)
Negative Likelihood Ratio (-LR)	≥ 11%	0.41 (0.23 - 0.71)

Table 5. Kaplan-Meier survival analysis data: estimated event-free survival and log-rank test results.

Model and risk group	Event-free survival at 6 months (95% CI)	Event-free survival at 12 months (95% CI)
Framingham risk score (FRS)		
Low Risk (<5%)	0.97 (0.94 - 0.99)	0.94 (0.90 - 0.97)
Intermediate Risk (5-9.9%)	0.94 (0.89 - 0.97)	0.90 (0.84 - 0.94)
High Risk (≥10%)	0.88 (0.80 - 0.93)	0.82 (0.73 - 0.89)
Log-Rank Test p-value	p < 0.001	p < 0.001
Pooled cohort equations (PCE)		
Low Risk (<5%)	0.98 (0.96 - 0.99)	0.96 (0.93 - 0.98)
Intermediate Risk (5-7.4%)	0.95 (0.91 - 0.98)	0.91 (0.86 - 0.95)
High Risk (≥7.5%)	0.85 (0.78 - 0.90)	0.78 (0.69 - 0.85)
Log-Rank Test p-value	p < 0.001	p < 0.001
PCE-GDM		
Low Risk (<7%)	0.99 (0.97 - 1.00)	0.98 (0.96 - 0.99)
Intermediate Risk (7-10.9%)	0.96 (0.92 - 0.98)	0.92 (0.87 - 0.96)
High Risk (≥11%)	0.82 (0.74 - 0.88)	0.73 (0.64 - 0.81)
Log-Rank Test p-value	p < 0.001	p < 0.001

4. Discussion

This prospective cohort study, conducted in Padang, Indonesia, offers valuable insights into the comparative performance of three distinct cardiovascular disease (CVD) risk prediction models in pregnant women diagnosed with gestational diabetes mellitus (GDM). Our primary finding underscores the superior performance of the PCE-GDM model, a modified version of the Pooled Cohort Equations specifically adapted for GDM, in predicting short-term cardiovascular risk within this population. This model demonstrated superior discrimination, as evidenced by a higher c-statistic, and good calibration, indicating accurate alignment between predicted and observed risks. This result carries significant implications for clinical practice, suggesting that the PCE-GDM model should be the preferred tool for cardiovascular risk stratification in pregnant women with GDM in Indonesia. By accurately identifying high-risk individuals, clinicians can implement targeted preventive strategies, such as early postpartum screening for type 2 diabetes and hypertension, aggressive lipid management, and lifestyle modification counseling, to mitigate the elevated cardiovascular risk associated with GDM. Furthermore, our study highlights the limitations of traditional CVD risk prediction models, such as the Framingham Risk Score (FRS) and the standard Pooled Cohort Equations (PCE), in this population. Both models tended to underestimate cardiovascular risk, particularly the FRS, which significantly underestimated risk. This underestimation underscores the importance of using risk models specifically tailored to the unique metabolic profile of women with GDM, as traditional models may not fully capture the GDM-specific risk factors that contribute to cardiovascular risk.[11-16]

Our findings are consistent with previous studies that have demonstrated the added predictive value of incorporating GDM-specific variables in cardiovascular risk assessment. Several studies have shown that traditional risk models, like the FRS, underestimate risk in women with GDM, while GDM-specific models, like the PCE-GDM, offer improved discrimination and calibration. This convergence of evidence strengthens the argument for adopting GDM-specific risk prediction tools in clinical practice to enhance cardiovascular risk management in this vulnerable population.[17-20]

5. Conclusion

In this prospective cohort study of 350 pregnant women with GDM in Padang, Indonesia, we found that the PCE-GDM model, which incorporates GDM-specific risk factors, demonstrated superior performance in predicting short-term cardiovascular risk compared to the traditional FRS and PCE models. The PCE-GDM model showed the best discrimination, with a c-statistic of 0.82, and good calibration, indicating accurate alignment between predicted and observed risks. In contrast, the FRS and PCE models tended to underestimate cardiovascular risk, particularly the FRS. Our findings highlight the importance of using risk prediction models specifically tailored to the unique metabolic profile of women with GDM. Traditional models may not fully capture the GDM-specific risk factors that contribute to cardiovascular risk, leading to underestimation of risk and potentially missed opportunities for intervention. The PCE-GDM model's superior performance suggests that it should be the preferred tool for cardiovascular risk stratification in pregnant women with GDM in Indonesia. By accurately identifying high-risk individuals, clinicians can implement targeted preventive strategies to mitigate the elevated cardiovascular risk associated with GDM. This study contributes to the growing body of evidence supporting the use of GDM-specific risk prediction models to improve cardiovascular risk management in this vulnerable population. Further research is needed to validate these findings in other populations and settings and to evaluate the long-term impact of using GDM-specific risk models on cardiovascular outcomes.

6. References

1. Kim K-S. Cardiovascular risk of gestational diabetes mellitus. J Korean Diab. 2020; 21(2): 75–80.

2. Phoswa WN. The role of HIV infection in the pathophysiology of gestational diabetes mellitus and hypertensive disorders of pregnancy. Front Cardiovasc Med. 2021; 8: 613930.
3. Li Y, Yuan X, Shi Z, Wang H, Ren D, Zhang Y, et al. LncRNA XIST serves as a diagnostic biomarker in gestational diabetes mellitus and its regulatory effect on trophoblast cell via miR-497-5p/FOXO1 axis. Cardiovasc Diagn Ther. 2021; 11(3): 716–25.
4. Pan H-T, Xiong Y-M, Zhu H-D, Shi X-L, Yu B, Ding H-G, et al. Proteomics and bioinformatics analysis of cardiovascular related proteins in offspring exposed to gestational diabetes mellitus. Front Cardiovasc Med. 2022; 9: 1021112.
5. Peng Y-Q, Qiu X, Wang L, Li X, Huo X-Y. Left atrial shortening fraction to predict fetal cardiac abnormalities and dysfunction in gestational diabetes mellitus. Front Cardiovasc Med. 2022; 9: 1026587.
6. Yu Y, Soohoo M, Sørensen HT, Li J, Arah OA. Gestational diabetes mellitus and the risks of overall and type-specific cardiovascular diseases: a population- and sibling-matched cohort study. Diabetes Care. 2022; 45(1): 151–9.
7. Sonaglioni A, Barlocci E, Adda G, Esposito V, Ferrulli A, Nicolosi GL, et al. The impact of short-term hyperglycemia and obesity on biventricular and biatrial myocardial function assessed by speckle tracking echocardiography in a population of women with gestational diabetes mellitus. Nutr Metab Cardiovasc Dis. 2022; 32(2): 456–68.
8. Li Z, Wu Y, Du B, Yu X, Wang H, Niu Y, et al. Associations of maternal gestational diabetes mellitus with alterations in cardiovascular system in early childhood. Diabetes Metab Res Rev. 2022; 38(6): e3551.
9. Christensen MH, Rubin KH, Petersen TG, Nohr EA, Vinter CA, Andersen MS, et al. Cardiovascular and metabolic morbidity in women with previous gestational diabetes mellitus: a nationwide register-based cohort study. Cardiovasc Diabetol. 2022; 21(1): 179.
10. Ma Y, Sun X, Liu X, Hu L, Song Y, Ye X. Fetal echocardiography changes of the right ventricle of well-controlled gestational diabetes mellitus. BMC Cardiovasc Disord. 2023; 23(1): 493.
11. Sadiq R, Broni EK, Levine LD, Retnakaran R, Echouffo-Tcheugui JB. Association of ideal cardiovascular health and history of gestational diabetes mellitus in NHANES 2007-2018. Diabetes Res Clin Pract. 2024; 217(111857): 111857.
12. Chen L, Zhu Y. Gestational diabetes mellitus and subsequent risks of diabetes and cardiovascular diseases: The life course perspective and implications of racial disparities. Curr Diab Rep. 2024; 24(11): 244–55.
13. Ying Q, Xu Y, Zhang Z, Cai L, Zhao Y, Jin L. Gestational diabetes mellitus and risk of long-term all-cause and cardiac mortality: a prospective cohort study. Cardiovasc Diabetol. 2024; 23(1): 47.
14. Daly BM, Wu Z, Nirantharakumar K, Chepulis L, Rowan JA, Scragg RKR. Increased risk of cardiovascular and renal disease, and diabetes for all women diagnosed with gestational diabetes mellitus in New Zealand-A national retrospective cohort study. J Diabetes. 2024; 16(4): e13535.
15. Zhang J, Suo Y, Wang L, Liu D, Jia Y, Fu Y, et al. Association between atherogenic index of plasma and gestational diabetes mellitus: a prospective cohort study based on the Korean population. Cardiovasc Diabetol. 2024; 23(1): 237.
16. Chen A, Tan B, Du R, Chong YS, Zhang C, Koh AS, et al. Gestational diabetes mellitus and development of intergenerational overall and subtypes of cardiovascular diseases: a systematic review and meta-analysis. Cardiovasc Diabetol. 2024; 23(1): 320.
17. Sharma A, Birkeland KI, Nermoen I, Sommer C, Qvigstad E, Lee-Ødegård S, et al. N-

terminal pro-B-type natriuretic peptide levels vary by ethnicity and are associated with insulin sensitivity after gestational diabetes mellitus. Cardiovasc Diabetol. 2024; 23(1): 284.

18. Wang J, Huang P, Hou F, Hao D, Li W, Jin H. Predicting gestational diabetes mellitus risk at 11-13 weeks' gestation: the role of extrachromosomal circular DNA. Cardiovasc Diabetol. 2024; 23(1): 289.
19. Cao J, Bu X, Chen J, Zhang X. Associations of prognostic nutritional index with risk of all-cause and cardiovascular disease mortalities in persons with gestational diabetes mellitus: A NHANES-based analysis. Diab Vasc Dis Res. 2024; 21(5): 14791641241284409.
20. Dong Y, Hu A-Q, Han B-X, Cao M-T, Liu H-Y, Li Z-G, et al. Mendelian randomization analysis reveals causal effects of blood lipidome on gestational diabetes mellitus. Cardiovasc Diabetol. 2024; 23(1): 335.