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Review Article

Influence of Prediabetes on Hospital Outcome after Coronary Artery Bypass Grafting

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2. Keywords

Prediabetes; Coronary artery disease; Coronary artery bypass grafting; Mortality

1. Absract

1.1. Background: Prediabetes is a precursor stage of Diabetes Mellitus (DM) affecting progress of coronary atherosclerosis.

12. Objective: To evaluate the association of prediabetes with adverse outcome after isolated coronary Artery Bypass Grafting (CABG).

1.3. Patients and Methods: This retrospective study of 3655 patients underwent CABG, identified 2150 non-diabetic patients after re-evaluation of glucose tests and HbA1c. Prediabetes was defined according to criteria of American Diabetic Association (ADA). Non-diabetic patients were divided into prediabetes (n=1068) and control (n=1082) groups. The primary outcome measures were early mortality and Major Cardiovascular And Cerebral Adverse Events (MACCE).

1.4. Results: Preoperative, operative and postoperative variables were similar between both groups. There was no significant association between prediabetes and postoperative adverse outcome. Receiver Operating Characteristic (ROC) plot demonstrates that HbA1c had a good accuracy to predict all-cause mortality, cardiac mortality, and MACCE. On multivariate logistic regression, the independent preoperative predictors of early mortality and MACCE in prediabetic patients were: age >70 years, dyslipidemia, and hypertension.

1.5. Conclusion: Prediabetes does not negatively affect early outcome after CABG, however coexistence of older age, dyslipidemia or hypertension with prediabetes could increase the odds of early mortality and MACCE. Preoperative screening for prediabetes using HbA1c, correction of the associated modifiable cardiovascular risk factors, and further studies are recommended.

3. Abbreviations

ADA: American Diabetic Association
CABG: Coronary Artery Bypass Grafting
CAD: Coronary Artery Disease
CCS: Canadian Cardiovascular Society
CHF: Congestive Heart Failure
COPD: Chronic Obstruction Pulmonary Disease
DM: Diabetes Mellitus
FPG: Fasting Plasma Glucose
HbA1c: Glycosated Hemoglobin
IFG: Impaired Fasting Glucose
IGT: Impaired Glucose Tolerance
LMS: Left Main Stem
MACCE: Major Adverse Cerebral And Cardiovascular Events
MI: Myocardial Infarction
NYHA: New York Heart Association
OGTT: Oral Glucose Tolerance Test
PCI: Percutaneous Coronary Intervention
PG: Postprandial Glucose

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4. Introduction

There is a close relation between Diabetes Mellitus (DM) and Coronary Artery Disease (CAD), with an increased risk for development of CAD in diabetic patients [1,2] and poorer prognosis in terms of short- and long-term mortality [3].

Prediabetes is an intermediate state between normoglycemia and DM associated also with an increased risk of cardiovascular disease [4,5]. On coronary angioscopic evaluation, coronary atherosclerosis severity and plaque vulnerability have been detected to be more advanced in prediabetic than in non-diabetic patients and comparable to that in diabetic patients [6].

The unfavorable impact of prediabetes on the natural course of CAD has been reported in patients with acute coronary syndrome [7], and in patients undergoing angiography [8] or Percutaneous Coronary Intervention (PCI) [9].

Diabetes mellitus has been considered by many authors as a significant predictor for morbidity and mortality after CABG [10-12]. However, little is known about the link between abnormal glucose states and adverse outcome after CABG in patients with no history of DM [13,14].

This study was designed to evaluate the association of prediabetes as determined by fasting plasma glucose (FPG), 2 hours postprandial glucose (2h PG) or hemoglobin A1C (HbA1c), with unfavorable outcome after CABG.

5. Patients and Methods

5. 1. Study design and setting

This retrospective study included a cohort of patients underwent isolated primary on-pump CABG between January 2011 and December 2015 at departments of cardiothoracic surgery in Nasser Institute Hospital, Mini University Hospital and Suez Canal University Hospital, Egypt.

5.2. Participants

The eligibility criteria were adult patients of both gender underwent primary CABG with exclusion of patients with history of DM, unrecognized DM, concomitant cardiac surgery, redo-CABG, off pump CABG, and invalid data regarding preoperative glucose tests or postoperative outcome of interest.

5.3. Variables

Primary outcome variables included: early mortality (all-cause and cardiac) and MACCE (all-cause death, nonfatal myocardial infarction, stroke, and repeat revascularization). The secondary operative and postoperative outcomes included: cross clamp time, bypass time, low cardiac output, postoperative arrhythmia, atrial fibrillation, atrial flutter, ventricular tachycardia, reoperation for bleeding, sternal re-suturing, duration of mechanical ventilation, respiratory complications, neurological complications, postoperative stroke, postoperative MI, wound infection, postoperative renal impairment and multisystem failure.

Early mortality was defined as death occurring at operative theatre or during the same hospital stay. We defined Major Cardiovascular and Cerebral Adverse Events (MACCE) as death, acute nonfatal myocardial infarction, need for coronary re-vascularization or stroke. The cross-clamp time was considered as prolonged when it was longer than 60 minutes, and the bypass time was prolonged when it was more than 120 minutes. The need for mechanical ventilatory support for more than 48 hours was referred to as prolonged mechanical ventilation. Low cardiac output was defined as the need for postoperative Intra-Aortic Balloon Pump (IABP) or inotropes for more than 30 minutes in ICU to maintain hemodynamic status. Prolonged hospital stay was defined as hospitalization for longer than 7 days after surgery.

To define predictors, patient was considered obese when his Body Mass Index (BMI) was ≥ 30 kg/m2. Dyslipidemia was defined by elevated plasma cholesterol, Triglycerides (TGs), or both, or a low High-Density Lipoprotein (HDL) level. Preoperative renal insufficiency was defined when serum creatinine >2 mg/dL or patient had chronic renal failure on dialysis. Left ventricular Ejection Fraction (EF) of 50% or lower was considered low. The surgery was defined as elective when it was scheduled in advance and non-elective (urgent or emergent) when it was performed immediately or within 48 hours of admission for life threatening conditions. Multi-vessel disease was recognized by involvement of at least two or three epicardial coronary arteries.

5.4. Data sources and measurements

Preoperative risk factors and comorbidities were recognized from documented evidence, or related investigatory reports. Postoperative outcome measures were determined from registry database or documented notes in the medical records. Prediabetes was defined according to the criteria of American Diabetic Association (ADA) [15], which include: Fasting Plasma Glucose (FPG) 100 mg/dL (5.6mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG), or 2 hours postprandial glucose (2-h PG) in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT), or HbA1C 5.7-6.4%.

5.5. Bias

We tried to reduce the potential sources of bias and strengthen the study by: first, exclusion of diabetic patients was not only based on the reported history of DM but also patients with unrecognized preoperative DM were excluded after re-evaluation of glucose tests and HbA1c; and second, we decided to conduct a multicenter study for recruitment of a larger number of patients and increasing the generalizability of the results.

5.6. Study size

Flow diagram of patient selection for the study is shown in **Figure 1**.

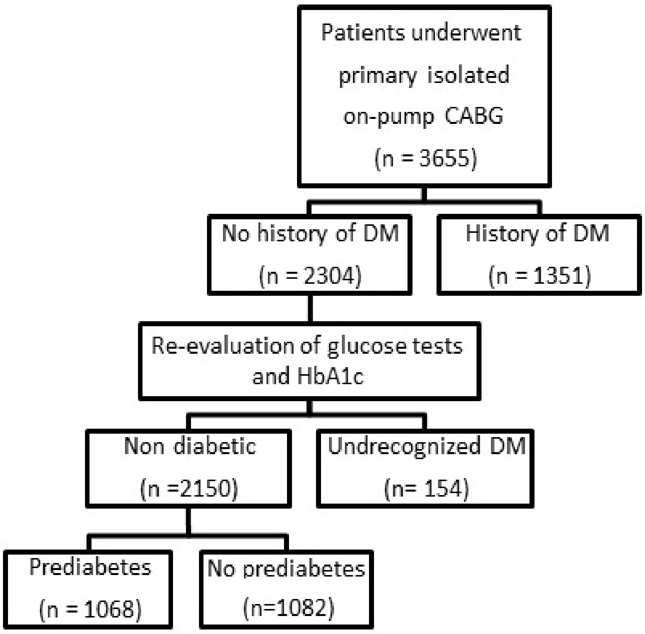

Figure 1: Flow diagram of patient selection for observational cohort study.

Out of 3655 patients with valid data, 1351 patients with history of DM and 154 patients (3.3%) with unrecognized DM were excluded after re-evaluation of glucose tests and HbA1c. The remaining 2150 non-diabetic patients were further subdivided into 2 groups; a case group included 1068 patients (22.9% of all patients) with prediabetes and a control group included 1082 patients had no abnormal glucose state.

5.7. Statistical methods

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 18.0 (SPSS, Inc, Chicago, IL, USA) and R Statistical Software version 2.14.0 (Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± Standard Deviation (SD) and categorical variables were expressed as number and percent (%). Shapiro-Wilk's significance test was used to assess the normality of data, and Student's t-test was used to assess the equality of variances. Independent groups of continuous data were compared using Student t-test or Mann-Whitney for non-parametric data, while categorical data were compared using Chi-square or Fisher exact test. Multivariate binary logistic regression (enter method) was used to determine the association of prediabetes and other preoperative risk factors with postoperative outcome measures. Odds Ratio (OR) and its 95% Confidence Interval (CI) were calculated. The sensitivity analysis was performed using receiver Operating Characteristic (ROC) plots and its area under curve (AUC) were used to determine the accuracy of HbA1c and glucose tests for prediction of adverse events. Significant p-values were defined at level of 0.05.

6. Results

Preoperative demographic and clinical characteristics in group of patients with prediabetes versus control group are presented in **Table 1**.

Table 1: Preoperative characteristics of patients with prediabetes and control group.

Variables	Prediabetes (n=1068)	Control (n=1082)	P-value
Age >70 years	41(3.83)	31(2.8)	0.20
Female gender	107(10.01)	103(9.51)	0.68
Obesity	336(31.46)	334(30.86)	0.78
CCS III-IV	369(34.55)	708(65.42)	0.98
NYHA III-IV	455(42.60)	604(55.81)	0.45
Unstable angina	25(2.34)	16(1.47)	0.14
Previous MI	104(9.73)	92(8.50)	0.35
Previous CHF	17(1.59)	10(0.92)	0.16
Previous PCI	107(10.01)	98(9.05)	0.48
Dyslipidemia	323(30.24)	310(28.65)	0.42
Hypertension	513(48.03)	483(44.64)	0.09
Hypothyroidism	10(0.93)	11(1.01)	0.85
Current smoking	183(17.1)	180(16.63)	0.74
Liver dysfunction	10(0.93)	6(0.55)	0.30
Renal insufficiency	10(0.93)	4(0.37)	0.10
COPD	5(0.46)	7(0.64)	0.58
Cerebrovascular disease	17(1.59)	21(1.94)	0.54
Peripheral vascular disease	9(0.84)	13(1.20)	0.41
Preoperative arrhythmia	5(0.46)	6(0.55)	0.78
Low ejection fraction	236(22.07)	233(21.52)	0.85
Urgent/emergent surgery	30(2.8)	24(2.2)	0.37
Multi-vessel disease	964(90.3)	981(90.7)	0.74
LMS disease	40(3.7)	28(2.6)	0.12

Data are expressed as number (percent). CCS: Canadian Cardiovascular Society, NYHA: New York Heart Association, COPD: Chronic Obstruction Pulmonary Disease, MI: Myocardial Infarction, CHF: Congestive Heart Failure, PCI: Percutaneous Coronary Intervention, CAD: Coronary Artery Disease, LMS: Left Main Stem, * Significant at 0.05 level.

During the study period, preoperative HbA1c was not routinely performed for all patients at our institutions. It was measured only in 876 non-diabetic patients (**Figure 2**); 562 patients in prediabetes group and 314 patients in control group. There were 193 patients (22%) with HbA1c > 6%, versus 683 patients (78%) with HbA1c ≤ 6%. The average of HbA1c was 5.46±0.54% in all patients, 5.74±0.44% in prediabetes group and 4.97±0.31% in control group.

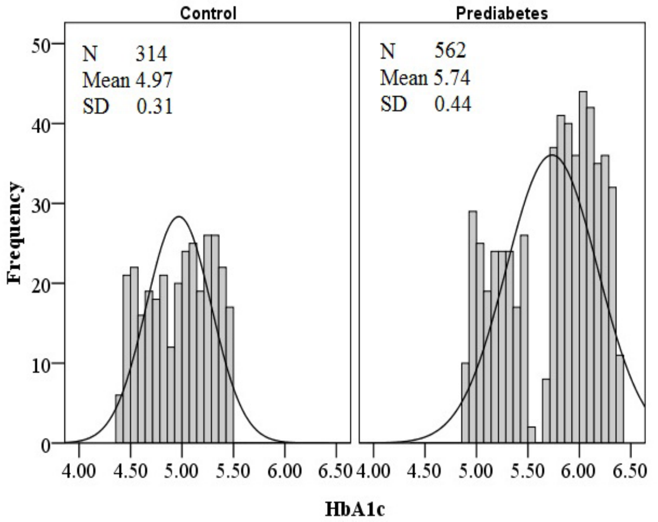

Figure 2: Histogram with normal distribution of HbA1c (%) measured in 562 prediabetics and 314 control patients.

The variables of operative and postoperative outcome were similar between patients with prediabetes and control **(Table 2)**.

Table 2: Operative and postoperative outcome of patients with prediabetes and control.

Variables	Prediabetes (n=1068)	Control (n=1082)	P-value
Cross clamp time > 60min	292(27.34)	271(25.04)	0.23
Bypass time > 120min	139(13.01)	123(11.36)	0.23
Low cardiac output	344(32.21)	315(29.11)	0.12
Postoperative arrhythmia	33(3.09)	36(3.32)	0.76
Atrial fibrillation	27(2.52)	30(2.77)	0.73
Atrial flutter	3(0.28)	4(0.37)	0.72
Ventricular tachycardia	3(0.28)	2(0.18)	0.64
Reoperation for bleeding	95(8.89)	91(8.41)	0.67
Sternal re-suturing	57(5.33)	65(6)	0.50
Prolonged ventilation >48 h	48(4.49)	33(3.05)	0.09
Respiratory complications	9(0.84)	6(0.55)	0.38
Neurological complications	8(0.74)	8(0.73)	0.77
Postoperative stroke	1(0.09)	4(0.37)	0.18
Postoperative MI	5(0.46)	2(0.18)	0.24
Wound infection	1(0.09)	2(0.18)	0.99
Postop renal impairment	10(0.93)	11(1.01)	0.53
Multisystem failure	2(0.18)	3(0.27)	0.66
All-cause mortality	55(5.15)	45(4.15)	0.27
Cardiac mortality	16(1.49)	15(1.38)	0.59
MACCE	58(5.43)	46(4.25)	0.19
Prolonged hospital stay	462(43.25)	437(40.38)	0.17

Data are expressed as number (percent). MI: Myocardial Infarction, MACCE: Major Adverse Cerebral And Cardiovascular Events.

Comparison between both groups revealed no significant differences. Incidences of the primary outcome measures in prediabetic group were not significantly different from the corresponding incidences in control group, including: all-cause mortality (5.15% versus 4.15%), cardiac mortality (1.49% versus 1.38%), and MACCE (5.43% versus 4.25%). Kaplan–Meier survival plots for early mortality after coronary artery bypass grafting in both groups is shown in **Figure 3**. The survival rate was 95.3% in all patients, 94.9% in prediabetes group and 95.8% in control group through mean follow-up period of 86.33 months.

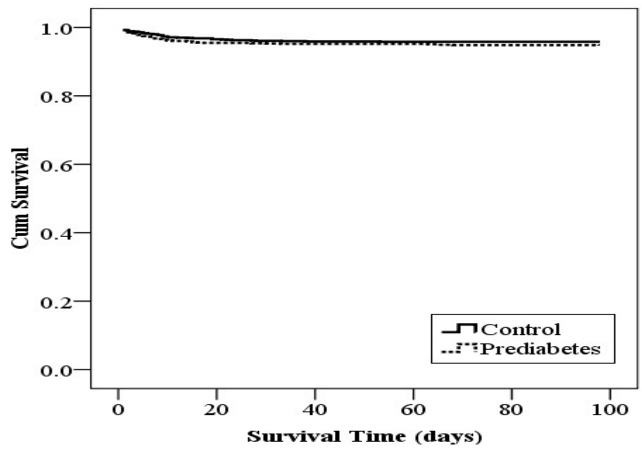

Figure 3: Kaplan–Meier survival plots for early mortality up to 100 days after coronary artery bypass grafting in groups of prediabetes and control.

Receiver Operating Characteristic (ROC) plots **(Figure 4)** in patients with prediabetes, demonstrate significant good area under curve (AUC) of HbA1c to predict all-cause mortality (AUC: 0.79, 95% CI: 0.72-86), cardiac mortality (AUC: 0.81, 95% CI: 0.72-0.90), and MACCE (AUC: 0.80, 95% CI: 0.73-0.87).

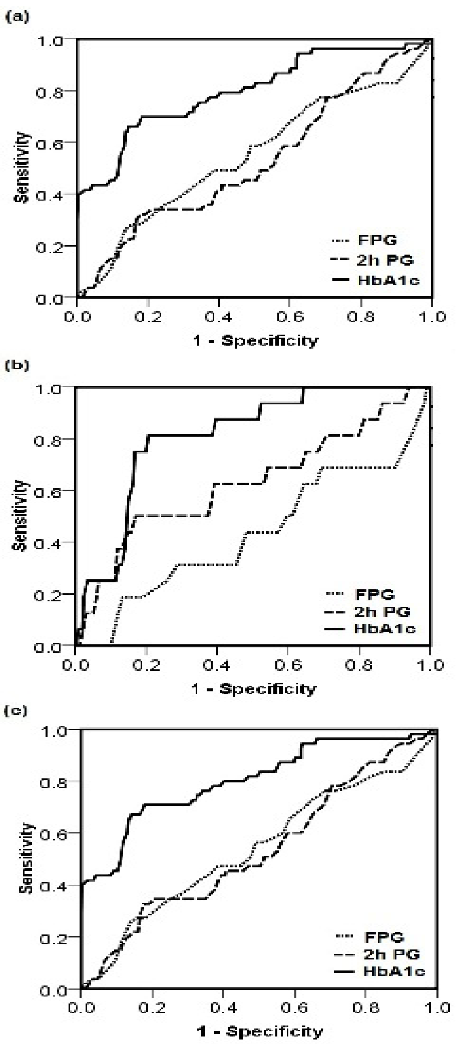

Figure. 4: ROC plots of Fasting Plasma Glucose (FPG), 2 hours postprandial glucose (2h PG), and HbA1c for prediction of: (a) all-cause mortality, (b) cardiac mortality and (c) Major Cardiovascular And Cerebral Adverse Events (MACCE).

For multivariate binary logistic regression of the risk factors of primary outcome measures in prediabetic patients, all preoperative variables were entered in a block in a single step (enter method). The independent predictors of early mortality in prediabetic patients **(Table 3)** were: age >70 years (OR: 3.01, 95% CI: 1.11-8.13, P =0.03), preoperative dyslipidemia (OR: 1.97, 95% CI: 1.12-3.44, P = 0.01), and hypertension (OR: 1.80, 95% CI: 1.01-3.20, P = 0.04). The independent predictors of MACCE in prediabetic patients (Table 3) included: age >70 years (OR: 2.82, 95% CI: 1.05-7.62, P = 0.04), dyslipidemia (OR: 1.91, 95% CI: 1.10-3.29, P = 0.02) and hypertension (OR: 1.82, 95% CI: 1.04-3.20, P = 0.03).

Table 3: Independent predictors of early all-cause mortality and major adverse cerebral and cardiovascular events (MACCE) in patients with prediabetes as determined by logistic regression.

Outcome	Predictors	Beta	SE	Wald	P-value	OR	95.0% CI for OR	
							Lower	Upper
Mortality	Age >70	1.10	0.50	4.71	0.03*	3.01	1.11	8.13
	Dyslipidemia	0.67	0.28	5.68	0.01*	1.97	1.12	3.44
	Hypertension	0.58	0.29	4.02	0.04*	1.80	1.01	3.20
MACCE	Age >70	1.04	0.50	4.22	0.04*	2.82	1.05	7.62
	Dyslipidemia	0.64	0.27	5.43	0.02*	1.91	1.10	3.29
	Hypertension	0.60	0.28	4.40	0.03*	1.82	1.04	3.20

SE: Standard Error. OR: Odds ratio. CI: Confidence Interval. * Significant at level of 0.05.

7. Discussion

The main finding of our study is the absence of a negative influence of prediabetes on early mortality and MACCE after CABG, however, the presence of modifiable cardiovascular risk factors, particularly dyslipidemia or hypertension increases the odds of prediabetes on early mortality and MACCE.

Determining the potential preoperative risk factors for adverse outcome after cardiac surgery, including Coronary Artery Bypass Grafting (CABG), is an important issue to ameliorate the morbidity and mortality by modifying the risk factors, offering specific preventive measures and improve outcome [8,16]. Assessment of the specific risk factors influencing postoperative outcome results in the development of a wide variety of risk stratification models during the last two decades [17,18].

The contemporary changes in the risk profile of patients undergoing CABG permits identification of further predictors [19]. The influence of prediabetes on adverse outcome after CABG in non-diabetic patients has not been extensively or exclusively evaluated. The available studies focus on detection of the prevalence of patients with undiagnosed DM or evaluate the diagnostic accuracy of preoperative glucose tests to determine dysglycemia in patients with no previous history of DM [13,14,20,21].

Detection of abnormal glycemic states in patients undergoing CABG with no history of DM is challenging due to absence of the consensus for a routine screening tool of preoperative dysglycemia. Our definition of prediabetes is based on the current ADA criteria which has the same cut-off value for IGT (140-200 mg/dL) as that in the criteria of World Health Organization (WHO), but it has a lower cut-off value for IFG (100-125 mg/dL) and additional HbA1c based criteria of a level of 5.7 to 6.4% [15]. These criteria are different from the past policies which focused on examination of blood glucose using fasting blood glucose and 2 hour Oral Glucose Tolerance Test (OGTT) to recognize an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal [22].

The best tool to detect patients with prediabetes is still controversial. The study Heianza et al. [23] concluded that diagnosis of prediabetes by both the HbA1c 5.7-6.4% ADA criterion and impaired fasting glucose identified individuals with an increased risk of progression to diabetes. However, the study by Olson et al. [24] showed that the proposed HbA1c diagnostic criteria by ADA were insensitive and racially discrepant for screening, missing most patients with undiagnosed diabetes and prediabetes.

Recently, it has been suggested that the measurement of HbA1c according to ADA criteria is a reliable diagnostic approach to identify patients at high risk for diabetes and cardiovascular disease especially in settings where OGTT is rarely used and never repeated as a confirmatory test, and eliminates a long series of biological and analytical limits [25].

Among individuals undergoing CABG with no previous history of diabetes, there is a substantial amount of undiagnosed dysglycemia [21]. Out of 3655 patients underwent CABG, we defined prediabetes in 29.2% and it accounts for 49.6% of 2150 non-diabetic patients. This ratio is consistent with the previously reported prevalence of prediabetes in patients with ischemic heart disease at our country which exceeds 23% [26].

In literature the variation in the prevalence of prediabetes in patients undergoing CABG might be contributed to the variable criteria used for definition of prediabetes. Our high percentage of patients with prediabetes is supported by other studies in literature. Gianchandani et al. [27] used the same ADA criteria reported prediabetes in 59% of 61 patients without diabetes with planned elective cardiac surgery procedures. McGinn et al. [21] used HbA1c as the sole criterion for diagnosing dysglycemia, and found that 57% out of 630 patients with no known diabetic history had HbA1c falling in the increased risk for diabetes range (5.7-6.4%), which represents 34% of 1045 consecutive patients undergoing CABG. In another study based on measurement of HbA1c, Engoren et al. [22] reported 57% of 163 non-diabetic patients had elevated HbA1c levels ≥ 6.0%, with 12% having levels ≥ 7.0%.

Using preoperative FPG, the study by Anderson et al. [28] included 1895 patients underwent primary CABG and demonstrated impaired FPG levels as a prediabetic state in 8.3% of all patients and in 11% after exclusion of patients with clinical diabetes. Based only on preoperative Oral Glucose Tolerance Test (OGTT) results, Greberski et al. [29] reported prediabetic states in the form of abnormal fasting glycaemia or impaired glucose tolerance in 30.8% of 117 patients selected for elective CABG and in 43.9% among patients without previously known glucose metabolism disturbances. In a prospective study by Petursson et al. [14] which included 244 patients undergoing CABG without previously known diabetes, 24% had prediabetes on the basis of OGTT.

Although our patients with prediabetes had poorer prognosis than patients with normoglycemia in regard to higher rates of early mortality and MACCE, we did not demonstrate a significant association between prediabetes and any of our analyzed postoperative adverse outcomes. Prediabetes increases the risk to develop DM and may still undiagnosed for many years, thus absence of its association with postoperative adverse outcomes does not reduce the importance of aggressive pre- and post-operative approaches for prevention and treatment. This view may be supported by the results of the study by Petursson et al. [14] who found that increasing the severity of abnormal glucose regulation could predict a poor outcome after CABG. In comparison with patients with normoglycaemia, patients with prediabetes had a higher risk of new long-term cardiovascular events after CABG including death, MI, stroke and need for revascularization.

In the present study, HbA1c has a good accuracy to predict all-cause mortality, cardiac mortality and MACCE in patients with prediabetes, which was comparable to that for FPG and 2h PG. The prognostic significance of HbA1c in patients hospitalized with CAD [30] and in unknown diabetic patients with acute MI [31] was proved in literature.

Our findings are supported by the study by Halkos et al. [32] which demonstrated a predictive role of elevated preoperative HbA1c level for adverse events after CABG, and testing of HbA1c may allow for more accurate risk stratification in these patients. Moreover, Hudson et al. [33] reported that an elevated preoperative HbA1c level (> 6%) in non-diabetics is predictive of early mortality after elective cardiac surgery.

In the present study, preoperative dyslipidemia and hypertension were independent predictors of early mortality and MACCE in patients with prediabetes. Hypertension and dyslipidemia are important risk factors of cardiovascular disease with higher prevalence in patients with prediabetes than in normoglycemics, indicating aggressive management of these risk factors [34,35]. Identification of the influence of other comorbidities on postoperative outcome emphasize the importance of screening for prediabetes, life style intervention including weight reduction and physical activity, in addition to management of the associated modifiable risk factors particularly dyslipidemia and hypertension that may help in preventing progression of the disease and improving outcome after surgery.

The present study has certain limitations: first, the retrospective nature with errors due to confounding; second, unavailability of data regarding follow-up duration longer than early stay; and third, non-routine measurement of HbA1c during the study period which reduces the role of HbA1c as a good screening tool for glycemic state. The external validity (generalizability) of these findings is limited because only 3% of the study population was above 70 years and only 10% were women. This is quite far from other contemporary reports from Europe and North-America, but it comes in accordance to the age structure at our country as older population accounts only for 4.22% of Egyptians and for 3.5% of total African population [36].

8. Conclusions

In conclusion, diabetes mellitus is well known risk factor to modify natural course of coronary artery disease and to affect outcome after coronary artery surgery. As a precursor stage, prediabetes has an important role in progress of cardiovascular diseases. The results of our cohort study concerning the impact of prediabetes on outcome after CABG did not show a direct association between prediabetes and adverse outcome, however presence of dyslipidemia or hypertension increases the odds of early mortality and MACCE. Until carrying out further studies in literature, identification of prediabetes and correction of associated modifiable risk factors are recommended before CABG.

9. Conflict of interest: None

10. Funding: None

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