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# The Predictors of Diabetes and Pre-Diabetes Incidentally Detected at the Time of Diagnosis of Acute Coronary Syndrome: A Cross-Sectional Study

## Akut Koroner Sendrom Tanısı Sırasında Rastlantısal Olarak Saptanan Diyabet ve Prediyabetin Öngörücüleri: Bir Kesitsel Çalışma

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**ABSTRACT Objective:** There is a strong relationship between diabetes mellitus (DM) and cardiovascular diseases-related mortality and morbidity. Patients with DM are more likely to have more serious cardiovascular diseases and have higher complication rates than non-diabetic individuals. We aimed to investigate the rates of DM and pre-DM that were detected incidentally at the time of index acute coronary syndrome (ACS) and the factors that could predict incidental DM and pre-DM. Also, to investigate the factors associated with major adverse cardiovascular events (MACE) due to ACS. **Material and Methods:** This retrospective study included 1,882 patients without known DM or pre-DM diagnoses who were hospitalized and treated for ACS. The patients were divided into the following three classes: non-DM (n=582), pre-DM (n=602), and undiagnosed DM (un-DM, n=698). **Results:** We found that higher age (p<0.001), female sex (p<0.001), higher body mass index (p<0.001), hyperlipidemia (p<0.001), previous peripheral artery disease (p=0.012), previous cerebrovascular disease (p=0.021), and renal diseases (p=0.017) were independently associated with pre-DM and un-DM. High age (p<0.001), renal diseases (p<0.001), ST-elevation myocardial infarction (p=0.008), un-DM (p<0.001), and pre-DM (p=0.044) were independently associated with an increased MACE risk, while hyperlipidemia (p<0.001) and antiaggregant use (p=0.012) were independently associated with a decreased MACE risk. **Conclusion:** The above-mentioned risk factors can be used to predict (pre)DM before ACS or to assess MACE risk after ACS. Such risk stratification may contribute to reducing cardiovascular mortality and morbidity that are increased by (pre)DM and MACE.

**Keywords:** Acute coronary syndrome; diabetes mellitus; major adverse cardiovascular events; pre-diabetes; ST-elevation myocardial infarction

**ÖZET Amaç:** Diabetes mellitus (DM) ile kardiyovasküler hastalıklara bağlı mortalite ve morbidite arasında güçlü bir ilişki vardır. DM'li hastaların diyabetik olmayanlara göre daha ciddi kardiyovasküler hastalıklara yakalanma ve daha yüksek komplikasyon oranlarına sahip olma olasılığı daha yüksektir. Bu çalışmada, indeks akut koroner sendrom (AKS) sırasında rastlantısal olarak saptanan DM ve pre-DM oranlarını ve rastlantısal DM ve pre-DM'yi öngörebilecek faktörleri araştırmayı amaçladık. Ayrıca AKS'ye bağlı majör advers kardiyovasküler olaylar [major adverse cardiovascular events (MACE)] ile ilişkili faktörleri araştırdık. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya, bilinen DM veya pre-DM tanıları olmayan ve AKS nedeniyle hastaneye yatırılarak tedavi edilen 1.882 hasta dâhil edildi. Hastalar şu 3 gruba ayrıldı: DM olmayan (n=582), pre-DM (n=602) ve tanı konmamış DM [undiagnosed DM (un-DM)] (n=698). **Bulgular:** İleri yaş (p<0,001), kadın cinsiyet (p<0,001), beden kitle indeksi artışı (p<0,001), hiperlipidemi (p<0,001), geçirilmiş periferik arter hastalığı (p=0,012), geçirilmiş serebrovasküler hastalık (p=0,021), böbrek hastalıklarının (p=0,017) pre-DM ve un-DM ile bağımsız olarak ilişkili olduğu bulunmuştur. İleri yaş (p<0,001), böbrek hastalıkları (p<0,001), ST elevasyonlu miyokard infarktüsü (p=0,008), un-DM (p<0,001) ve pre-DM (p=0,044) bağımsız olarak artmış MACE riski ile ilişkiliyken, hiperlipidemi (p<0,001) ve antiagregan kullanımı (p=0,012) bağımsız olarak azalmış MACE riski ile ilişkiliydi. **Sonuç:** Yukarıda belirtilen risk faktörleri AKS öncesinde (pre)DM ve AKS sonrasında MACE'yi öngörmek için kullanılabilir. Bu risk faktörleri kullanılarak yapılacak risk tabakalandırması, (pre)DM ve MACE ile artan kardiyovasküler mortalite ve morbiditenin azaltılmasına katkıda bulunabilir.

**Anahtar Kelimeler:** Akut koroner sendrom; diabetes mellitus; majör advers kardiyovasküler olay; prediyabet; ST elevasyonlu miyokard infarktüsü

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Nearly half of all deaths due to cardiovascular disease (CVD) are caused by ischemic heart disease.[1,2] Acute coronary syndrome (ACS) is a heterogeneous entity of CVD, comprised of unstable angina pectoris (USAP), ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI).[3]

Although there are considerable global differences in revascularization and long-term mortality rates after ACS, around 12% of disability-adjusted life years lost yearly worldwide are associated with ischemic heart disease.[2,4] There are global variations in ACS risks, incidence, availability of treatment, and outcomes.[5] In recent years, the prevalence of common ACS risk factors has increased, including older age, smoking, hyperlipidemia, hyperglycemia, obesity, hypertension and exposure to air pollution, particularly in low-income countries.[6,7]

Diabetes mellitus (DM) is widespread and mainly affects the cardiovascular system.[8-10] DM is related to a two- to three-fold higher risk of CVD, and this figure is markedly increased in young-onset, long-standing diabetes and in the presence of comorbidities such as previous vascular events, chronic kidney disease, and clustering of risk factors.[8] The 2019 ESC Guidelines recommended that fasting blood glucose and glycated hemoglobin (HbA1c) should be measured to exclude the presence of DM in individuals presenting with cardiovascular events, and the oral glucose tolerance test (OGTT) should be added if other tests are inconclusive.[8] CVD burden is increased in patients with DM and subjects with moderately elevated plasma glucose. Thus, the increase in pre-DM and DM could increase mortality in at-risk populations.[7]

Although the factors associated with CVD risk in patients with DM are partially known, the predictability of DM and pre-DM is unknown in patients with high risk for ACS but without dysglycemia. This is important because the parameters by which cardiologists can predict patients at higher risk for pre-DM and DM may help them to detect patients at critical risk for cardiovascular events, thereby allowing precautionary measures. In this study, the primary aim was to investigate the frequencies of incidental DM and pre-DM diagnoses at the time of index ACS diagnosis. In relation, we also sought to assess factors that could predict DM development in patients with ACS who did not have diabetes-related diagnoses. Second, we aimed to identify major adverse cardiovascular events (MACE) associated with ACS and to determine the factors associated with the development of these events.

## MATERIAL AND METHODS

### ETHICAL CONSIDERATIONS

Clinical Research Ethics Committee of Haseki Training and Research Hospital (date: September 14, 2022; no: 177-2022) performed a written evaluation of all planned processes that were part of this study and provided approval for the conduct of this research. The approval confirmed that all steps of the research were performed with respect to the ethical standards of the Declaration of Helsinki.

### RESEARCH DESIGN

This cross-sectional study was conducted in the department of cardiology of our hospital. The study included 1,882 patients who were hospitalized and treated for ACS in the cardiology inpatient ward or coronary intensive care unit of our hospital, between January 2016 and December 2021. Patients aged younger than 18 years, patients who could not be followed up and treated for ACS due to treatment refusal, those with known DM or pre-DM diagnosis or those using antidiabetic therapy before index ACS diagnosis, those with missing data, and patients who did not undergo laboratory research for DM or pre-DM were excluded from the study.

### DATA COLLECTION

The patients' sociodemographic data such as age, sex, and race, anthropometric data such as height and weight, smoking status, medical history, and information about the period they were followed with the diagnosis of ACS including laboratory results, type and treatment of ACS, diabetes status detected during the index ACS diagnosis, type and time of MACE during hospitalization, and hospital length of stay were obtained from hospital computer records, patient files, and the national registry system of the

Ministry of Health, Türkiye (https://enabiz.gov.tr/). Body mass index (BMI; kg/m$^2$) was obtained by dividing weight (kg units) by the square of height (meter units). The presence of hypertension, hyperlipidemia, chronic obstructive pulmonary disease, previous cerebrovascular disease, previous pulmonary embolism, renal disease, thyroid disease, malignancy, other chronic diseases, and the presence and type of previous coronary artery disease, previous peripheral artery disease, and previous deep vein thrombosis were investigated in the clinical history of the patients. Hyperlipidemia diagnosis was based on ESC and European Atherosclerosis Society guidelines.[11]

## ROUTINE MEASUREMENTS

Quantification was performed in certified local laboratories using routine and calibrated devices. The following parameters were examined, all of which were studied from the first venous blood taken after the patients were hospitalized for the diagnosis of ACS and before any intervention: glucose, HbA1c, urea and creatinine levels, and platelet counts. HbA1c measurement is routinely performed in patients with ACS in our clinic.

Based on the Diet in Renal Disease study, we used the modified equation to calculate estimated glomerular filtration rate (in mL/min per 1.73 m$^2$).[12] Creatinine clearance was calculated using the Cockcroft-Gault equation.[13] HbA1c levels were determined using immunoturbidimetric assays on a COBAS 400 device (Roche; Germany).

## ACS MANAGEMENT AND RELATED VARIABLES

ACS diagnosis, classification, and management were performed according to ESC guidelines.[14-16] ACS subtypes were defined as USAP, STEMI, and NSTEMI according to the electrocardiography and the cardiac biomarkers levels. STEMI was defined as: characteristic myocardial ischemia + ST elevation + release of cardiac biomarkers (troponin and creatine kinase-MB). Positive ST segment elevation was: ST elevation at the J point that was present in at least two contiguous leads (0.2 mv or 0.1 mv depending on lead and sex).[16,17] USAP and NSTEMI were described as electrocardiographic ST-segment depression or prominent T-wave inversion and/or positive cardiac enzymes in the absence of ST-segment elevation. Specifically, presence of cardiac enzyme elevation was defined as NSTEMI while absence was defined as USAP.[18]

After diagnosing ACS, angiography was ordered, particularly to ascertain vessel involvement with higher precision in patients with STEMI. It was performed within 24 hours via the Judkins techniques or radial approach.[19]

MACE was defined as cardiac death or any cardiac or vascular problem requiring intervention. The time of MACE was calculated as the day on which MACE developed after hospitalization with a diagnosis of ACS. Hospital length of stay was calculated as the time between admission with a diagnosis of ACS and discharge or in-hospital death.

After discharge, regular antiplatelet use was prescribed for a minimum of 6 months in those using dual antiplatelet drugs, and for a minimum of 1 year in those using single antiplatelet drugs.

## DIABETES DIAGNOSIS AND MANAGEMENT

Diabetes and pre-DM diagnoses and management were carried out according to most recent internationally-accepted diagnostic criteria.[20,21] HbA1c levels were measured from samples obtained immediately after hospitalization for ACS and the patients were classified into three groups: Non-DM was defined as a HbA1c level of <5.7%. Pre-DM was defined as 5.7% ≤HbA1c <6.5% in the absence of pre-DM or DM. Undiagnosed DM (un-DM) was defined as a HbA1c value greater than 6.4% in the absence of DM or pre-DM.

In this manuscript, (pre)DM refers to both DM and pre-DM.

## STATISTICAL ANALYSIS

Descriptive and comparative analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). All comparative analyses were based on a significant p value threshold of <0.05. Histogram and Q-Q plots were used to determine whether continuous variables were normally distributed. Normally distributed continuous variables were analyzed using the independent samples t-test or one-way

analysis of variance depending on the number of groups. Non-normally distributed continuous variables were analyzed using the Mann-Whitney U test or Kruskal-Wallis test depending on the number of groups. Categorical variables were analyzed using chi-square tests (Fisher's exact or Fisher-Freeman-Halton). Pairwise comparisons were adjusted using Bonferroni correction. Multivariable logistic regression analyses (forward conditional selection) were performed to determine significant factors independently associated with the pre-DM, un-DM, and MACE.

## RESULTS

The majority (79.12%, n=1,489) of the patients were male and the mean age was 57.40±11.54 years. Five hundred and eighty-two (30.92%) patients were in the non-DM group, 602 (31.99%) patients were in the pre-DM group, and 698 (37.09%) patients were in the un-DM group. MACE developed in 551 (29.28%) patients (Table 1).

Age, female sex proportion, and BMI were higher in the pre-DM and un-DM groups compared to non-DM ($p<0.001$ for all). Hypertension, hyperlipidemia, and previous cerebrovascular disease were more frequent in the pre-DM and un-DM groups compared to non-DM ($p<0.001$ for all). In the un-DM group, history of peripheral artery disease ($p=0.022$) and renal disease ($p<0.001$) were more common relative to non-DM. Glycemic parameters demonstrated the expected differences between groups ($p<0.001$) (Table 2). The un-DM group had significantly higher creatinine values compared to non-DM ($p=0.002$). Interestingly, the frequencies of antiaggregant use, MACE, and cardiac mortality were higher in the un-DM group compared to both of the other groups ($p<0.001$ for all). Hospital stay was longer among pre-DM and un-DM patients compared to non-DM ($p<0.001$ for both) (Table 2).

Logistic regression showed that higher age ($p<0.001$), female sex ($p<0.001$), higher BMI ($p<0.001$), hyperlipidemia ($p<0.001$), previous peripheral artery disease ($p=0.012$), previous cerebrovascular disease ($p=0.021$), and renal diseases ($p=0.017$) were independently associated with pre-

**TABLE 1:** Summary of variables.

| | |
|---|---|
| Age, years | 57.40±11.54 |
| Sex | |
| Female | 393 (20.88%) |
| Male | 1489 (79.12%) |
| Race | |
| Domestic | 1757 (93.36%) |
| Immigrant | 125 (6.64%) |
| Height, cm | 169.64±7.29 |
| Weight, kg | 81.36±11.45 |
| Body mass index, kg/m$^2$ | 28.28±3.70 |
| Smoking status | |
| Non-smoker | 352 (18.70%) |
| Passive smoker | 135 (7.17%) |
| Ex-smoker | 366 (19.45%) |
| Smoker | 1009 (53.61%) |
| Unknown | 20 (1.06%) |
| Hypertension | 863 (45.86%) |
| Hyperlipidemia | 1117 (59.35%) |
| Chronic obstructive pulmonary disease | 120 (6.38%) |
| Previous coronary artery disease | 445 (23.65%) |
| PTCA | 3 (0.16%) |
| PTCA+stent | 344 (18.28%) |
| CABG | 76 (4.04%) |
| CABG>stent | 22 (1.17%) |
| Previous peripheral artery disease | 60 (3.19%) |
| Right internal carotid artery | 1 (0.05%) |
| Left internal carotid artery | 8 (0.43%) |
| Bilateral internal carotid artery | 1 (0.05%) |
| Right lower extremity | 14 (0.74%) |
| Left lower extremity | 13 (0.69%) |
| Bilateral lower extremity | 23 (1.22%) |
| Previous cerebrovascular disease | 83 (4.41%) |
| Previous pulmonary embolism | 5 (0.27%) |
| Previous deep vein thrombosis | 8 (0.43%) |
| Right lower extremity | 1 (0.05%) |
| Left lower extremity | 4 (0.21%) |
| Bilateral lower extremity | 3 (0.16%) |
| Renal diseases | 145 (7.70%) |
| Thyroid diseases | 85 (4.52%) |
| Malignancy | 44 (2.34%) |
| Other chronic diseases | 57 (3.03%) |
| Glucose, mg/dL | 141 (114-203) |
| HbA1c, % | 6.5 (5.9-8.8) |
| Diabetes mellitus assessment | |
| No diabetes mellitus | 582 (30.92%) |
| Pre-diabetes mellitus | 602 (31.99%) |
| Undiagnosed diabetes mellitus | 698 (37.09%) |
| Urea, mg/dL | 32.5 (27-41) |
| Creatinine, mg/dL | 0.88 (0.76-1.05) |
| Creatinine clearance (mL/min/1.73 m$^2$) | 104.20±37.77 |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | 86.21±23.39 |
| Platelet (x10$^3$) | 246 (206-295) |

**TABLE 1:** Summary of variables *(continued)*.

| | |
|---|---|
| Type of ACS | |
| Unstable angina pectoris | 97 (5.15%) |
| NSTEMI | 758 (40.28%) |
| STEMI | 1027 (54.57%) |
| Anterior | 448 (23.80%) |
| Anteroseptal | 1 (0.05%) |
| Anterolateral | 8 (0.43%) |
| Lateral | 26 (1.38%) |
| High lateral | 19 (1.01%) |
| Posterolateral | 2 (0.11%) |
| Posterior | 37 (1.97%) |
| Inferior | 476 (25.29%) |
| Inferoposterior | 10 (0.53%) |
| Antiaggregant | 429 (22.79%) |
| Acetylsalicylic acid | 280 (14.88%) |
| Clopidogrel | 38 (2.02%) |
| Acetylsalicylic acid+clopidogrel | 88 (4.68%) |
| Acetylsalicylic acid+ticagrelor | 23 (1.22%) |
| Anticoagulant | 26 (1.38%) |
| Warfarin | 7 (0.37%) |
| Dabigatran | 2 (0.11%) |
| Apixaban | 4 (0.21%) |
| Edoxaban | 4 (0.21%) |
| Rivaroxaban | 9 (0.48%) |
| Major adverse cardiovascular event1 | 551 (29.28%) |
| Cardiogenic shock | 25 (1.33%) |
| Complete AV block | 42 (2.23%) |
| Cerebrovascular disease | 34 (1.81%) |
| Deep vein thrombosis | 1 (0.05%) |
| Heart failure | 132 (7.01%) |
| Pulmonary embolism | 1 (0.05%) |
| Pericardial tamponade | 1 (0.05%) |
| Reinfarction | 15 (0.80%) |
| Urgent revascularization>CABG | 43 (2.28%) |
| Urgent revascularization>PCI | 88 (4.68%) |
| Ventricular fibrillation | 18 (0.96%) |
| Ventricular fibrillation>arrest>CPR | 54 (2.87%) |
| Ventricular tachycardia | 30 (1.59%) |
| Cardiac mortality | 248 (13.18%) |
| Time of major adverse cardiac event, days | 1 (1-2) |
| Length of hospital stay, days | 3 (2-4) |

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. 1Patients may have more than one of the following; PTCA: Percutaneous transluminal coronary angioplasty; CABG: Coronary artery bypass grafting; HbA1c: Glycated hemoglobin; ACS: Acute coronary syndrome; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; AV: Atrioventricular; PCI: Percutaneous coronary intervention; CPR: Cardiopulmonary resuscitation.

DM and un-DM. Other variables included in the analysis, height (p=0.942), weight (p=0.953), smoking status (p=0.121), hypertension (p=0.274), previous coronary artery disease (p=0.057), and antiaggregant use (p=0.951), were found to be non-significant (Table 3).

Next, we compared patients with and without MACE. Patients with MACE were older than those without (p<0.001). Hyperlipidemia was significantly rarer in the MACE group (p<0.001), but previous cerebrovascular disease (p=0.002) and renal disease (p<0.001) were more frequent. MACE was associated with higher fasting glucose, urea, and creatinine levels (p<0.001 for all). The frequency of un-DM was significantly higher in patients with MACE (p<0.001 for both) (Figure 1). STEMI was more common in the MACE group, while NSTEMI and USAP were more common in those without MACE (p<0.001). Hospital stay was longer in the presence of MACE (p<0.001) (Table 4).

Logistic regression revealed that high age (p<0.001), renal diseases (p<0.001), and STEMI (p=0.008) were independently associated with increased MACE risk; whereas hyperlipidemia (p<0.001) and antiaggregant use (p=0.012) were independently associated with lower MACE risk. Patients with un-DM had a 1.927-fold higher risk of MACE than patients with non-DM (p<0.001) and patients with pre-DM had a 1.327-fold higher risk of MACE than patients with non-DM (p=0.044). Other variables included in the analysis, smoking status (p=0.232) and previous cerebrovascular disease (p=0.077), were found to be non-significant (Table 5).

## DISCUSSION

The current study revealed that the incidentally-detected un-DM rate was 37.09% and the pre-DM rate was 31.99% in patients who developed ACS without a previously known diagnosis of (pre)DM. Advanced age, female sex, high BMI, hyperlipidemia, previous peripheral artery and cerebrovascular disease, and renal diseases were independently associated with incidental (pre)DM in patients with ACS. Advanced age, renal diseases, incidental (pre)DM diagnosis, and the presence of STEMI were independent risk factors for MACE. Antiaggregant use and hyperlipi-

**TABLE 2:** Summary of variables with regard to DM assessment.

| | DM assessment | | | |
|---|---|---|---|---|
| | **Non-DM (n=582)** | **Pre-DM (n=602)** | **Unknown DM (n=698)** | **p value** |
| Age, years | 54.63±11.38 | 58.05±11.89* | 59.15±10.95* | **<0.001** |
| Sex | | | | |
| Female | 69 (11.86%) | 128 (21.26%)* | 196 (28.08%)*,# | **<0.001** |
| Male | 513 (88.14%) | 474 (78.74%) | 502 (71.92%) | |
| Race | | | | |
| Domestic | 540 (92.78%) | 568 (94.35%) | 649 (92.98%) | 0.489 |
| Immigrant | 42 (7.22%) | 34 (5.65%) | 49 (7.02%) | |
| Height, cm | 171.08±6.79 | 169.64±7.34* | 168.45±7.46*,# | **<0.001** |
| Weight, kg | 79.38±10.5 | 80.50±11.47 | 83.76±11.77*,# | **<0.001** |
| Body mass index, kg/m$^2$ | 27.11±3.22 | 27.96±3.52* | 29.53±3.85*,# | **<0.001** |
| Smoking status | | | | |
| Non-smoker | 72 (12.48%) | 100 (16.81%) | 180 (26.09%)*,# | **<0.001** |
| Passive smoker | 30 (5.20%) | 65 (10.92%)* | 40 (5.80%)# | |
| Ex-smoker | 90 (15.60%) | 122 (20.50%) | 154 (22.32%)* | |
| Smoker | 385 (66.72%) | 308 (51.76%)* | 316 (45.80%)* | |
| Hypertension | 206 (35.40%) | 267 (44.35%)* | 390 (55.87%)*,# | **<0.001** |
| Hyperlipidemia | 292 (50.17%) | 352 (58.47%)* | 473 (67.77%)*,# | **<0.001** |
| Chronic obstructive pulmonary disease | 34 (5.84%) | 39 (6.48%) | 47 (6.73%) | 0.803 |
| Previous coronary artery disease | 108 (18.56%) | 132 (21.93%) | 205 (29.37%)*,# | **<0.001** |
| Previous peripheral artery disease | 9 (1.55%) | 22 (3.65%) | 29 (4.15%)* | **0.022** |
| Previous cerebrovascular disease | 10 (1.72%) | 25 (4.15%)* | 48 (6.88%)* | **<0.001** |
| Previous pulmonary embolism | 1 (0.17%) | 2 (0.33%) | 2 (0.29%) | 0.999 |
| Previous deep vein thrombosis | 3 (0.52%) | 2 (0.33%) | 3 (0.43%) | 0.910 |
| Renal diseases | 26 (4.47%) | 36 (5.98%) | 83 (11.89%)*,# | **<0.001** |
| Thyroid diseases | 23 (3.95%) | 28 (4.65%) | 34 (4.87%) | 0.719 |
| Malignancy | 12 (2.06%) | 14 (2.33%) | 18 (2.58%) | 0.830 |
| Other chronic diseases | 17 (2.92%) | 21 (3.49%) | 19 (2.72%) | 0.712 |
| Glucose, mg/dL | 112 (100-124) | 143 (117-161)* | 234 (181-315)*,# | **<0.001** |
| HbA1c, % | 5.4 (5.27-5.5) | 6.0 (5.8-6.1)* | 8.7 (7.2-10.1)*,# | **<0.001** |
| Urea, mg/dL | 30.9 (25.3-38) | 33 (27.3-40.7)* | 34 (27.95-44)*,# | **<0.001** |
| Creatinine, mg/dL | 0.86 (0.75-0.99) | 0.87 (0.76-1.04) | 0.90 (0.76-1.11)* | **0.002** |
| Creatinine clearance (mL/min/1.73 m$^2$) | 109.20±36.23 | 102.78±35.75* | 101.26±40.28* | **<0.001** |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | 91.53±21.74 | 86.77±21.11* | 81.31±25.50*,# | **<0.001** |
| Platelet (x10$^3$) | 246 (206-289) | 246 (207-295) | 246 (203-298) | 0.874 |
| Type of ACS | | | | |
| Unstable angina pectoris | 26 (4.47%) | 36 (5.98%) | 35 (5.01%) | 0.217 |
| NSTEMI | 230 (39.52%) | 226 (37.54%) | 302 (43.27%) | |
| STEMI | 326 (56.01%) | 340 (56.48%) | 361 (51.72%) | |
| Antiaggregant | 105 (18.04%) | 130 (21.59%) | 194 (27.79%)*,# | **<0.001** |
| Anticoagulant | 3 (0.52%) | 9 (1.50%) | 14 (2.01%) | 0.072 |
| Major adverse cardiovascular event | 129 (22.16%) | 172 (28.57%)* | 250 (35.82%)*,# | **<0.001** |
| Cardiac mortality | 58 (9.97%) | 57 (9.47%) | 133 (19.05%)*,# | **<0.001** |
| Time of major adverse cardiac event, days | 1 (1-2) | 1 (1-2) | 1 (1-3) | 0.688 |
| Length of hospital stay, days | 3 (2-3) | 3 (2-4)* | 3 (2-4)* | **<0.001** |

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. *Significantly different from "Non-DM"; #Significantly different from "Pre-DM"; DM: Diabetes mellitus; HbA1c: Glycated hemoglobin; ACS: Acute coronary syndrome; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

**TABLE 3:** Significant factors independently associated with the pre and unknown DM, multivariate logistic regression analysis.

| | β coefficient | Standard error | p value | Exp(β) | 95% CI for Exp(β) | |
|---|---|---|---|---|---|---|
| Age | 0.024 | 0.005 | **<0.001** | 1.024 | 1.015 | 1.034 |
| Sex, female | 0.545 | 0.152 | **<0.001** | 1.725 | 1.280 | 2.324 |
| Body mass index | 0.130 | 0.016 | **<0.001** | 1.139 | 1.103 | 1.176 |
| Hyperlipidemia | 0.483 | 0.106 | **<0.001** | 1.621 | 1.316 | 1.996 |
| Previous peripheral artery disease | 0.952 | 0.378 | **0.012** | 2.591 | 1.234 | 5.439 |
| Previous cerebrovascular disease | 0.818 | 0.355 | **0.021** | 2.266 | 1.129 | 4.549 |
| Renal diseases | 0.556 | 0.232 | **0.017** | 1.743 | 1.107 | 2.746 |
| Constant | -4.658 | 0.533 | <0.001 | 0.009 | | |

Nagelkerke $R^2$=0.139; DM: Diabetes mellitus; CI: Confidence interval.

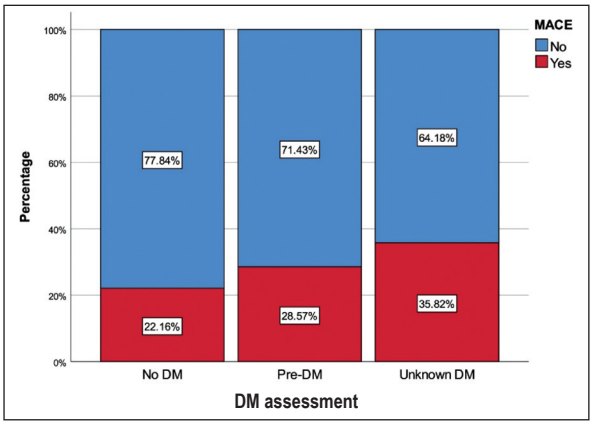


**FIGURE 1:** Major adverse cardiovascular event percentages with regard to DM assessment.
DM: Diabetes mellitus.

demia were independently associated with reduced risk for MACE.

Significant changes have occurred in the relationship between cardiologists and patients with diabetes, especially due to new drugs that improve cardiovascular outcomes as well as being effective in diabetes management.[22] Current literature demonstrates that there is a strong association between DM and the prevalence and severity of coronary artery diseases.[7,10,23] Patients with diabetes generally have worse cardiovascular outcomes than patients without diabetes, regardless of the treatment modalities used.[8,22] Moreover, the burden of coronary atherosclerosis is higher in the presence of diabetes.[19] A strong association has been observed between pre-diabetes and all-cause/cardiovascular death, recurrent MACE, and hospitalization. Of particular concern is the finding that the risk of cardiovascular events is still quite high in patients in the pre-diabetes group, even if blood glucose levels are restored to normal.[7]

There is a global epidemic of diabetes and the current fact is that almost one out of every three patients is pre-diabetic. DM is considered a condition equivalent to coronary heart disease in terms of cardiovascular event risk.[10,22] As such, early detection of high risks for DM or pre-DM is an important factor for cardiologists.[24] Therefore, early detection of patients with diabetes or pre-diabetes, intensive management of their risk factors, and patient-specific follow-up will significantly improve cardiovascular outcomes. Unfortunately, DM and pre-DM are often diagnosed during ACS management, but research focusing on the prediction of these relationships are limited. In the present study, the rate of incidentally-detected un-DM in patients with ACS was 37.09% and the rate of pre-DM was 31.99%, consistent with previous reports.[7,25] Advanced age, female sex, high BMI, hyperlipidemia, previous peripheral artery disease, previous cerebrovascular disease, and renal diseases were identified as independent predictors of incidentally-diagnosed (pre)DM during the diagnosis of ACS.

Despite advances in medical care and diagnostics, ACS remains the major cause of morbidity. Risk estimation is therefore an ongoing challenge among these patients.[26] MACE estimation is an issue that is important and widely researched because it has a substantial effect on medical decision-making for the care and treatment of patients with ACS.[27] MACE in relation with ACS generally occurs suddenly, resulting in high mortality and morbidity.[27] Therefore,

**TABLE 4:** Summary of variables with regard to major adverse cardiovascular event.

| | Major adverse cardiovascular event | | |
|---|---|---|---|
| | **No (n=1,331)** | **Yes (n=551)** | **p value** |
| Age, years | 56.08±10.89 | 60.60±12.43 | **<0.001** |
| Sex | | | |
| Female | 263 (19.76%) | 130 (23.59%) | 0.063 |
| Male | 1068 (80.24%) | 421 (76.41%) | |
| Race | | | |
| Domestic | 1251 (93.99%) | 506 (91.83%) | 0.087 |
| Immigrant | 80 (6.01%) | 45 (8.17%) | |
| Height, cm | 169.73±7.41 | 169.42±7.01 | 0.404 |
| Weight, kg | 81.38±11.76 | 81.32±10.69 | 0.919 |
| Body mass index, kg/m$^2$ | 28.25±3.78 | 28.35±3.51 | 0.603 |
| Smoking status | | | |
| Non-smoker | 235 (17.75%) | 117 (21.75%) | **0.030** |
| Passive smoker | 107 (8.08%) | 28 (5.20%) | |
| Ex-smoker | 253 (19.11%) | 113 (21.00%) | |
| Smoker | 729 (55.06%) | 280 (52.04%) | |
| Hypertension | 604 (45.38%) | 259 (47.01%) | 0.519 |
| Hyperlipidemia | 841 (63.19%) | 276 (50.09%) | **<0.001** |
| Chronic obstructive pulmonary disease | 85 (6.39%) | 35 (6.35%) | 0.978 |
| Previous coronary artery disease | 306 (22.99%) | 139 (25.23%) | 0.299 |
| Previous peripheral artery disease | 40 (3.01%) | 20 (3.63%) | 0.577 |
| Previous cerebrovascular disease | 46 (3.46%) | 37 (6.72%) | **0.002** |
| Previous pulmonary embolism | 2 (0.15%) | 3 (0.54%) | 0.153 |
| Previous deep vein thrombosis | 4 (0.30%) | 4 (0.73%) | 0.243 |
| Renal diseases | 69 (5.18%) | 76 (13.79%) | **<0.001** |
| Thyroid diseases | 59 (4.43%) | 26 (4.72%) | 0.786 |
| Malignancy | 25 (1.88%) | 19 (3.45%) | 0.060 |
| Other chronic diseases | 41 (3.08%) | 16 (2.90%) | 0.956 |
| Glucose, mg/dL | 135 (112-187) | 162 (125-250) | **<0.001** |
| HbA1c, % | 6.4 (5.9-8.8) | 6.7 (5.9-9.1) | 0.453 |
| Diabetes mellitus assessment | | | |
| Non diabetes mellitus | 453 (34.03%) | 129 (23.41%) | **<0.001** |
| Pre-diabetes mellitus | 430 (32.31%) | 172 (31.22%) | |
| Unknown diabetes mellitus | 448 (33.66%) | 250 (45.37%) | |
| Urea, mg/dL | 31.4 (26-38.1) | 36 (29-47.5) | **<0.001** |
| Creatinine, mg/dL | 0.86 (0.74-0.99) | 0.95 (0.79-1.18) | **<0.001** |
| Creatinine clearance (mL/min/1.73 m$^2$) | 109.62±36.48 | 91.07±37.64 | **<0.001** |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | 90.08±20.82 | 76.82±26.45 | **<0.001** |
| Platelet (x10$^3$) | 246 (207-291) | 246 (203-299) | 0.884 |
| Type of ACS | | | |
| Unstable angina pectoris | 79 (5.94%) | 18 (3.27%) | **<0.001** |
| NSTEMI | 586 (44.03%) | 172 (31.22%) | |
| STEMI | 666 (50.04%) | 361 (65.52%) | |
| Antiaggregant | 325 (24.42%) | 104 (18.87%) | **0.009** |
| Anticoagulant | 17 (1.28%) | 9 (1.63%) | 0.700 |
| Length of hospital stay, days | 3 (2-4) | 3 (2-6) | **<0.001** |

Data are given as mean±standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables; HbA1c: Glycated hemoglobin; ACS: Acute coronary syndrome; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

**TABLE 5:** Significant factors independently associated with the major adverse cardiovascular event, multivariable logistic regression analysis.

| | β coefficient | Standard error | p value | Exp(β) | 95% CI for Exp(β) | |
|---|---|---|---|---|---|---|
| Age | 0.032 | 0.005 | **<0.001** | 1.032 | 1.023 | 1.042 |
| Hyperlipidemia | -0.523 | 0.110 | **<0.001** | 0.593 | 0.478 | 0.735 |
| Renal diseases | 0.929 | 0.188 | **<0.001** | 2.533 | 1.752 | 3.662 |
| Diabetes mellitus assessment[1] | | | | | | |
| Pre-diabetes mellitus | 0.283 | 0.141 | **0.044** | 1.327 | 1.007 | 1.750 |
| Unknown diabetes mellitus | 0.656 | 0.136 | **<0.001** | 1.927 | 1.475 | 2.517 |
| Type of event[2] | | | | | | |
| NSTEMI | 0.054 | 0.282 | 0.848 | 1.056 | 0.607 | 1.836 |
| STEMI | 0.737 | 0.277 | **0.008** | 2.090 | 1.214 | 3.599 |
| Antiaggregant | -0.344 | 0.136 | **0.012** | 0.709 | 0.543 | 0.926 |
| Constant | -3.243 | 0.393 | **<0.001** | 0.039 | | |

[1]Reference category: No diabetes mellitus; [2]Reference category: Unstable angina pectoris, Nagelkerke $R^2$=0.133; CI: Confidence interval; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

knowing the predictors of MACE beforehand is vital in terms of risk classification in ACS.

Many risk factors for MACE have been reported in patients with ACS, such as anemia, male sex, advanced age, diabetes, not using anticoagulants, myocardial infarction history, the triglyceride-glucose index, smoking, dyslipidemia, hypertension, renal dysfunction, higher lipoprotein (a), hyperuricemia, shock, anxiety, lower left ventricular ejection fraction, malnutrition and various laboratory markers.[26,28-31] In the present study, advanced age, renal diseases, (pre)DM, and STEMI were identified as independent predictors of MACE. Antiaggregant use was found to be an independent protective factor for MACE. Our results largely support many of the MACE risk factors reported in previous studies. However, interestingly, an inverse relationship was found between hyperlipidemia and MACE, contradicting the literature and conventional understanding. The fact that the percentage of patients with MACE was almost one-third of those without MACE might have contributed to this interesting result.

In summary, considering that (pre)DM is an independent risk factor for MACE and that advanced age, female sex, higher BMI, hyperlipidemia, the presence of previous peripheral artery disease, previous cerebrovascular disease, and renal diseases are independent predictors of (pre)DM in patients with ACS, we recommend that patients with these characteristics should be closely monitored for possible current (pre)DM and possible future (pre)DM and ACS. Also, patients in whom (pre)DM is detected should be subjected to a program that includes the recommendations of the ESC for the screening, risk assessment, and prevention of CVD.[32] Furthermore, considering that advanced age, renal diseases, (pre)DM and STEMI are independent risk factors for death and MACE in patients with ACS, it can be concluded that more caution should be exercised in the management of patients with ACS who present these characteristics. Finally, our results support the hypothesis that antiaggregant use is an independent parameter that reduces the risk of MACE in ACS. When the results of the present study and previous studies are evaluated together and the high (pre)DM rates in patients with ACS are taken into account, the need is clear for more research to assess pre-DM and DM in patients presenting with ACS. As a result, a significant number of patients with occult (pre)DM may be diagnosed as having pre-DM or DM, which can lead to enacting of necessary measures to protect patients against complications caused by DM. While investigating patients with ACS for pre-DM and DM, it would be appropriate for cardiologists to consider higher risks among patients with advanced age, female sex, higher BMI, hyperlipidemia, history of peripheral artery disease, history of cerebrovascular disease, and renal diseases.

## STUDY LIMITATIONS

The important strengths of the study are that it provided information about the rates of DM and pre-DM that were detected incidentally in patients without known diabetes before ACS, and most importantly, it investigated the risk factors for incidental (pre)DM. However, it also has some limitations. Important parameters such as the effect of antidiabetic regimens on MACE, post-discharge MACE rates, factors affecting long-term post-discharge MACE, and the long-term effects of (pre)DM on recurrent ACS could not be investigated in the study because the data were obtained retrospectively. Only in-hospital MACE was investigated. Reference values of fasting blood glucose levels specified for the diagnosis of pre-DM and DM were not used because the blood taken after the diagnosis of ACS cannot be guaranteed to be fasting blood. In addition, because the OGTT test would not be practical or effective during the diagnosis of ACS in these patients, OGTT-based analyses were not done. Pre-DM and DM diagnoses were solely based on HbA1C values. This may have resulted in lower pre-DM and DM rates.

## CONCLUSION

Incidental pre-DM and DM rates detected during the diagnosis of ACS were consistent with the literature. Advanced age, female sex, higher BMI, hyperlipidemia, previous peripheral artery disease, previous cerebrovascular disease, and renal diseases were independent markers for incidental (pre)DM. Advanced age, renal disease, (pre)DM, and STEMI were independent factors that increased the risk of MACE, and the use of antiaggregant treatment decreased the risk of MACE. These risk factors can be used to predict (pre)DM before ACS or to assess risk for MACE after ACS. Risk stratification using these factors may contribute to reducing cardiovascular mortality and morbidity that are increased by (pre)DM and MACE.

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### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Özlem Özbek;* ***Design:*** *Özlem Özbek;* ***Control/Supervision:*** *Mehmet Mustafa Can;* ***Data Collection and/or Processing:*** *Özlem Özbek;* ***Analysis and/or Interpretation:****Özlem Özbek, Mehmet Mustafa Can;* ***Literature Review:*** *Özlem Özbek;* ***Writing the Article:*** *Özlem Özbek;* ***Critical Review:*** *Mehmet Mustafa Can;* ***References and Fundings:*** *Özlem Özbek;* ***Materials:*** *Özlem Özbek.*

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