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ORIGINAL RESEARCH

Amyloid β1-40 Predicts Long-Term Mortality Rate in Patients With Acute Myocardial Infarction

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BACKGROUND: Amyloid β1-40 (Aβ1-40) contributes to atherosclerosis, being involved in plaque formation and destabilization. The prognostic role of Aβ1-40 in patients with acute myocardial infarction is currently limited to non–ST-segment–elevation myocardial infarction (NSTEMI). We examined the prognostic value of Aβ1-40 in a real-world cohort of patients with acute myocardial infarction (both ST-segment–elevation myocardial infarction [STEMI] and NSTEMI) and identified predictors for its elevated levels.

METHODS AND RESULTS: Our population included 1119 consecutive patients (mean age, 67 years; 72% men; and STEMI, 68%). The median Aβ1-40 concentration on admission was 86.9 (interquartile range, 54.5–128.9) pg/mL, and there was no difference in Aβ1-40 levels between NSTEMI and STEMI (P=0.1). Higher Aβ1-40 levels were predicted by older age, lower left ventricular ejection fraction, glycated hemoglobin >39 mmol/mol and glomerular filtration rate <60 mL/min per m^2. From the final multivariable model, a nomogram was computed to determine probability of high Aβ1-40. During the median follow-up of 57 months, 193 patients (17.2%) died. Kaplan–Meier analysis revealed higher mortality risk in patients with Aβ1-40 levels above the median (P<0.01), consistent across STEMI (P<0.01) and NSTEMI (P=0.01) subgroups. At Cox multivariable analysis including the entire cohort, Aβ1-40 levels were predictive of death (hazard ratio, 1.03; P=0.01), together with older age, higher high-sensitivity C-reactive protein levels, smoking, glomerular filtration rate <60 mL/min per m^2, worse left ventricular ejection fraction, and previous ischemic events. In the STEMI subcohort, Aβ1-40 remained a significant predictor, along with advanced age, worse left ventricular ejection fraction, smoking, and elevated high-sensitivity C-reactive protein. No such association was found in patients with NSTEMI (P=0.17), likely due to the smaller cohort size and low event rate.

CONCLUSIONS: Aβ1-40 is an independent predictor of death and improves risk stratification in patients with acute myocardial infarction.

Key Words: acute myocardial infarction ■ amyloid β1-40 ■ death ■ NSTEMI ■ risk stratification ■ STEMI

Coronary artery disease (CAD) is among the most frequent causes of death worldwide despite major advances in diagnosis and treatment.[1] This is driven by an aging population and soaring cardiovascular risk factors such as insulin resistance, diabetes, obesity, dyslipidemia, poor diet, and inactive indoor lifestyle.[2,3] Moreover, it is estimated that the number of CAD cases, as well as other age-related diseases, will increase even further in the coming decades.[2,3]

As acute myocardial infarction (AMI) is a life-threatening manifestation of CAD, where time is of the essence in the management of patients,[4] better

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CLINICAL PERSPECTIVE

What Is New?

- Amyloid β1-40 is an independent predictor of long-term mortality rate in a real-world cohort of patients with acute myocardial infarction, including both ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction.
- This is the first study to establish the predictive value of amyloid β1-40 for death specifically in a cohort of patients with ST-segment–elevation myocardial infarction, reinforcing its role in cardiovascular risk assessment.

What Are the Clinical Implications?

- Admission amyloid β1-40 levels improve risk stratification and identify high-risk patients after an acute myocardial infarction.

Nonstandard Abbreviations and Acronyms

APP	amyloid precursor protein
Aβ1-40	amyloid β1-40

early stratification and treatment are crucial to improve outcomes. This requires the identification of novel molecular pathways and associated biomarkers underlying AMI, enabling a shift toward more personalized medicine.[2,3,5]

For a long time, amyloid β peptides have been studied in the brain and its associated vasculature.[6] In particular, amyloid β1-40 (Aβ1-40) and amyloid β1-42, proteolytic fragments of APP (amyloid precursor protein), have been extensively investigated in the pathogenesis of cerebral amyloid angiopathy and Alzheimer disease (AD). APP is a transmembrane protein with a significant role in blood coagulation and cell adhesion. When the balance between clearance and production of amyloid β peptides is disrupted due to the presence of various factors such as aging, diabetes, hypertension, smoking, oxidative stress, inflammation, and genetic components, the concentrations of amyloid β peptides increase, which leads to their accumulation in the brain, blood, and vessel walls.[7–10] Following the observation of a significant overexpression of APP in regions of the thoracic aorta prone to atherosclerosis in animal models, it was assumed that APP levels were associated with plaque development.[11] Thereafter, Aβ1-40's vascular preference was noted and it was hypothesized that this molecule had proinflammatory effects not only in the brain, but also in the wall of the carotid artery, the aorta or coronary arteries, and in the heart itself.[9]

Indeed, several studies demonstrated that significant amounts of Aβ1-40 are produced by platelets in atherosclerotic plaques.[5,6,9,12] More specifically, activated platelets massively release αgranules, rich in coagulation mediators and amyloid β peptides, which, once released as in a vicious cycle, act as activators of other platelets, favoring the increase of its plasma concentration and promoting the inflammatory state.[5,6,9,12] For those reasons, Aβ1-40 has emerged as a promising prognostic biomarker in the cardiovascular field due to its proinflammatory and proatherosclerotic properties.[9]

However, only a few studies until recently have examined the relationship between Aβ1-40 and cardiovascular risk and death. It was demonstrated that in patients with chronic stable coronary disease, patients hospitalized for unstable angina and non–ST-segment–elevation myocardial infarction (NSTEMI) and in patients with heart failure, higher Aβ1-40 values were significantly associated with increased risk of adverse outcomes.[5,6,12,13] There are no data regarding the prognostic role of Aβ1-40 in patients with ST-segment–elevation myocardial infarction (STEMI).

The aim of the present study was to investigate the prognostic role of plasma Aβ1-40 for death in a large, real-world cohort of consecutive patients with AMI, both STEMI and NSTEMI, during long-term follow-up. Furthermore, detection and quantification of well-known and readily available key mediators of cardiac inflammation, such as high-sensitivity C-reactive protein, were performed to provide additive information regarding the inflammatory state of the patients and explore the prognostic information of these markers.[14,15]

METHODS

Data Availability

All data are incorporated into the article and its online supplementary material.

Population, Definitions, End Point, and Follow-Up

The study population included 1119 consecutive patients diagnosed with AMI admitted to the Cardiology Department of the University Hospital of Trieste (Trieste, Italy) between 2014 and 2023. Specifically, all patients who fulfilled the eligibility criteria, including being of legal age (>18 years), admitted to our hospital for AMI within 24 hours of symptom onset, and who were able to understand the aim of the study, were invited to participate in the project entitled "Approccio multimarker per la migliore stratificazione prognostica dei pazienti con infarto miocardico acuto" ("Multimarker Approaoch for Better Prognostic Stratification of Patients With Acute Myocardial Infarction"), and those who accepted signed a written informed consent and had a blood sample taken. This project, approved by the local ethics committee (N°67/2015, update CEUR-2021-Em-220 dd. 22/06/2021 PROT 0025024/P/GEN/ARCS), complies with the Declaration of Helsinki and is still ongoing.

Diagnosis and treatment of AMI were performed according to the European Society of Cardiology guidelines.[16] Multivessel critical CAD was defined as >70% stenosis in at least 2 coronary vessels on coronary angiography. Chronic kidney disease (CKD) was defined as a glomerular filtration rate (GFR)≤60 mL/min per 1.73 m^2.[17]

Each patient underwent clinical examination, standard laboratory analysis, and instrumental evaluation: ECG, transthoracic echocardiogram, and coronary angiography. For each enrolled patient, baseline characteristics; medical treatment on admission, during hospitalization, and at discharge; performed medical procedures; clinical and laboratory data; and previous clinical history as well as family history were collected from electronic health records software, Cardionet (INSIEL, Trieste, Italy) and G2 Clinical (INSIEL, Trieste, Italy). With regard to ECG, patients with STEMI and patients with very-high-risk and high-risk NSTEMI underwent serial echocardiographic evaluation. The first ECG was performed before percutaneous coronary intervention (PCI), then within the first 24 hours after PCI, and the last one at hospital discharge (median hospital stay 5 [interquartile range, 3–7] days). In patients with uncomplicated NSTEMI (intermediate and low risk), only 1 ECG was performed during the hospital stay after PCI. Therefore, for the purposes of this study, the echocardiographic data used in our analyses were the discharge ECG in patients with STEMI and the single post-PCI ECG in patients with NSTEMI, to ensure consistency in data presentation.

For the purposes of this study, we selected all patients enrolled in the project from the beginning until October 2, 2023. Therefore, no patients were excluded at this point. Importantly, no patients were added or excluded on the basis of cardiovascular risk reported from the electronic health record, and all patients were treated equally.

In addition, the end point was defined as all-cause death. The follow-up time for each patient was determined from the date of the initial analytic start time until the defined data at the end of our study, which was October 2, 2023, or the date of death of the patient. Therefore, data of interest during follow-up (alive versus dead status) was also collected using the same electronic health record software (Cardionet and G2 Clinical). No patients were lost during follow-up.

Sample Preparation

Peripheral blood was collected from patients in K_2EDTA tubes within 8 hours of admission. Right after blood draw, the samples were centrifuged at 2500*g* for 15 minutes at 4°C. Plasma was aliquoted and stored at −80 °C until analysis was performed.

Biomarker Quantification

The measurements of Aβ1-40 and inflammatory cytokine interleukin-1β levels were performed on frozen aliquots of plasma by the ELISA sandwich method following the manufacturer's indications. The commercial kit Human Aβ40 ELISA Kit (Invitrogen, Life Technologies) was used for Aβ1-40 measurement. The assay sensitivity range was 7.8 to 500 pg/mL, and the theoretical minimal identifiable concentration of Aβ1-40 was 6 pg/mL. The absorbance was detected with a Multiscan FC (Thermo Scientific, Life Technologies) according to the manufacturers' indications.

C-reactive protein was measured with an immune-turbidimetric test, performed on an AU5800 (Beckman Coulter, Brea, CA) analyzer.

All ELISA experiments were performed by the same laboratory technician, as consistency in the person performing the experiments helps to reduce potential sources of variability.

Statistical Analysis

Statistical calculations were performed using SPSS Statistics version 24 (IBM, Armonk, NY) and the R package version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with "survival," "Rms," and "timeROC" libraries. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables are presented as mean±SD or median (interquartile range), as appropriate. The ANOVA test was used for variables meeting normality, while the Mann–Whitney *U* test was used for nonnormally distributed variables. Categorical variables are presented as proportions, and the χ^2 test or the Fisher exact test was used as needed.

To identify factors that contribute to an increase in Aβ1-40 levels, multivariable binary logistic regression analysis was performed using a backward conditional method. For this analysis, Aβ1-40 levels were dichotomized on the basis of the median value across the entire cohort, with levels above the median classified as "elevated." Variables that were significant in the univariable logistic regression were considered for inclusion as potential independent predictors of elevated Aβ1-40 levels, taking into consideration as well their clinical relevance and after the review of the relevant literature. The variables included in the final model were computed in a nomogram, whereby the total score is associated with the probability that a patient with specific characteristics will have Aβ1-40 levels above the median value observed in our study.

The Kaplan–Meier method was used to estimate the survival probability during follow-up according to the median value of Aβ1-40 in our entire cohort. Then, the prognostic value of Aβ1-40 was evaluated using the univariable Cox regression followed by a multivariable model, which was performed using a backward stepwise regression, to show whether Aβ1-40 was an independent predictor of all-cause death. The CI was set at 95%. The cox.zph function of the R library "Survival" was used to check proportional hazards assumptions as proposed by Grambsch and Therneau.[18] Linearity assumption was checked for the continuous variables by means of a nonparametric smoother implemented through the "plsmo" function in the R library "Rms." To assess the performance of the multivariable model, the time-dependent receiver operating characteristic analysis for censored data was performed. All statistical tests were 2-sided, and results were valued as significant at $P \le 0.05$.

RESULTS

Population Characteristics

The study included 1119 consecutive patients with AMI. The mean age of the cohort was 67.4±12 years, and the majority of patients were men (72.2%; Table 1). Most patients presented with a first ischemic event (83%), with STEMI presentation (68.4%) in Killip class 1 (83.6%). The most common cardiovascular risk factors were hypertension (64%), dyslipidemia (52.8%), and smoking (46.5%).

The majority of patients underwent PCI (74.1%) and were discharged on optimal medical treatment in New York Heart Association I/II with left ventricular ejection fraction (LVEF) >50% at echocardiographic evaluation.

The median Aβ1-40 plasma concentration was 86.9 (interquartile range, 54.5–128.9) pg/mL. Patients with Aβ1-40 above the median value were older ($P<0.01$) and more frequently had hypertension ($P=0.02$), diabetes ($P<0.01$), peripheral artery disease ($P<0.01$), GFR<60 mL/min per 1.73 m^2 ($P<0.01$), and multivessel disease ($P<0.01$). All clinical and biochemical differences after stratification according to Aβ1-40 plasma concentration are reported in Table 1.

There were no significant differences in Aβ1-40 levels among STEMI versus NSTEMI (85.3 [53–129] pg/mL versus 94 [61–131], respectively; $P=0.1$). Tables S1 and S2 show the baseline characteristics of patients separated by diagnoses (NSTEMI and STEMI). Furthermore, there was no sex difference in Aβ1-40 levels (women, 86.3 [56–136] versus men, 87 [54–127] pg/mL, respectively; $P=0.4$). Instead, higher levels of Aβ1-40 were measured in older individuals, patients with worse LVEF and worse renal function, and in patients with diabetes (Figure 1).

Impact of Aβ1-40 on Patients' Outcome During Follow-Up

During the median follow-up period of 57 (interquartile range, 30–80) months, 193 (17.2%) patients died. The baseline characteristics of all patients with AMI stratified by end point are shown in Table 2.

Median plasma concentrations of Aβ1-40 measured at hospital admission were significantly higher in deceased patients (113.1 [68–160] pg/mL versus 84 [53–123] pg/mL; $P<0.01$). After stratification according to the type of AMI (STEMI and NSTEMI), it was noted the same fashion in Aβ1-40 levels between deceased and alive patients: STEMI (110.7 [64–164] versus 82.7 [51–122]; $P<0.01$) and NSTEMI (113.9 [74–156] versus 86.6 [57–125]; $P<0.01$; Table S2).

At the Kaplan–Meier survival analysis, considering the entire cohort, Aβ1-40 levels over the median were associated with higher mortality risk ($P<0.01$), and the same pattern was observed when stratifying patients according to STEMI ($P<0.01$) and NSTEMI ($P=0.01$) diagnosis separately (Figure 2).

Moreover, Aβ1-40 (hazard ratio, 1.03; $P=0.01$) remained an independent predictor of death even after multivariable adjustment for sex, hypertension, and New York Heart Association class, at Cox regression analysis, together with advanced age, higher high-sensivity C-reactive protein levels, smoking, GFR <60 mL/min per m^2, worse LVEF, and previous ischemic events considering the entire cohort (Table 3). Moreover, the hypothesis of the proportionality of risks for the multivariable model was confirmed.

After stratification of the cohort according to diagnosis (STEMI and NSTEMI), the value of Aβ1-40 remained an independent predictor of death in patients with STEMI together with advanced age, worse LVEF, smoking, and higher high-sensitivity C-reactive protein levels adjusted for sex, hypertension, New York Heart Association class, GFR <60 mL/min per m^2, and previous ischemic events (Table 4). However, no such association was observed in patients with NSTEMI ($P=0.17$).

Furthermore, the receiver operating characteristic-curve was used to evaluate the predictive value of our final multivariable model on the risk of death. At receiver operating characteristic analysis, the performance of the multivariable model yielded an area under the curve of 0.84 (95% CI, 0.8–0.88) for the overall cohort ($P<0.01$) and an area under the curve of 0.84 (95% CI, 0.79–0.88) in the STEMI subcohort ($P<0.01$; Figure 3).

Predictors of High Aβ1-40 Levels

At logistic regression analysis, the parameters that predicted higher Aβ1-40 levels were older age, worse LVEF, and comorbidities such as glycated hemoglobin (HbA_{1C}) levels exceeding 39 mmol/mol (above the upper normal limit) and the presence of CKD (Table 5).

Table 1. Baseline Characteristics of Total Patients With AMI and Stratified by Median Levels of Aβ1-40

	Overall (n=1119)	Aβ1-40<86.9 pg/mL (n=559)	Aβ1-40≥86.9 pg/mL (n=560)	*P* value
Age, y, mean ±SD	67.4±11.6	64.3±11.5	68.3±11.4	<0.01
Male sex, %	72.2	71.9	72.5	0.83
BMI, kg/m^2, median (IQR)	26.2 (24–29.4)	26.4 (24–29.4)	26.1 (23.9–29.3)	0.49
SBP at admission, mm Hg, mean ±SD	130±23.2	132.9±23	133.4±23.3	0.72
DBP at admission, mm Hg, median (IQR)	80 (70–85)	80 (70–85)	80 (70–85)	0.64
Heart rate, bpm, median (IQR)	75 (65–85)	73 (65–82)	75 (65–88)	0.01
Atrial fibrillation, %	7.1	5.2	9.1	0.01
Cardiac arrest, %	4.1	3.6	4.6	0.37
Left bundle branch block, %	4.1	3	5.2	0.07
Diagnosis, %				0.16
NSTEMI	31.3	29.3	33.2	
STEMI	68.7	70.7	66.8	
Killip II–IV, %	16.4	14.8	17.8	0.17
Hypertension, %	64	60.6	67.4	0.02
Diabetes, %	22.1	18.4	25.7	<0.01
Smoking, %	46.5	52.4	40.5	<0.01
Dyslipidemia, %	52.8	55.1	50.4	0.12
Positive family history for Ischemic heart disease, %	20.7	21.5	19.9	0.51
Known GFR <60 mL/min per 1.73 m^2, %	7.7	2.5	12.9	<0.01
Peripheral artery disease, %	5.5	2.9	7.3	<0.01
Previous MI/PCI/CABG, %	17	15.6	18.4	0.21
Anemia at admission, %	24.3	15.8	32.7	<0.01
Total cholesterol, mg/dL, mean ±SD	187±47.7	192.6±45.9	185.6±49.2	0.02
HDL cholesterol, mg/dL, median (IQR)	43 (36–51)	44 (37.5–52)	42 (35.3–51)	0.08
LDL cholesterol, mg/dL, mean ±SD	118±40.23	122.9±39.4	115.1±40.7	<0.01
Triglycerides, mg/dL, median (IQR)	112.5 (83–150)	112 (82–148)	113 (84–153)	0.27
Troponin I max, ng/L, median (IQR)	16 132 (3615–56059.5)	17756.8 (4347.5–53 176)	14 000 (3170–57 820)	0.33
HbA_{1C}, mmol/mol, median (IQR)	41 (37–48)	40 (36–45)	42 (39–51)	<0.01
Na^+ at discharge, mEq/L, median (IQR)	139 (138–141)	139 (138–141)	139 (138–141)	0.17
Hemoglobin at discharge, g/dL, mean ±SD	12.8±1.8	12.8±1.7	12.4±1.8	<0.01
Creatinine at discharge, mg/dL, median (IQR)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1 (0.8–1.2)	<0.01
GFR at discharge, mL/min per 1.73 m^2	80.6 (63.8–96.9)	85 (70.8–101.8)	75.2 (55.6–92.6)	<0.02
GFR <60 mL/min per 1.73 m^2 at discharge, %	20.8	11.5	30.1	<0.01
GRACE score at 6 mo, mean ±SD	132±33.5	125.6±32.6	138.7±33.1	<0.01
LVEDD, median (IQR)	2.5 (2.3–2.7)	2.5 (2.3–2.7)	2.5 (2.3–2.7)	0.82
LVESD, median (IQR)	1.7 (1.5–2)	1.7 (1.5–1.9)	1.7 (1.5–2)	0.17
LVEDV, median (IQR)	50.1 (41.4–59.7)	49.3 (41.1–58.9)	50.8 (41.7–60.8)	0.12
LVESV, median (IQR)	23.8 (17.9–30.7)	22.9 (17.6–29.2)	24.5 (18.1–32.7)	0.01
Interventricular septum, cm,median (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.07
Fractional shortening, %, mean ±SD	31±10.6	32.6±10.6	30.8±10.6	0.01
E/A, median (IQR)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.7–1.2)	0.01
E/E′, median (IQR)	10 (8–13)	10 (8–13)	11 (9–13.8)	<0.01
Wall motion score index, median (IQR)	1.4 (1.19–1.8)	1.5 (0.4)	1.6 (0.4)	0.01
Left ventricular mass, g, mean ±SD	201±62.2	207±59.1	214.2±65.3	0.09
Left ventricular ejection fraction, %, mean ±SD	52.5±10.5	52.3±10	50.3±11	<0.01
Mitral insufficiency, %	66.4	65.3	67.4	0.47

(*Continued*)

Table 1. Continued

	Overall (n=1119)	Aβ1-40<86.9 pg/mL (n=559)	Aβ1-40≥86.9 pg/mL (n=560)	*P* value
Mitral insufficiency grade, %				
Absent	33.7	34.7	32.6	0.49
Mild	59.6	60	59.3	0.81
Moderate	5.9	4.6	7.3	0.06
Severe	0.8	0.8	0.8	0.99
Therapy at admission, %				
Medical therapy	18.9	18	20.9	0.1
PCI	74.1	76.4	71.8	0.08
CABG	5.8	5.5	6.1	0.71
First PCI and then CABG	1.2	1.1	1.3	0.78
Glycoprotein IIb/IIIa inhibitors, %	15.4	17.1	13.6	0.16
Multivessel disease >70%, %	38	32.6	43.5	<0.01
Severe hemorrhage, %	1.1	1.3	0.9	0.56
Supraventricular arrhythmias, %	7.3	6.3	8.2	0.21
Ventricular arrhythmias, %	12.9	14.9	11	0.05
Bradyarrhythmias, %	6.1	5.9	6.3	0.82
hs-CRP, mg/L, median (IQR)	4.6 (1.7–13.4)	5.2 (1.9–14.2)	4.4 (1.7–12)	0.22
Aβ1-40 at admission, pg/mL, median (IQR)	86.9 (54.5–128.9)	54.5 (35.5–71.2)	128.9 (106.4–160.6)	
Therapy at discharge, %				
ACE-I/ARB	73.2	74.6	71.8	0.3
β blockers	78.4	78.7	78.1	0.8
Digital	0.7	0.5	0.9	0.48
Amiodarone	7.2	5.8	8.7	0.06
Antialdosteronic agents	13.5	11	16.1	0.01
Loop diuretics	25.2	20.5	30	<0.01
Aspirin	92.5	93.5	91.5	0.21
$P2Y_{12}$ inhibitors				
Clopidogrel	29.5	27.4	31.6	0.28
Prasugrel	22.3	26.8	17.7	0.31
Ticagrelor	34.4	34.4	34.3	0.57
Statins	89.9	89.7	90.1	0.85
Oral antidiabetics	13.1	9.7	16.4	<0.01
Insulin	7.9	5.6	10.3	<0.01
Oral anticoagulants	6.2	6.3	6.1	0.91
New oral anticoagulants	3	3.6	1.9	0.41
NYHA class at discharge, %				
1	84.7	89.9	79.5	<0.01
2	13.9	9.4	18.5	<0.01
3	1.4	0.7	2	0.07

Aβ1-40 indicates amyloid beta 1-40; ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; E/A, early to atrial wave ratio; E/E', early mitral inflow velocity to early diastolic mitral annular velocity ratio; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and STEMI, ST-segment–elevation myocardial infarction.

Further, from the final multivariable model, a nomogram was computed to determine an individual's probability of having high levels of Aβ1-40 (Figure 4). The total score is determined by adding the single points of factors from the final multivariable model, including age, GFR <60 mL/min per m^2, HbA_{1C} >39, and LVEF.

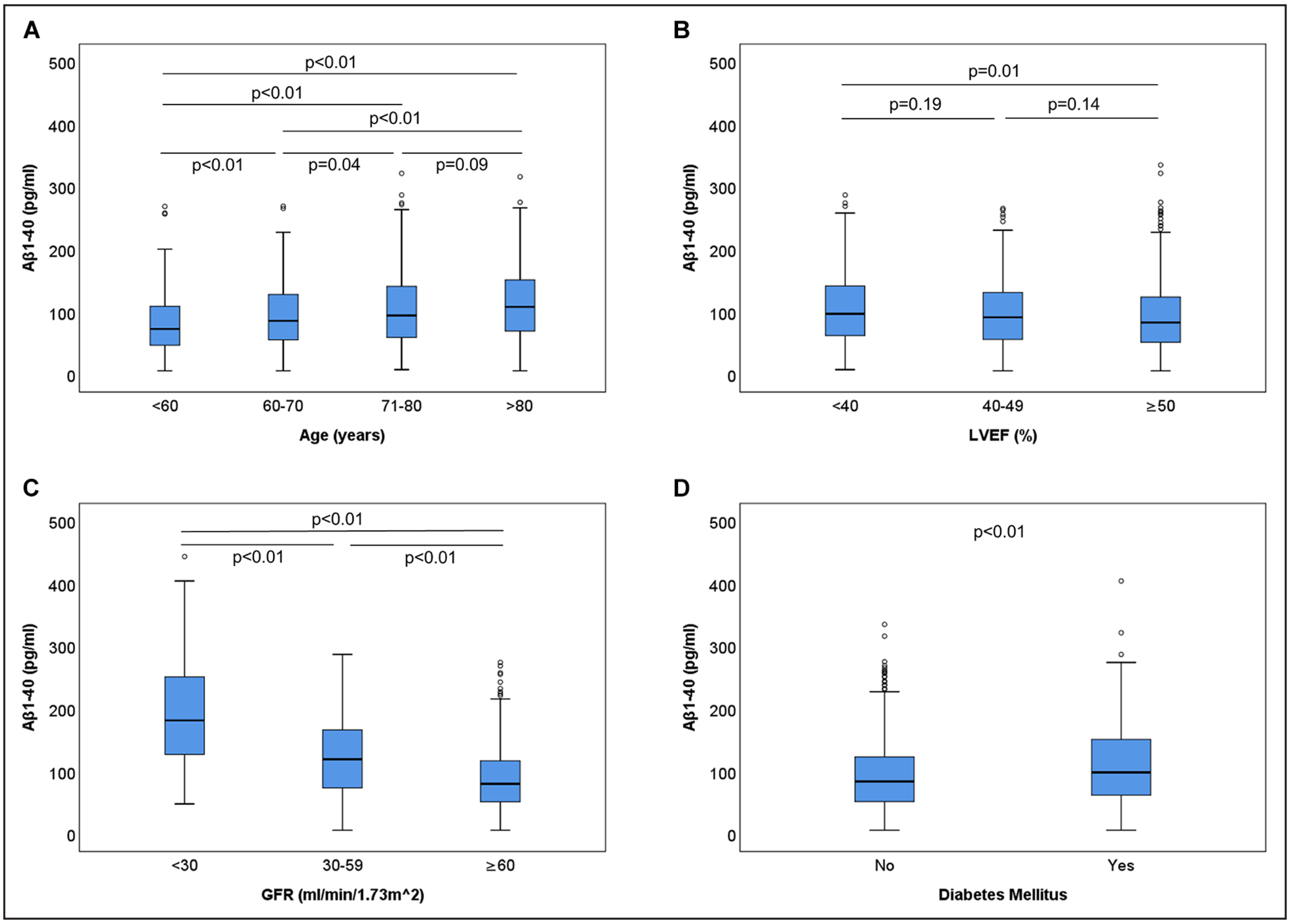


Figure 1. Aβ1-40 values stratified according to (A) age, (B) LVEF, (C) GFR, and (D) diabetes.
Aβ1-40 indicates amyloid-β 1-40; GFR, glomerular filtration rate; and LVEF, left ventricular ejection fraction.

The total score can then be used to determine the individual probability of having high levels of Aβ1-40. For instance, a patient who is aged 60 years (40 points), has kidney disease (79 points), has an HbA_{1C} level >39 (30 points), and has an LVEF of 50 (50 points) has a total of 199 points, which corresponds to an ≈80% probability of having high levels of Aβ1-40. In contrast, a patient with the same age and LVEF but without CKD and normal HbA_{1C} will have a lower probability of having high levels of Aβ1-40.

DISCUSSION

For the first time, we demonstrated that a single measurement of plasma Aβ1-40 at hospital admission predicts long-term all-cause death in a real-world cohort of patients with AMI, encompassing both STEMI and NSTEMI cases. Furthermore, we uniquely established the predictive value of Aβ1-40 for death specifically in patients with STEMI. This finding is particularly noteworthy, as previous studies on Aβ1-40 in acute settings have been restricted to patients with NSTEMI.[12] Unfortunately, in this study, we were unable to confirm the predictive value of Aβ1-40 in patients with NSTEMI, likely due to the relatively small number of enrolled patients with this diagnosis, coupled with an observed low number of deaths within the subcohort.

Previous studies have underscored the clinical significance of Aβ1-40 across a range of cardiovascular conditions. In particular, it has been linked to subclinical atherosclerosis in the general population,[19] serving as a biomarker for early disease detection, and has shown prognostic value for death in patients with chronic stable CAD.[5] In a recent study, Delialis et al[20] have reported that elevated blood levels of Aβ1-40 are associated with high carotid echolucency, which is a clinical marker of plaque instability, in patients without evident atherosclerotic cardiovascular disease. Specifically, high carotid echolucency is an indicator of more lipid-rich plaque and its vulnerability. The echographic data were supported by histological evaluation, which revealed an inverse correlation between Aβ1-40 concentrations and plaque calcification.[20] The

Table 2. **Baseline Characteristics of Total Patients With AMI and Stratified by the End Point All-Cause Death**

	Alive (n=926)	Death (n=193)	*P* value
Age, y, mean ±SD	64.31±11.06	75.96±8.97	<0.01
Male sex, %	74.1	63.2	<0.01
BMI, median (IQR), kg/m^2	26.4 (24.2–29.6)	25.2 (23–28)	<0.01
SBP at admission, mmHg, mean ±SD	133.35±22.6	132.2±25.8	0.54
DBP at admission, mmHg, median (IQR)	80 (70–85.5)	75 (70–80)	<0.01
Heart rate, bpm, median (IQR)	75 (65–85)	78 (68–90)	0.01
Atrial fibrillation, %	5	17.6	<0.01
Cardiac arrest, %	3.9	5.2	0.41
Left bundle branch block, %	2.6	11.4	<0.01
Diagnosis, %			0.02
NSTEMI	29.8	38.3	
STEMI	70.2	61.7	
Killip II–IV, %	11.7	38.9	<0.01
Hypertension, %	60.9	79.2	<0.01
Diabetes, %	19.3	35.2	<0.01
Smoking, %	48.1	38.9	0.2
Dyslipidemia, %	52.2	55.7	0.37
Positive family history for ischemic heart disease, %	21.9	14.6	0.02
Known GFR<60mL/min per 1.73m^2, %	4.3	24	<0.01
Peripheral artery disease, %	2.8	16.1	<0.01
Previous MI/PCI/CABG, %	14.5	29	<0.01
Anemia at admission, %	18.2	53.4	<0.01
Total cholesterol, mg/dL, mean ±SD	192.2±47.1	174.1±48	<0.01
HDL cholesterol, mg/dL, median (IQR)	43 (36–51)	43 (36–52)	0.86
LDL cholesterol, mg/dL, mean ±SD	121.85±39.91	105.34±39.03	<0.01
Triglycerides, mg/dL, median (IQR)	114 (84–151)	108 (81–142.5)	0.14
Troponin I max, ng/L, median (IQR)	16 132 (3823.5–53 852)	15 619.5 (3084.25–68 840)	0.68
HbA_{1C}, mmol/mol, median (IQR)	41 (37–48)	43 (39–50.5)	<0.01
Na^+ at discharge, mEq/L, median (IQR)	139 (138–141)	139 (137–141)	0.71
Hemoglobin at discharge, g/dL, mean ±SD	12.88±1.7	11.48±1.7	<0.01
Creatinine at discharge, mg/dL, median (IQR)	0.92 (0.8–1.1)	1.1 (0.9–1.5)	<0.01
GFR at discharge, mL/min per 1.73m^2, median (IQR)	82.4 (68.1–98.9)	60.9 (41.4–82.3)	<0.01
GFR <60mL/min per 1.73m^2 at discharge, %	14.9	48.7	<0.01
GRACE score at 6mo, mean ±SD	128.09±31.8	151.88±34.4	<0.01
LVEDD, median (IQR)	2.5 (2.7–2.7)	2.6 (2.4–2.9)	0.03
LVESD, median (IQR)	1.7 (1.5–1.9)	1.8 (1.6–2.1)	0.02
LVEDV, median (IQR)	49.8 (41.2–59.4)	52 (43.1–62.1)	0.82
LVESV, median (IQR)	23.3 (17.6–29.9)	26.4 (20.1–36.8)	0.11
Interventricular septum, cm, median (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.08
Fractional shortening, %, mean ±SD	32.1±10.4	30±11.6	0.02
E/A, median (IQR)	0.9 (0.7–1.2)	0.8 (0.7–1.4)	0.67
E/E′, median (IQR)	10 (8–12.5)	13 (10–17)	<0.01
Wall motion score index, mean ±SD	1.5±0.4	1.7±0.5	0.031
Left ventricular mass, g, mean ±SD	207.5±60.7	227.49±68.2	<0.01
Left ventricular ejection fraction, %, mean ±SD	52.13±10.2	47.04±11.1	<0.01
Mitral insufficiency, %	64.7	74.7	0.01

(*Continued*)

Table 2. Continued

	Alive (n=926)	Death (n=193)	*P* value
Mitral insufficiency grade, %			
Mild	60.2	56.9	0.42
Moderate	4	15.5	<0.01
Severe	0.5	2.3	0.01
Therapy at admission, %			0.01
Medical therapy	16.8	29	<0.01
PCI	76.2	63.7	<0.01
CABG	5.7	6.2	0.79
First PCI and then CABG	1.2	1	1
Glycoprotein IIb/IIIa inhibitors, %	16.2	10.9	0.12
Multivessel disease >70%, %	35	53	<0.01
Severe hemorrhage, %	0.6	3.1	<0.01
Supraventricular arrhythmias, %	4.9	18.9	<0.01
Ventricular arrhythmias, %	12.8	13.8	0.71
Bradyarrhythmias, %	5.4	9.5	0.03
hs-CRP, mg/L, median (IQR)	4 (1.5–10.6)	11 (3.9–31)	<0.01
Aβ1-40 at admission, pg/mL, median (IQR)	84 (52.5–122.6)	113.1 (67.9–159.5)	<0.01
Therapy at discharge, %			
ACE-I/ARB	74.8	65.2	0.01
β blockers	80.2	69.4	<0.01
Digital	0.3	2.7	<0.01
Amiodarone	5.7	14.8	<0.01
Antialdosteronic agents	12.3	19.5	0.01
Loop diuretics	20.3	50	<0.01
Aspirin	94.1	84.8	<0.01
$P2Y_{12}$ inhibitors			<0.01
Clopidogrel	25.1	51.6	<0.01
Prasugrel	24.8	9.8	<0.01
Ticagrelor	38.2	15.2	<0.01
Statins	92.3	77.7	<0.01
Oral antidiabetics	12.4	16.3	0.16
Insulin	5.9	17.9	<0.01
Oral anticoagulants	5	12.5	<0.01
New oral anticoagulants	3.3	1.6	0.49
NYHA class at discharge, %			0.24
1	89.6	59.9	<0.01
2	9.9	34.6	<0.01
3	0.5	5.5	<0.01

Aβ1-40 indicates amyloid beta 1-40; ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; E/A, early to atrial wave ratio; E/E', early mitral inflow velocity to early diastolic mitral annular velocity ratio; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and STEMI, ST-segment–elevation myocardial infarction.

authors have also described that, at longitudinal evaluation over a median follow-up period of ≈3 years, basal levels of Aβ1-40 were predictive of a steady increase of echolucency of the carotid walls and an expansion in the size of the plaques.[20] Therefore, the observation of these results underscores the potential role of Aβ1-40 as an early biomarker of vascular vulnerability and atherosclerosis progression in asymptomatic individuals. Such findings are confirmatory of previous data on postmenopausal women without evident

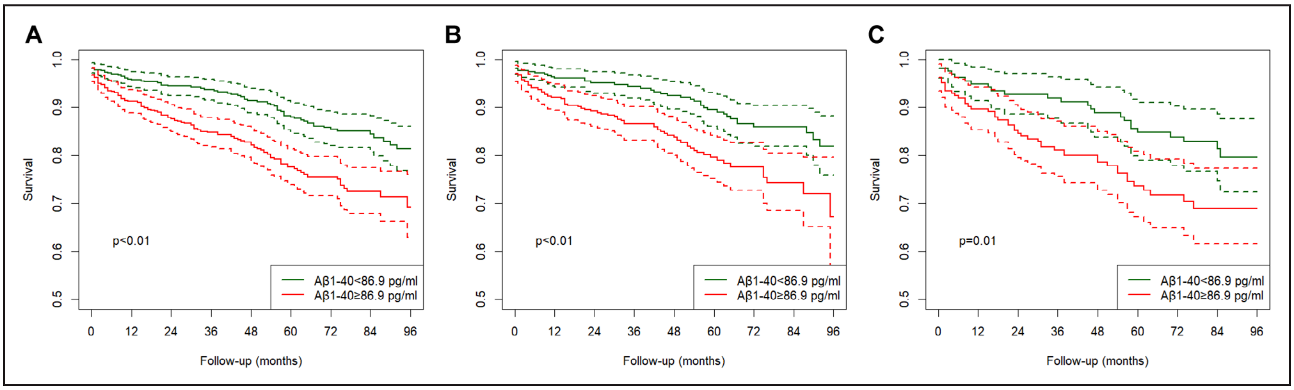


Figure 2. Kaplan–Meier analysis.
The curve of survival for (**A**) the overall cohort, (**B**) STEMI, and (**C**) NSTEMI cohorts. Aβ1-40 indicates amyloid-β 1-40; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-elevation myocardial infarction.

atherosclerotic cardiovascular disease.[21] In particular, it was noted that increasing or persisting high Aβ1-40 levels between baseline and after a median follow-up of ≈2 years were patterns of a more rapid progression of increased thickening of the carotid wall.[21] The association between circulating Aβ1-40 levels and CAD has been described as specific and was not observed with amyloid β1-42.[22] A similar relation has also been observed in the presence of diabetes.[22]

In addition, Aβ1-40 has been associated with adverse outcomes in patients hospitalized for unstable angina and NSTEMI,[12] as well as in those with heart failure, where it is indicative of disease severity and progression.[13]

The main reasons why Aβ1-40 is associated with a higher mortality risk during follow-up are attributed to its proinflammatory and prothrombotic properties. Although Aβ1-40 is mainly recognized as a specific biomarker for AD, several authors have observed that its pathophysiological properties are responsible for the prognostic role in various other diseases, including antiphospholipid syndrome and cardiovascular diseases.[9,23,24] In particular, Aβ1-40 intensifies cytokines and reactive oxidative species secretion, promoting an inflammatory state.[5]

Simultaneously, inflammatory markers also promote the production of Aβ1-40.[25] These processes are interrelated in a vicious circle of interdependency and exacerbation over time. However, it is worth mentioning here that in the early phase after AMI, acute inflammation represents a physiological response acting as a short-term protective mechanism for restoring myocardial architecture and function.[26] Yet the release of cytokines favors the establishment of a persistent systemic inflammatory state.[27,28]

In cardiovascular settings, Aβ1-40 is primarily sourced from activated platelets, but it can also originate from endothelial cells and myocytes in the vascular walls.[6] Importantly, cardiovascular risk factors such as advanced age, CKD, and diabetes are upstream regulators of Aβ1-40 concentration,[5,9,29,30] which is also confirmed in our study. With aging, low-grade inflammation increases and promotes the Aβ1-40 production,[9] while the presence of kidney disorders

Table 3. Multivariable Cox Proportional Hazards Regression Analysis for End Point Death in Patients With AMI (Both STEMI and NSTEMI)

Variable	HR (95% CI)	*P* value
Age, per 5-y increase	1.55 (1.42–1.7)	<0.01
GFR <60 mL/min per 1.73 m², yes vs no	1.75 (1.25–2.46)	<0.01
LVEF, %, per 5-point % decrease	1.17 (1.1–1.26)	<0.01
Smoking, yes vs no	1.6 (1.16–2.2)	<0.01
Aβ1-40, per 10-unit increase	1.03 (1.01–1.05)	0.01
Previous AMI/PCI/CABG, yes vs no	1.6 (1.14–2.24)	0.01
hs-CRP, mg/L, per 10-unit increase	1.03 (1.01–1.05)	0.04

After correction for sex, hypertension, and New York Heart Association class (III vs I–II. Aβ1-40 indicates amyloid-β 1-40; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; GFR, glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Table 4. Multivariable Cox Proportional Hazards Regression Analysis for End Point Death in Patients With STEMI

Variable	HR (95% CI)	*P* value
Age, per 5-y increase	1.77 (1.59–1.97)	<0.01
LVEF, %, per 5-point % decrease	1.14 (1.05–1.25)	<0.01
Smoking, yes vs no	1.81 (1.2–2.72)	<0.01
Aβ1-40, per 10-unit increase	1.03 (1.01–1.05)	0.01
hs-CRP, mg/L, per 10-unit increase	1.05 (1.01–1.09)	0.04

After correction for sex, hypertension, New York Heart Association class (III vs I–II), glomerular filtration rate <60 mL/min per 1.73 m² and previous ischemic events. Aβ1-40 indicates amyloid-β 1-40; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction; and STEMI, ST-segment–elevation myocardial infarction.

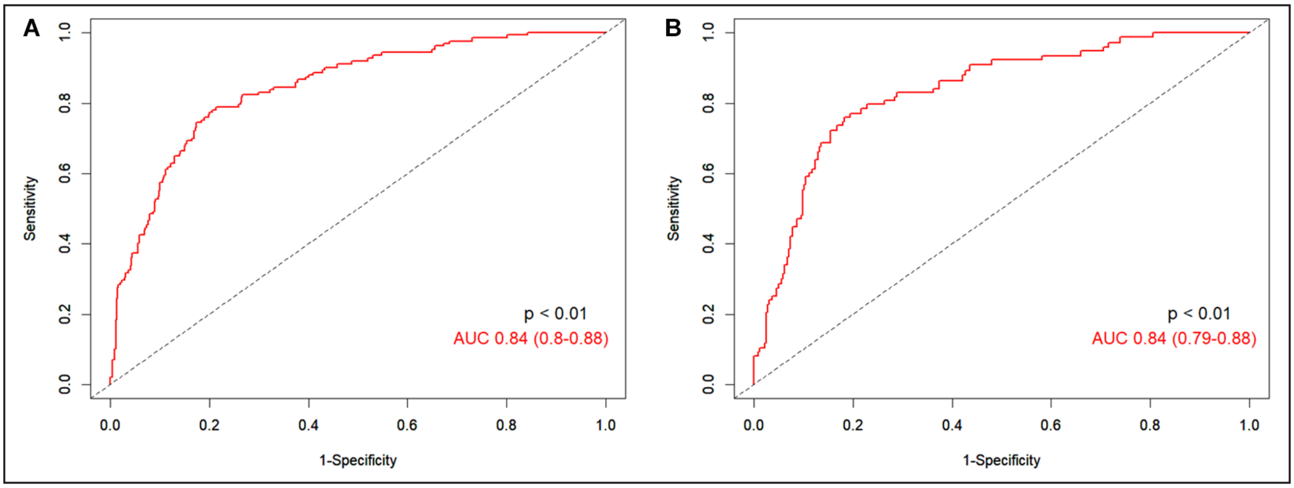


Figure 3. Time-dependent receiver operating characteristics analysis for the multivariable model including Aβ1-40 (A) in the overall cohort and (B) STEMI subcohort.
AUC indicates area under the curve; Aβ1-40 amyloid-β 1-40; and STEMI, ST-segment–elevation myocardial infarction.

influence Aβ1-40 accumulation due to impaired clearance.[30] Regarding the relationship between diabetes and increased Aβ1-40 levels, it is suggested that this may be due to increased inflammation and oxidative stress resulting from hyperglycemia, which further promotes Aβ1-40 production. Additionally, it has been observed that insulin resistance leads to a reduction in insulin-degrading enzyme levels, which is 1 of >20 enzymes that can degrade Aβ1-40.[7] As a result, the accumulation of Aβ1-40 leads to altered phosphorylation of downstream effectors of insulin and insulin-like growth factor-1, resulting in the aggravation of insulin resistance, creating a vicious cycle.[8] In addition, some recent evidence suggests that increased Aβ1-40 levels are associated with high platelet reactivity after recent myocardial revascularization in patients with diabetes treated with aspirin and clopidogrel, reiterating the utility of this biomarker in predicting adverse outcomes in patients with CAD.[31] The interplay between increased Aβ1-40 levels, insulin resistance, and altered insulin-like growth factor-1 pathways has been identified in the pathophysiology of AD.[32] Interestingly, according to literature data, these mechanisms could be analogous in patients with cardiovascular disease,

Table 5. Predictors of Aβ1-40 Levels

Variable	OR (95% CI)	*P* value
Age, per 5-y increase	1.13 (1.06–1.21)	<0.01
GFR <60 mL/min per 1.73 m^2, yes vs no	4.37 (2.14–8.92)	<0.01
HbA_{1C} ≥39 mmol/mol, yes vs no	1.75 (1.25–2.46)	<0.01
LVEF, %, per 5-point % decrease	1.14 (1.06–1.24)	<0.01

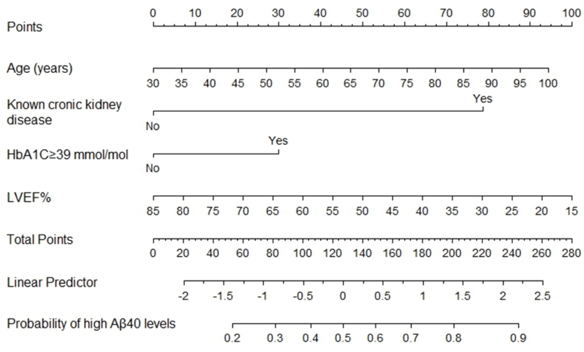
Aβ1-40 indicates amyloid-β 1-40; GFR, glomerular filtration rate; HbA_{1C}, glycosylated hemoglobin; LVEF, left ventricular ejection fraction; and OR, odds ratio.

given the systemic roles of these 3 factors.[32] However, further investigations are required to confirm this hypothesis.

Furthermore, it is of utmost importance to emphasize that certain lifestyles such as smoking, sleep deprivation, sedentary lifestyle, incorrect diet, and obesity[9,10] can lead to Aβ1-40 accumulation, which explains the elevated levels of Aβ1-40 in the young population as well.

All the aforementioned upstream regulators of Aβ1-40 levels in blood are also associated with vascular disease. Therefore, these mechanisms explain the molecular basis described in the proatherosclerotic role of the peptide in clinical studies.[20,21]

It is worth mentioning here that seminal studies have shown that reducing Aβ1-40 levels may slow the progression of AD and improve cognitive function.[33,34] Hence, introducing targeted medication to lower Aβ1-40 levels in patients with AMI holds promising potential for enhancing prognosis. However, further validation of its efficacy within the group of patients with AMI is still required for ensuring its clinical effectiveness. In vitro and in vivo studies have reported a significant decrease in Aβ1-40 production following treatment with cholesterol-lowering drugs such as simvastatin and lovastatin.[33] Indeed, statin-mediated cholesterol reduction influences the colocalization of secretases and APP on cell membranes, thus interfering with the transport of APP in the subcellular compartment where the proteolytic activity of secretases takes place.[35,36] In their study, Wang and colleagues screened 1600 drugs to determine their potential role in influencing APP processing.[34] Some cardiovascular drugs with antitensive properties were observed to effectively lower Aβ1-40 concentration.[34] However, A



B

Age (years)	Points	Chronic kidney disease	Points	LVEF%	Points
30	0	No	0	15	100
35	7	Yes	79	20	93
40	13			25	86
45	20			30	79
50	27	**HbA1C≥39 mmol/mol**	**Points**	35	71
55	34	No	0	40	64
60	40	Yes	30	45	57
65	47			50	50
70	54			55	43
75	61			60	36
80	67			65	29
85	74			70	21
90	81			75	14
95	88			80	7
100	94			85	0

Total points	Probability of high Aβ40 levels
53	0.2
82	0.3
105	0.4
127	0.5
149	0.6
172	0.7
201	0.8
244	0.9

Figure 4. Nomogram for Aβ1-40 levels prediction (A) and clinical variables (derived from the nomogram) and relative score used to predict the Aβ1-40 levels (B).
Aβ1-40 indicates amyloid-β 1-40; HbA_{1c}, glycosylated hemoglobin; and LVEF, left ventricular ejection fraction.

angiotensin-converting enzyme inhibitors such as trandolapril and quinapril were found to promote an increase in Aβ1-40 production in vitro, consistent with the degrading activity of angiotensin-converting enzyme on the peptide.[34] Similarly, chronic use of sacubitril/valsartan for the treatment of hypertension inhibits the activity of neprilysin, an important enzyme involved in Aβ1-40 clearance, which may accelerate its accumulation.[37] Therefore, long-term use of these drugs may have potentially concerning effects on the generation of Aβ1-40 and risk of AD development.

Finally, in light of the extreme necessity for novel biomarkers to better stratify the risk of patients with AMI, we propose a simple nomogram that consists of 4 parameters—age, GFR, HbA_{1C}, and LVEF—to calculate the probability of high Aβ1-40 values given that this biomarker may help to better stratify patients with AMI, and indicate the application of some therapeutic strategies as soon as possible (eg, dual antiplatelet therapy, high-dose statins). As Aβ1-40 is not a routine laboratory practice during hospitalization, our model provides a solution for effective estimation of the marker using parameters that are typically part of clinical routine. Of course, this nomogram should be validated in larger cohorts in future studies; however, following a critical analysis of the parameters included in the nomogram, it can be concluded that the basis for this nomogram is in accordance with the literature. This is because elevated Aβ1-40 values are expected in patients with CKD due to inadequate cleansing, as well as in patients with diabetes due to hyperglycemia and increased chronic inflammation. Furthermore, the findings of this study demonstrate a correlation between Aβ1-40 and LVEF, which is consistent with the existing literature. According to the available data on the general population without established cardiovascular disease, high levels of Aβ1-40 have been associated with increased levels of N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T.[19] This suggests the possibility of impaired LVEF, which is indicated by increased filling pressures and myocardial damage. Furthermore, a correlation between Aβ1-40 levels and reduced left ventricular stroke volume, as well as decreased exercise capacity, has been demonstrated.[19] In addition, the intracellular accumulation of Aβ1-40 in cardiomyocytes, as reported in patients with heart failure, is hypothesized to be a mechanism of toxicity induced by this peptide, thus impacting systolic function.[38]

The model is easily reproducible and does not require additional cost. In specificity, the total score calculated for the sum of single points determined by each variable provides the probability of high Aβ1-40 values. It is important to emphasize that although this model indicates the increased Aβ1-40 concentration, the afterwards dosage of this marker is advised.

Finally, this study has several limitations. First, Aβ1-40 levels were not measured during follow-up; therefore, we do not have longitudinal data that would allow us to investigate the dynamic of this marker during follow-up and its prognostic value. All statistical analyses were based on a single measurement taken during hospital admission. Second, we performed the statistical analysis for all-cause death, as the distinction between cardiovascular and noncardiovascular causes of death could not be assessed due to lack of information (data not available). In addition, this was a single-center study. However, this also guarantees homogeneity of treatment and follow-up, which were carried out according to the latest European guidelines. Furthermore, a significant limitation of the present study is the absence of a validation cohort, which impacts the clinical applicability of our findings. Indeed, while the prognostic value of the biomarker has been demonstrated previously in patients with NSTEMI,[12] future studies are needed to validate these findings specifically in a population of patients with AMI and STEMI separately. This will be critical to establishing the broader relevance and utility of our results in clinical practice.

In conclusion, despite advances in diagnosis and treatment, CAD is the third-leading cause of death worldwide, accounting for ≈17.8 million deaths annually,[1] and AMI represents its life-threatening manifestation.[4] In AMI settings, time is crucial in the initial patient management, and there is a necessity for better risk stratification toward more personalized medicine. To the best of our knowledge, this is the first study that demonstrated the prognostic value of Aβ1-40 for all-cause death in a large real-world cohort of patients with AMI, encompassing both STEMI and NSTEMI. Furthermore, this is the first study that demonstrated the predictive value of Aβ1-40 for death in patients with STEMI. Indeed, prior research on Aβ1-40 has been restricted to NSTEMI populations. Finally, as Aβ1-40 can help identify patients at higher risk of adverse outcomes, this study provides a simple nomogram that allows estimation of the probability of high values of this marker. The model is cost-effective and uses parameters that are usually part of clinical routine including age, LVEF, HbA_{1C}, and GFR, to calculate the probability of high Aβ1-40 presence.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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