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Classification rule for ten year MACE Risk in primary care tarragona older adults with type2 diabetes: a CHAID decision-tree analysis

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Abstract

Background Cardiovascular disease is the leading cause of mortality among individuals with Type 2 Diabetes Mellitus (T2DM). This study developed a simple tool to predict the 10-year risk of major adverse cardiovascular events (MACE) in T2DM patients over 60 years within primary care.

Methods A retrospective cohort study was conducted on patients with T2DM who were over 60 years old in Tarragona, spanning from 01/01/2009–31/12/2018. Primary outcome was MACE, which included acute myocardial infarction (AMI), stroke, and cardiovascular death, all of which were identified using ICD-9 diagnostic codes. Other variables were age, sex, comorbidities, risk factors, as well as clinical and laboratory parameters.

A Chi-Square Automatic Interaction Detector (CHAID) decision tree classification was utilized to assess the 10-year risk of developing a new MACE.

Results Five thousand five hundred fifty-four patients with T2DM were identified. Among the 4,666 with T2DM and without previous MACE, 779 patients went on to develop a new MACE.

The CHAID model categorizes individuals into three risk groups based on the primary predictor variable, which is age. For patients under the age of 71 with hypertension, having HDL-c levels less than 39 mg/dL increases the risk of developing a new MACE to 19.9%. Among individuals aged 71 to 75 years, having fasting glucose levels greater than 177 mg/dL elevates the risk to 27.2%.

Conclusion Classification trees based on CHAID allow for the development of decision rules and simplify the stratification of cardiovascular risk in patients with T2DM, making it a valuable tool for risk assessment within a primary care setting.

Keywords Diabetes, MACE, CHAID, Decision tree

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Background

Diabetes Mellitus (DM) is one of the most prevalent chronic diseases in the world, affecting 537 million people and expected to increase to 783 million by 2045. Type 2 diabetes (T2DM) is the most common type of diabetes, over 90%, of all diabetes worldwide [1].

Cardiovascular Disease (CVD) is the most prevalent cause of morbidity and mortality among T2DM patients, which, moreover, have double the risk of death from heart disease or stroke [2].

The World Health Organization (WHO) has declared CVD as one of the priority diseases within their action plan, aiming to reduce CVD-related mortality by 25% by 2025. A key requirement to achieve this goal is to improve the prediction of incident CVD events. This requires identification of individuals at highest risk of major adverse cardiovascular events (MACE) to target effective interventions, personalize treatments and maximize the benefit of those treatments [3–5].

Cardiovascular (CV) risk calculators, based on multivariable models, are designed to allow a more accurate estimate of the absolute risk that a particular person, theoretically healthy and asymptomatic, has of presenting an event. Since the 1998"Framingham risk score", multiple risk calculators have been developed, some adapted to specific ethnic or geographical areas.

In Spain, the cohort REGICOR allowed validation of its own risk equation, adapted to the rates of event incidence and prevalence of CV risk factors in the Girona area. It is currently the risk calculator used in Primary Care Health Centers (PCHC) of Catalonia.

Typically these predictive models analyze individual prognostic factors in isolation but ignore the interaction between them, often overlooking their interactions, such as those observed in several studies involving age and gender [6].

The main advantage of using a CHAID (Chi-Square Automatic Interaction Detector) decision tree analysis is the ability to convert complicated risk equations into an organized flowchart, which can be easily navigated to identify the appropriate risk and interaction effect among prognostic factors.

This is important in clinical practice, where short consultation times can make more complex risk stratification tools less amenable to being used [7]. A simple, practical and user-friendly approach can encourage clinicians to make more valid, risk-based decisions regarding interventions.

An important limitation of most risk scores is that the population cohort data from which they were derived have included individuals whose median age is typically less than 70 years [8].

However, with the aging of high-income countries, most cardiovascular events now occur in the elderly, beyond the range of most existing equations.

As an example, the European Society of Cardiology (ESC) Systematic COronary Risk Evaluation 2 (SCORE2) is limited to the age range from 40 to 65 years and the median age of the recently published LIFE-CVD cohorts was approximately 60 years [9].

Several studies have demonstrated that SCORE, Framingham and other similar algorithms are less effective in predicting cardiovascular events in the elderly [10]. Thus, classic ESC guidelines do not recommend their use in individuals over 70 years, as the risk for cardiovascular events might be overestimated due to competing causes of death [9].

In fact, to resolve this limitation, the 2021 ESC guidelines on cardiovascular disease prevention in clinical practice, introduce the new SCORE2-OP to estimate 10 year risk of CVD death and CVD morbidity (non-fatal myocardial infarction, non-fatal stroke) for people between 70 and 89 years [11].

More specifically, few studies have focused on the natural history of CVD in the very old population, since frail older people are usually excluded from randomized controlled trials [12–14].

The aim of this study is to develop a simple classification tool to assess the 10-year risk of experiencing a MACE in older T2DM patients.

Methods

Study design

This study is nested within a population-based, retrospective and multicentric cohort located in Tarragona, Spain.

Study population and setting

The reference population comprises individuals included in the CAPAMIS (Community-Acquired Pneumonia, Myocardial Infarction, and Stroke) cohort. All of these individuals were 60 years or older at the beginning of the study and were assigned to nine PCHCs and two reference hospitals in the Tarragona region, an urban area with a residential-industrial character located on the Mediterranean coast of Southern Catalonia, Spain. Persons with a T2DM diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification [ICD- 9] code 250.0) were included in the present study ($n = 5554$). More information about the CAPAMIS cohort characteristics can be found at BMC Public Health. 2010 Jan 19;10:25 [15].

Follow-up

The follow-up period was set for ten consecutive years, spanning from January 1, 2009, to December 31, 2018. All cohort members were monitored from the inception of the study until the occurrence of a major cardiovascular event (MACE), transfer to a different PCHC (other than the nine included in the study), death, or the conclusion of the study.

Data sources

All participating PCHCs utilize a computerized clinical record system that encompasses administrative data, medical conditions, prescriptions, laboratory results and diagnosis associated with hospital and outpatient visits. This electronic clinical record system (working since 1999) was used to identify comorbidities and underlying conditions in order to establish baseline characteristics of the cohort at the beginning of the study.

The ICD- 9 diagnostic codes from the annual listings of the Basic Data Minimum Set (CMBD) of the two reference hospitals (Joan XXIII and Santa Tecla) were initially employed to identify occurrences of major CV events (hospitalizations for myocardial infarction or stroke) among cohort members during the 10-year tracking period. All cases underwent subsequent validation through a review, conducted by a medical researcher, of the clinical hospital records of patients who experienced one of the studied events.

Study variables

Outcome

The primary outcome was a major adverse cardiovascular event (MACE), which included AMI, stroke, and CV death, all of which were identified using ICD- 9 diagnostic codes (ICD- 9: 410).

Covariates.

Baseline characteristics of cohort members included socio-demographic factors (age and sex), comorbidities (chronic pulmonary disease, chronic liver disease, chronic renal disease), risk factors (current smoking, obesity, hypertension, and dyslipidaemia), as well as clinical parameters (systolic [SBP] and diastolic blood pressure [DBP]) and laboratory parameters (total cholesterol, low-density lipoprotein-cholesterol [LDL-c], high-density lipoprotein-cholesterol [HDL-c], basal glucose, and haemoglobin A1c [HbA1c]).

Clinical and laboratory parameters were recorded every two years. Satisfactory or unsatisfactory control was defined for each parameter at baseline (basal control) or at any time during the study period (total control) according to the following criteria: Unsatisfactory control for basal glucose was defined as ≥ 130 mg/dl. Unsatisfactory control for HbA1c was defined as $\geq 7\%$. Unsatisfactory control for blood pressure was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Unsatisfactory control for cholesterol was determined based on lipid profile criteria (total cholesterol ≥ 240 mg/dl, LDL-c ≥ 100 mg/dl, HDL-c < 50 mg/dl in women and < 40 mg/dl in men). These criteria were based on the recommendations of the American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) [8].

Statistical analyses

A descriptive analysis was conducted, calculating absolute and relative frequencies for categorical variables and mean and standard deviation (SD) for continuous ones, for both the overall study population and the subgroup without a previous history of MACE. Within this subgroup, the prevalence of study comorbidities and risk factors were compared using the chi-square test, while the values of clinical or analytical continuous parameters were compared using the Student's t test.

The chi-square test was also utilized to compare the percentage of new MACE cases between groups with satisfactory and unsatisfactory control (according to the previous definition) for each clinical and laboratory variable at two time points: at the beginning of the study and at any point during the study period.

Cox regression models were employed to calculate hazard ratios (HRs) along with their respective 95% confidence intervals (95% CI) in order to estimate the association between covariates and the risk of developing MACE during the study period. The final multivariable Cox model was adjusted for all relevant study variables after assessing potential confounders, interactions, and multicollinearity among them.

Statistical significance was set at $p < 0.05$ (two tailed). The analyses were performed using SPSS 26.0 (IBM SPSS Statistics for Windows Version 26.0. IBM Corp. Released 2019, Armonk, NY: IBM Corp).

Chi-squared Automatic Interaction Detector (CHAID)

A CHAID tree is a graphic representation of a series of decision rules. Beginning with a root node that includes all cases, the tree branches are divided into different child nodes that contain a subgroup of cases. The criterion for branching (or partitioning) is selected after examining all possible values of all available predictive variables. In the terminal nodes, a grouping of cases is obtained, such that the cases are as homogeneous as possible with respect to the value of the dependent variable. CHAID decision trees are nonparametric procedures that make no assumptions of the underlying data. This algorithm determines how continuous and/or categorical independent

variables best combine to predict a binary outcome based on "if–then" logic by portioning each independent variable into mutually exclusive subsets based on data homogeneity. Statistical analysis with the CHAID method was carried out through the CHAID node included in the statistical program SPSS 26.0 (IBM SPSS Statistics for Windows Version 26.0. IBM Corp. Released 2019, Armonk, NY: IBM Corp).

Two decision trees were built in T2DM population without previous cardiovascular events. In both, study covariates, including age, sex, and comorbidities were included. In the first tree, clinical and laboratory parameters at baseline were introduced as continuous variables; while in the second one, these parameters were introduced after categorisation into satisfactory or unsatisfactory basal control.

Results

Of the total 27.204 cohort members, an amount 5.554 patients with T2DM were identified. At baseline, the mean age of study subjects was 71.8 years (SD 8.1) and 48% were male. The most prevalent underlying conditions were hypertension (70.1%), dyslipidaemia 45.6%) and obesity (33.6%).

The baseline characteristics of the study cohort, categorized by the presence or absence of MACE (either prior to the study's commencement or developed during the study period), are presented in Table 1. Among the total 5.554 individuals with T2DM, 4.666 (84%) had no prior history of MACE. Within this subgroup, 2,522 (54%) were women, 69.2% had hypertension, and their HDL-c levels averaged 50.4 mg/dl (SD 12.5). Among the 4.666 individuals with T2DM and without previous MACE, 779 patients went on to develop a new MACE, with an average age of 73.4 years (SD 8). Within this group, 53.5% were women, 75.4% had hypertension, and their HDL-c levels averaged 48.8 mg/dl (SD 12.2). Table 1 also presents the p-values obtained by applying the chi-square test to compare the prevalence of comorbidities and risk factors between the group with new MACE and the group without. Significant differences in age were observed, with a mean of 73.4 (SD: 8) in the group with new MACE, compared to 71.1 (SD: 7.9) in the group without. There were also differences in the prevalence of hypertension (75.4% vs. 68%) and the baseline HDL-c levels (mean 48.8; SD 12.2 vs. 50.8; SD: 12.6). In all three cases p was < 0.001.

Table 2 presents and compares the frequencies (both absolute and relative) of individuals with satisfactory/unsatisfactory control (both basal and total) for each clinical and laboratory study parameter between the group with new MACE and the group without. It also provides p-values after applying the chi-square test. Significant differences should be noted between the groups with and without new MACE in terms of control for both

Table 1 Baseline characteristics according to the presence or not of previous MACE

	T2DM *N* = 5554 (20.4)	**T2DM without previous MACE *N* = 4666 (17.2)**	**T2DM without previous MACE And NO NEW MACE *N* = 3887 (14.2)**	**T2DM without previous MACE And NEW MACE *N* = 779 (2.8)**	**p-value**	**Overall *N* = 27,204**
Age, years	71.8 (8.1)	71.5 (8)	71.1 (7.9)	73.4 (8)	< 0,001	70.7 (8.6)
Sex, male	2667 (48)	2144 (46)	1782 (45.8)	362 (46.5)	0.7	12,137 (44.6)
Chronic pulmonary disease	383 (6.9)	398 (8.5)	338 (8.7)	60 (7.7)	0.5	1475 (5.4)
Chronic liver disease	164 (3)	145 (3.1)	128 (3.3)	17 (2.2)	0.1	622 (2.3)
Chronic renal disease	209 (3.7)	134 (2.8)	104 (2.7)	30 (3.9)	0.2	659 (2.4)
Current smoking	583 (10.5)	499 (10.7)	419 (10.8)	80 (10.3)	0.7	2796 (10.3)
Obesity	1866 (33.6)	1556 (33.3)	1286 (33.1)	270 (34.7)	0.4	6658 (24.5)
Hypertension	3893 (70.1)	3229 (69.2)	2642 (68)	587 (75.4)	< 0.001	14,549 (53.5)
Dyslipidaemia	2552 (45.9)	2134 (45.7)	1783 (45.8)	351 (45.1)	0.2	9962 (36.6)
SBP, mmHg	139.3 (18.7)	139.7 (18.5)	139.5 (18.2)	140.7 (19.5)	0.9	136.07 (17.8)
Total cholesterol mg/dl	194.5 (39.4)	196.9 (38.6)	197.3 (37.9)	195.2 (41.7)	0.2	208.5 (38.6)
HDL-cholesterol mg/dl	49.9 (12.6)	50.4 (12.5)	50.8 (12.6)	48.8 (12.2)	< 0.001	55.3 (13.9)
LDL- cholesterol mg/dl	115.9 (33.1)	117.8 (32.7)	118.2 (32)	116.9 (34.7)	0.3	128.4 (33.5)
HbA1c, %	6.8 (1.5)	6.8 (1.5)	6.8 (1.5)	6.9 (1.6)	0.2	6.1 (1.5)

Data are presented with frequencies (%), or the mean (standard deviation), according to the type of variable (categorical or continuous variables, respectively)

MACE major adverse cardiovascular events, *T2DM* Type 2 Diabetes Mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *HbA1c* haemoglobin A1c

Table 2 Baseline clinical and laboratory values according to the presence or not of previous MACE

	T2DM ***N*** **= 5554 (%)**	**T2DM without previous MACE** ***N*** **= 4666 (84)**	**T2DM without previous MACE And NO NEW MACE** ***N*** **= 3887 (83.3)**	**T2DM without previous MACE And NEW MACE** ***N*** **= 779 (16.7)**	***p*-value**
Age, years	71.8 (8.1)	71.5 (8)	71.1 (7.9)	73.4 (8)	< 0.001
Sex, male	2667 (48)	2144 (46)	1782 (45.8)	362 (46.5)	0.7
Basal Control BP					
No	2768 (49.8)	2371 (50.8)	1958 (50.4)	413 (53)	0.5
Yes	2786 (50.2)	2295 (49.2)	1929 (49.6)	366 (47)	
Basal Control Total Cholesterol					
No	107 (2)	91 (2)	78 (2)	13 (1.7)	0.5
Yes	5447 (98)	4575 (98)	3809 (98)	766 (98.3)	
Basal Control LDL cholesterol					
No	3509 (63.2)	3061 (65.6)	2554 (65.7)	507 (65.1)	0.7
Yes	2045 (36.8)	1605 (34.4)	1333 (34.3)	272 (34.9)	
Basal Control HDL Cholesterol					
No	1249 (22.5)	989 (21.2)	790 (20.3)	199 (25.5)	0.001
Yes	4305 (77.5)	3677 (78.8)	3097 (79.7)	580 (74.5)	
Basal Control HbA1c					
No	872 (15.7)	718 (15.4)	589 (15.2)	129 (16.6)	0.3
Yes	4682 (84.3)	3948 (84.6)	3298 (84.8)	650 (83.4)	
Total Control BP					
No	4514 (81.3)	3830 (82)	3179 (81.8)	651 (83.6)	0.2
Yes	1040 (18.7)	836 (18)	708 (18.2)	128 (16.4)	
Total Control Total Cholesterol					
No	1205 (21.7)	1062 (22.8)	877 (22.6)	185 (23.7)	0.5
Yes	4349 (78.3)	3604 (77.2)	3010 (77.4)	594 (76.3)	
Total Control LDL Cholesterol					
No	4411 (79.4)	3822 (82)	3193 (82.1)	629 (80.7)	0.3
Yes	1143 (20.6)	844 (18)	694 (17.9)	150 (19.3)	
Total Control HDL Cholesterol					
No	3584 (64.5)	2977 (63.8)	2421 (62.3)	556 (71.4)	< 0.001
Yes	1970 (35.5)	1689 (36.2)	1466 (37.7)	223 (28.6)	
Total Control HbA1c					
No	3964 (71.4)	3334 (71.5)	2750 (70.7)	584 (75)	0.01
Yes	1590 (28.6)	1332 (28.5)	1137 (29.3)	195 (25)	

Data are presented with frequencies (%), or the mean (standard deviation), according to the type of variable (categorical or continuous variables, respectively)

Unsatisfactory control was defined: for haemoglobin (Hb) A1c as ≥ 7%; for blood pressure (BP) as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg; for total cholesterol as ≥ 240 mg/dl, for low-density lipoprotein (LDL)-cholesterol as ≥ 100 mg/dl, for high-density lipoprotein (HDL)-cholesterol as < 50 mg/dl in women and < 40 mg/dl in men. These criteria were based on the recommendations of the American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) (8)

MACE major adverse cardiovascular events, *T2DM* Type 2 Diabetes Mellitus

basal and total HDL-c. In the group with new MACE, the percentage of individuals with unsatisfactory basal control was 25.5% (compared to 20.3% in the group without; $p = 0.001$), and the percentages with unsatisfactory total control were 71.4% in the group with new MACE and 62.3% in the group without ($p < 0.001$). Differences were also observed between the groups in terms of the percentage of individuals with total poor control of their T2DM (unsatisfactory total control of HbA1c), with 75% in the group with new MACE compared to 70.7% in the group without ($p = 0.01$).

Table 3 shows Cox regression analyses assessing the association between the different baseline conditions and the risk of developing a new MACE among the study cohort. In the multivariable-adjusted analysis, age (HR: 1.06; 95% CI:1.05–1.07), male sex (HR: 1.3;

Table 3 Cox regression analysis evaluating predictors to suffer a new MACE in the study population

	T2DM without previous MACE and NO NEW MACE *N* = 3887 (83.3%)	**T2DM without previous MACE and NEW MACE *N* = 779 (16.7%)**	**Unadjusted HR (95% CI), p**	**Multivariable-adjusted HR (95% CI), p**
Age, years	71.1 (7.9)	73.4 (8)	1.06 (1.05–1.07), < 0.001	1.06 (1.05–1.07), < 0.001
Sex, male	1782 (45.8) 2105 (54.2)	362 (46.5) 417 (53.5)	1.02 (0.88–1.18), 0.77	1.3 (1.03–1.65), 0.03
Hypertension	2642 (68)	587 (75.4)	1.43 (1.22–1.69), < 0.001	1.18 (0.98–1.44), 0.09
Chronic pulmonary disease	338 (8.7)	60 (7.7)	1.48 (1.14–1.93), 0.004	1.37 (1.03–1.83), 0.03
Chronic liver disease	128 (3.3)	17 (2.2)	0.76 (0.47–1.22), 0.25	0.87 (0.53–1.44), 0.58
Chronic renal disease	104 (2.7)	30 (3.9)	1.99 (1.38–2.87), < 0.001	1.2 (0.79–1.83), 0.39
Current smoking	419 (10.8)	80 (10.3)	0.93 (0.73–1.17), 0.53	0.95 (0.69–1.3), 0.74
Obesity	1286 (33.1)	270 (34.7)	1.1 (0.95–1.27), 0.21	1.31 (1.05–1.65), 0.02
Dyslipidaemia	1783 (45.8)	351 (45.1)	0.74 (0.48–1.14), 0.17	1.04 (0.89–1.22), 0.65
SBP_basal, No control	1958 (50.4)	413 (53)	1.08 (0.94–1.24), 0.3	0.94 (0.75–1.19), 0.6
Total cholesterol_basal, No control	78 (2)	13 (1.7)	1.78 (1.03–3.08), 0.04	3.14 (1.74–5.66), < 0.001
HDL-cholesterol_basal, No control	790 (20.3)	199 (25.5)	1.54 (1.31–1.81), < 0.001	1.49 (1.19–1.87), < 0.001
LDL-cholesterol_basal, No control	2554 (65.7)	507 (65.1)	0.92 (0.79–1.06), 0.22	0.98 (0.76–1.26), 0.87
Glucose_basal, No control	689 (17.7)	137 (18)	1.33 (1.11–1.60), 0.002	1.32 (1.01–1.66), 0.01
HbA1c_basal, No control	589 (15.2)	129 (16.6)	1.33 (1.1–1.61), 0.003	1 (0.77–1.29), 0.98
BMI_08, Kg/m^2	30.4 (4.9)	30.6 (5.2)	1 (0.98–1), 0.78	0.99 (0.97–1.01), 0.59
SBP_08, mmHg	139.5 (18.2)	140.7 (19.5)	1 (0.99–1), 0.14	1 (1–1.01), 0.02
DBP_08, mmHg	76.1 (9.9)	74.8 (10.5)	0.98 (0.98–0.99), < 0.001	0.99 (0.98–0.99), 0.003
Glucose_08, mg/dl	146.1 (51.9)	149.4 (56.8)	1 (1–1.003), 0.04	1 (0.99–1), 0.57
HbA1c_08, % mean (SD)	6.8 (1.5)	6.9 (1.6)	1.06 (1.01–1.11), 0.02	1.05 (0.98–1.12), 0.2
Total Cholesterol_08, mg/dl	197.3 (37.9)	195.2 (41.7)	0.99 (0.99–1), 0.04	0.99 (0.99–1), 0.55
LDL-Cholesterol_08, mg/dl	118.2 (32)	116.9 (34.7)	0.99 (0.99–1), 0.11	1 (0.99–1.01), 0.59
HDL-Cholesterol_08, mg/dl	50.8 (12.6)	48.8 (12.2)	0.98 (0.98–0.99), < 0.001	0.99 (0.98–1), 0.14

Data are presented with frequencies (%), or the mean (standard deviation), according to the type of variable (categorical or continuous variables, respectively)

MACE major adverse cardiovascular events, *T2DM* Type 2 Diabetes Mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *HbA1c* aemoglobin A1c, *BMI* body mass index

95% CI: 1.03–1.65), obesity (HR: 1.31; 95% CI: 1.05–1.65), Chronic pulmonary disease (HR: 1.37; 95% CI: 1.03–1.83), total cholesterol_basal (HR: 3.14; 95% CI: 1.74–5.66), HDL-c_basal (HR: 1.49; 95% CI:1.19–1.87), glucose_basal (HR: 1.32; 95% CI: 1.01–1.66) emerged as significantly associated with an increased risk of developing a new MACE among the study population.

CHAID results

In the first figure, corresponding to the tree made using the values of the continuous variables at the initial study moment, it can be observed that the primary predictor for the development of a new cardiovascular event in a T2DM population without previous MACE is age.

The CHAID model divides individuals into three risk groups based on the variable age: < 71 years (node 1), 71–75 years (node 2), and > 75 years (node 3) with corresponding increased risks of 13%, 18.1%, and 21.9% for developing a MACE, respectively.

In the population group aged < 71 years (node 1) with hypertension (node 5), having HDL-c levels < 39 mg/dL (node 11) increases the risk of experiencing a MACE to 19.9%. Among the population aged 71 to 75 years (node 2), basal glucose levels further divide them into two nodes: levels > 177 mg/dL (node 7) increase the risk of developing a new MACE to 27.2%, while those with basal glucose levels < 177 mg/dL (node 6) and the presence of HDL-c levels < 52 mg/dL (node 13) face a 19.6% increased risk. Finally, in the group aged > 75 years (node 3) with a baseline risk of 21.9% for developing a MACE, the next prognostic variable is the LDL-c level, values below 89 mg/dl (node 8) are associated with a 28.6% risk of developing a new MACE. Conversely, LDL-c values above 89 mg/dl (node 9) carry a 21% probability of

experiencing a CV event. This paradoxical effect may be attributed to the baseline treatment of patients with high cholesterol and a high underlying cardiovascular risk.

Figure 1 corresponds to the CHAID tree model performed using basal control categorized as satisfactory or unsatisfactory (as described in the Methods section). It can be observed that age remains the main prognostic variable for developing a new MACE. This model also divides the sample into three age groups: <71 years (node 1), 71–75 years (node 2), and >75 years (node 3), with respective risks of 13%, 18.1%, and 21.9% for developing a MACE. Within the patient groups aged <71 years and 71–75 years, the next significant variable in the prognosis is the presence or absence of hypertension. If hypertension is present, the risk of developing a new MACE increases to 14.3% (node 5) for patients <71 years and 20% (node 7) for patients aged 71–75. Furthermore, unsatisfactory basal control of HDL-c levels is associated with an elevated risk of developing a MACE. Patients aged <71 years with hypertension and unsatisfactory

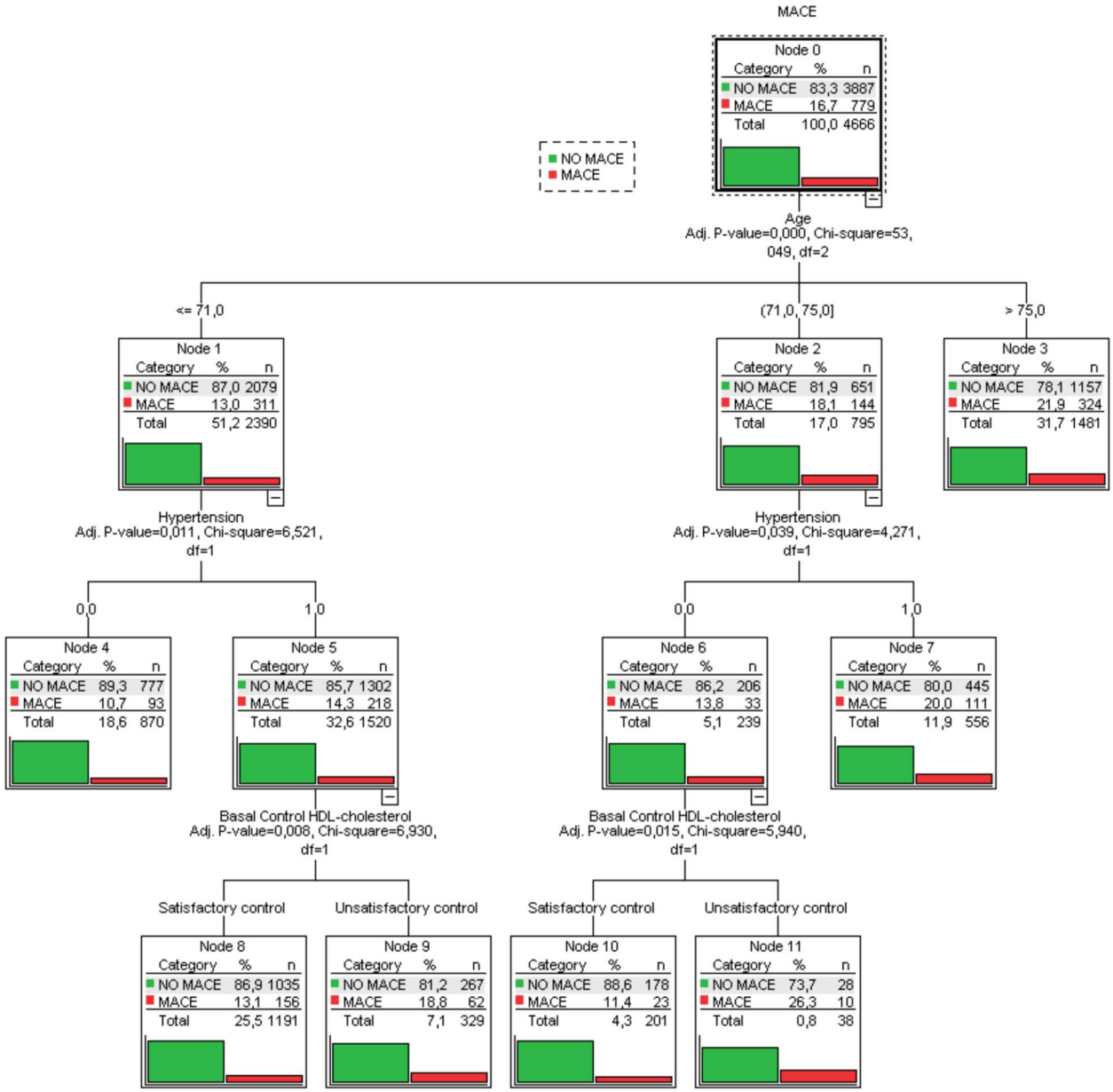

Fig. 1 MACE tree 10-year risk in total T2DM without previous MACE. Basal control values. MACE: major adverse cardiovascular events; T2DM: Type 2 Diabetes Mellitus; HDL: high-density lipoprotein

basal HDL-c control experience an increased risk of MACE at 18.8% (node 9). In the case of patients aged 71–75 years without hypertension (node 6), their risk of experiencing a new MACE rises to 26.3% (node 11) if they also have unsatisfactory basal control of HDL-c, making this group the highest-risk category for developing a new MACE.

Discussion

We conducted a comprehensive population-based cohort study in a well-defined geographical area. Our objective was to investigate the risk of developing a new MACE among T2DM individuals who were over 60 years old and had no previous MACE. We examined this risk in relation to the presence or absence of specific underlying risk conditions and the levels of key clinical and laboratory parameters. This study aimed to assess the influence of these variables on the risk of developing a new MACE in the study population.

As main findings, our data indicates that the risk of developing a new MACE increases with age, especially among individuals aged 75 years or older. Age is also the primary prognostic variable in the CHAID tree model.

Until recently, prediction models for cardiovascular risk were inadequate for elderly patients. Efforts to address this age limitation and develop cardiovascular risk prediction models for the elderly have been made through models proposed by Van Bussel and Griffith et al. [12, 13] and the more recent SCORE2-OP proposed by ESC [11]. CVD in very elderly patients exhibit specific characteristics in some respects. For instance, they often have higher prevalences of risk factors such as hypertension, obesity, and high cholesterol levels, leading to a consequently greater impact of these CV risk factors [16].

In the multivariable analysis, besides age and male sex being identified as risk factors associated with the development of a new MACE, the presence of obesity, unsatisfactory basal control of total cholesterol, HDL-c, and fasting glucose levels are also associated with an increased risk of experiencing a new MACE. Although hypertension and smoking habits were linked to an increased risk, they did not emerge as statistically significant factors in our multivariable models. However, in our decision tree model, hypertension behaves as a variable in the prognosis of MACE development.

Hypertension is recognized as an independent and modifiable risk factor for the development of CVD and is a leading cause of disability worldwide [17]. The Framingham Study not only established hypertension as a major cardiovascular risk factor but also quantified its potential for atherogenic CVD [18]. Several studies have sought to investigate the relationship between age and hypertension prognosis, revealing an association with a higher risk of CVD and all-cause mortality. These associations were found to be stronger when hypertension developed at a younger age. The mechanisms underlying the associations of higher risks of CVD and all-cause mortality among younger hypertensive participants remain unclear. This can be attributed to the complexity of hypertension, which is influenced by both genetic predisposition and exposure to environmental factors [19].

Likewise, total cholesterol, HDL-c, and basal glucose are also considered prognostic variables in the decision tree model. Concerning HDL-c, previous studies have already indicated a gradual and inverse relationship between HDL-c levels and CVD and total mortality, emphasizing that higher HDL-c is associated with better outcomes. The Framingham study was the first and most important epidemiological essay to prove this. Many other observational studies have shown that low levels of HDL-c are associated with a higher risk of heart disease [20]. This protective effect has conventionally been attributed to its role in transporting excess cholesterol from peripheral tissues to the liver [21], as well as its anti-inflammatory properties, antioxidants, and antithrombotic effects, all of which contribute to its atheroprotective effects. However, the causality of HDL-c in the development of CVD remains controversial. Cohort studies contradict this inversely linear relationship between HDL-c and cardiovascular diseases [22, 23]. In a meta-analysis by Emanuele Di Angelantonio [24], which included 68 potential long-term cohort studies and involved 302,430 individuals without initial vascular disease, the findings revealed that there is no additional decrease in coronary heart disease events when HDL-c values exceed 60 mg/dL (1.5 mmol/L). Wilkins et al. [25] and Madsen et al. [26] also observed evidence of a plateau effect for coronary risk in HDL-c values. Similarly, Bowe et al. [27] found a U-shaped association between HDL-c levels and the risk of mortality, where the risk of death increases at both low and high HDL-c levels.

Thus, CHAID tree decision models utilizing continuous variables enable the determination of a critical threshold beyond which the probability of an event becomes statistically significant. Therefore, the primary advantage of the current decision tree model is its capability to establish a decision rule and patient profile, facilitating the stratification of the risk of developing a new MACE in T2DM population [28].

In summary, age is the primary determinant. Patients over 75 years have the highest estimated MACE risk (21.9%), and in this group, achieving LDL cholesterol levels below 89 mg/dL may be less relevant. For those aged 71–75 years, fasting glucose becomes a key factor, making it particularly important to maintain levels below 177 mg/dL. For patients aged 71 years or younger, controlling

blood pressure and ensuring adequate HDL cholesterol levels is crucial. This stratification of risk groups is illustrated in Fig. 2.

Strength and limitations

The main strength of this study lies in its population-based design, which includes a substantial cohort of 27,204 individuals. It's important to emphasize the thoroughness of validating all reported cases of MACE by carefully reviewing clinical records and reports. Additionally, considering the characteristics of the Catalan health system, which is public, universal, and provides easy access to hospitals in our study area, it's worth noting that only a few cases were managed outside of the two reference hospitals included.

As for limitations, this study did not take into account different treatments used by patients and certain lifestyle-related variables that can increase cardiovascular risk and mortality, such as diet, physical inactivity, or stress levels, were not assessed in the cohort. Therefore, we were unable to adjust for these variables. Furthermore, we were unable to adjust for the degree of therapeutic adherence or consider'new'cardiovascular risk factors (e.g., PCR, Lp[a]), which are not currently employed as risk markers, at least in primary care settings.

Additional limitations should be mentioned. Firstly, our study utilized a retrospective design, which may introduce biases when compared to a prospective study. Another significant limitation in our study's design is the lack of observation of albuminuria or glomerular filtration rate, as demonstrated in studies using CHAID decision trees [7] or in the meta-analysis conducted by Matsushite K. et al. [29] and the MADIABETES cohort study [30], where the presence of albuminuria or alterations in glomerular filtration rate were identified as independent risk factors for developing CVD in T2DM populations.

Finally, before translating these results into clinical practice, an external validation study would be essential. Such a study will incorporate medications taken by patients as key adjusting variables, especially considering that new antidiabetic drugs (such as SGLT2i and GLP- 1)

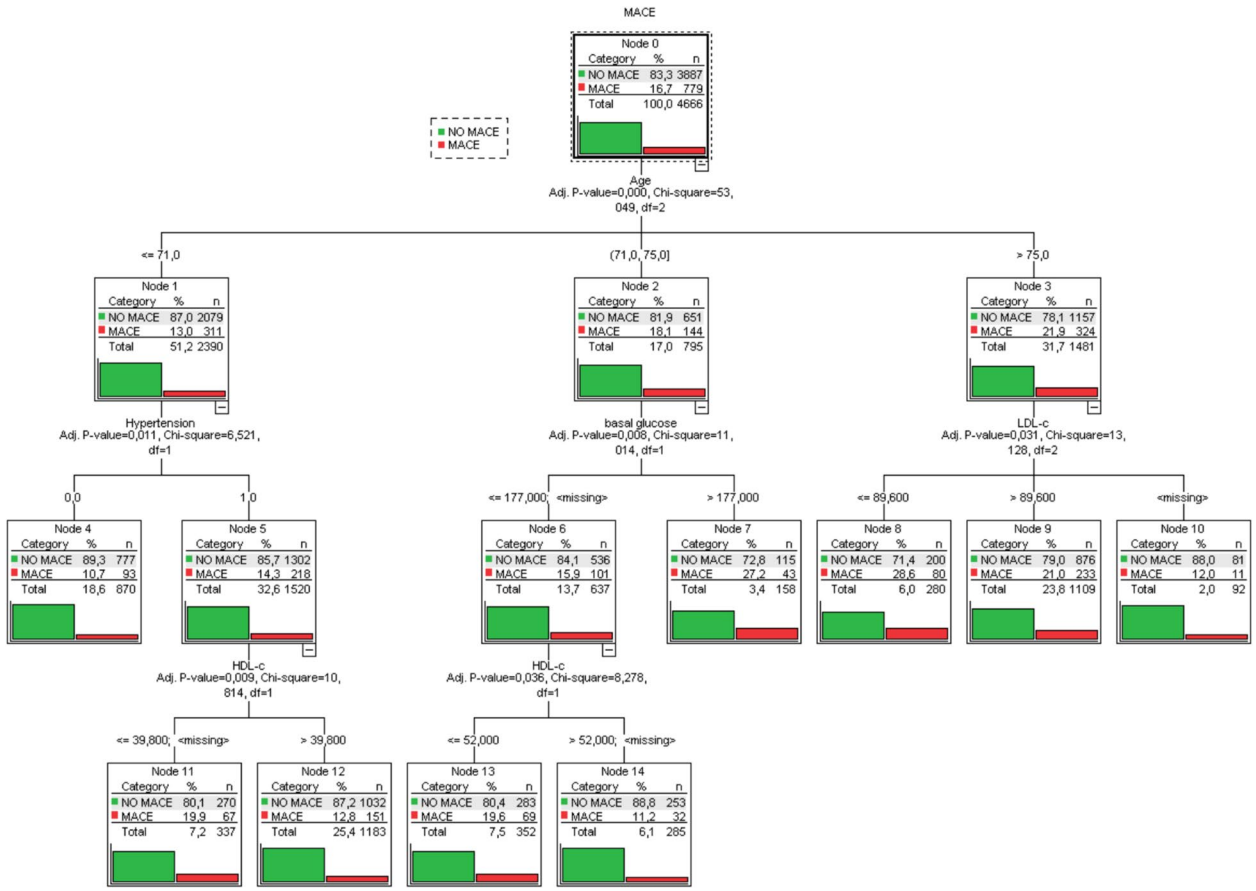

Fig. 2 MACE tree 10-year risk in total T2DM without previous MACE. Baseline values MACE: major adverse cardiovascular events; T2DM: Type 2 Diabetes Mellitus; LDL: low-density lipoprotein; HDL: high-density lipoprotein

have been shown to reduce cardiovascular risk. This is considered a future research direction of our team.

Conclusion

In conclusion, decision tree-based analysis enables the reliable prediction of the risk of developing a new MACE in T2DM population. CHAID tree models can serve as a valuable decision-making tool for clinicians, guiding risk-based interventions considering the interaction of various risk factors rather than relying solely on individual risk factors.

Abbreviations

ADA/EASD	American Diabetes Association and European Association for the Study of Diabetes
AMI	Acute myocardial infarction
CAPAMIS	Community-Acquired Pneumonia, Myocardial Infarction, and Stroke
CV	Cardiovascular
CVD	Cardiovascular Disease
CHAID	Chi-Square Automatic Interaction Detector
DM	Diabetes Mellitus
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
HRs	Hazard ratios
HbA1c	Hemoglobin A1c
HDL-c	High-density lipoprotein-cholesterol
ICD- 9	International Classification of Diseases, 9th Revision, Clinical Modification
LDL-c	Low-density lipoprotein-cholesterol
MACE	Major Adverse Cardiovascular Events
PCHC	Primary Care Health Centers
SD	Standard deviation
SCORE2	Systematic COronary Risk Evaluation 2
SBP	Systolic blood pressure
T2DM	Type 2 diabetes
WHO	World Health Organization
95% CI	95% Confidence intervals

Authors' contributions

DRS, MJF, AVC, CD, OOG, FML, and ES contributed to the conception of the work. DRS and ES contributed to the analysis and interpretation of data for the work. DRS drafted the manuscript. DRS, MJC, AVC, CD, FM and ES critically revised the manuscript. All authors read and approved the final manuscript.

Declarations

This study corresponds to a subanalysis in the framework of the CAPAMIS (Evaluation of the effectiveness of the 23-valent pneumococcal vaccine to prevent pneumonia and acute vascular events in the population over 60 year) project, which was reviewed and endorsed by the ethics committee of IDIAP Jordi Gol in 2009 (file 4R09/019). The project protocol was published in BMC Public Health Journal (https://doi.org/10.1186/1471-2458-10-25). It also received a grant from the of the"Carlos III Health Institute"(file PI09/0043) whose budget has already been exhausted. The project contemplated a subsequent follow-up of the cohort with the updating of monitoring variables and study events. This information was provided to the research team in a pseudonymized way by a member of the institutional Unit of Information and Communication Technologies.

Funding

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All the authors: D Ribas Seguí, M José Forcadell, Angel Vila-Córcoles, Cinta de Diego, Olga Ochoa-Gondar, Francisco Martin Lujan and Eva Satué consent to participate in the manuscript.

Consent for publication

This study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of good clinical practice. Due to the retrospective nature of the study, the Ethics Committee for Clinical Research (CEIC) of the Instituto de Investigación en Atención Primaria (IDIAP) Jordi Gol waived the need to obtain informed consent. This study was conducted within the framework of the CAPAMIS project, (Evaluation of the effectiveness of the pneumococcal 23-valent vaccine to prevent pneumonia and acute vascular events in the population over 60 years) project,which was reviewed and approved by the IDIAP Jordi Gol ethics committee in 2009 (file 4R09/019). The protocol of the project was published in BMC Public Health Journal (https://doi.org/10.1186/1471 - 2458 - 10 - 25). Also received a grant from the"Instituto de Salud Carlos III"(file PI09/0043) whose budget has already been exhausted. The project included a follow-up of the cohort with the update of monitoring variables and study events. This information was provided to the research team in pseudonym by a member of the institutional Information and Communication Technology Unit.

Competing interests

The authors declare no competing interests.

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