

Factors influencing Systemic Coronary Risk Estimation 2 (SCORE2)

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Abstract

Background: This study aimed to identify factors associated with the 10-year risk of fatal and non-fatal cardiovascular disease (CVD) events in apparently healthy individuals aged 40–69 years.

Methods: 148 patients without established CVD were divided into low-risk (70 patients) and high-risk (78 patients) groups based on their CVD risk in SCORE2.

Results: High-risk patients presented with higher left atrial volume index (LAVI) ($p = 0.003$), left ventricular mass index (LVMI) ($p < 0.001$), and ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion (E/E') ($p < 0.001$) but lower oxygen uptake at anaerobic threshold (VO_{2AT}) ($p = 0.02$) and maximal oxygen uptake (VO_{2max}) ($p = 0.008$), compared to their counterparts. High-risk patients also had higher values of high-sensitivity cardiac troponin T (hs-cTnT) ($p < 0.001$) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) ($p < 0.001$), and lower level of glomerular filtration rate (GFR) ($p < 0.001$). In a multiple logistic regression model, $E/E' > 6.75$ cm/s (OR 3.9, 95% CI: 1.5-10.3; $p = 0.004$) and hs-cTnT > 4.8 pg/mL (OR 6.02, 95% CI: 2.3-15.8; $p < 0.001$) were independently associated with high and very high CVD risk. SCORE2 (%) correlated positively with metabolic age (R Spearman = 0.79; $p < 0.001$), hs-cTnT ($R = 0.6$; $p < 0.001$), and NT-proBNP ($R = 0.5$; $p < 0.001$) and negatively with GFR ($R = -0.5$; $p < 0.001$) and VO_{2max} (mL/min/kg) ($R = -0.3$; $p < 0.001$).

Conclusions: Elevated E/E' and higher hs-cTnT level independently predict high and very high risk in SCORE2. The increasing 10-year cardiovascular disease risk correlates with higher metabolic age, higher levels of NT-proBNP and hs-cTnT, and lower level of GFR.

Keywords: SCORE2, CVD risk, coronary artery disease, atherosclerosis, spiroergometry

Introduction

Cardiovascular disease (CVD) continues to be one of the leading causes of morbidity and mortality worldwide, making accurate and early risk assessment crucial for effective prevention and manage-

ment [1, 2]. In this pursuit, medical researchers and experts have developed a groundbreaking tool known as Systematic Coronary Risk Estimation 2 (SCORE2) [3]. This innovative approach to cardiovascular risk assessment is poised to revolutionize the way we evaluate an individual's risk

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of developing heart disease and guide personalized preventive strategies. SCORE2 builds upon the success of its predecessor, the original SCORE system, which provided a standardized method for estimating an individual's risk of experiencing a fatal cardiovascular event over a 10-year period [4]. However, with advances in medical knowledge and an increased understanding of the complex interplay of risk factors, the need for a more comprehensive and accurate risk assessment tool became evident. The primary objective of SCORE2 is to refine the estimation of cardiovascular risk by incorporating additional risk factors, such as family history, high-sensitivity levels of C-reactive protein (hs-CRP), and measures of subclinical atherosclerosis. By considering a broader range of factors, including both traditional risk factors (such as age, gender, blood pressure, and cholesterol levels) and emerging markers of risk, SCORE2 provides a more nuanced and personalized assessment of an individual's susceptibility to developing coronary artery disease (CAD) [5, 6]. What sets SCORE2 apart is its integration of advanced statistical models and large-scale, population-based data from diverse cohorts, allowing for more precise risk prediction. This sophisticated tool takes into account the multifaceted nature of cardiovascular risk and provides clinicians with a more accurate and holistic picture of a patient's risk profile [7, 8]. In this article, we explore the factors influencing SCORE2. Through a comprehensive understanding of SCORE2, healthcare professionals and researchers can harness its power to identify at-risk individuals earlier, tailor preventive strategies more effectively, and ultimately reduce the burden of CVD on a global scale.

Methods

A total of 148 consecutive patients from Lodz Voivodeship, Poland without established atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, chronic kidney disease (CKD), or familial hypercholesterolemia were enrolled in this study. This group was divided into a low-risk group with low-to-moderate CVD risk in SCORE2 (70 patients) and a high-risk group with high and very high CVD risk (78 patients). The subjects were hospitalized in the Department of Cardiology and Congenital Heart Diseases of Adults between December 2020 and December 2021 for diagnosis of cardiac complications after COVID-19. All subjects gave written informed consent to participate in the study. After informed consent was signed,

the clinical data of the patients in the study were collected. The patients underwent a physical examination based on the standard internal medicine protocol. We paid particular attention to the inclusion and exclusion criteria during enrolment in the trial. The study complies with the Declaration of Helsinki and was approved by the Bioethics Commission of the Polish Mother's Memorial Hospital Research Institute (PMMHRI-BCO.75/2020). Exclusion criteria: established atherosclerotic cardiovascular disease (past myocardial infarction, ischemic stroke, critical limb ischemia), uncontrolled hypertension; diagnosis of heart failure (HF) or typical symptomatic HF; left ventricular ejection fraction (LVEF) < 50%; documented: hyperandrogenism, hyperestrogenism, insulin resistance, diabetes mellitus, premature ovarian failure, polycystic ovary syndrome; diagnosis of cardiomyopathy (hypertrophic, dilated, restrictive, peripartum, arrhythmogenic); lysosomal storage disorders; transient ischemic attack, intracerebral hemorrhage in medical history; severe hyper- and hypothyroidism; pregnancy and lactation; CKD (stages IV and V according to the National Kidney Foundation) and dialysis treatment; documented neoplastic process; the patient's inability to cooperate and/or provide informed consent to participate in the research; active autoimmune disease; treatment with immunosuppressants, cytostatic drugs, glucocorticosteroids, or antiretroviral drugs; a history of bone marrow transplant or other organ transplant treatment with blood products in the last 6 months; active systemic infection; hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) carrier or positive for hepatitis B surface antigen (HBsAg) or antibodies to HCV; surgery or serious injury within the last month; and patients who did not give their informed consent to participate in the study.

Laboratory tests were performed in the hospital laboratory, after a minimum 12-hour period since the last meal. Routine laboratory tests included high-sensitivity cardiac troponin T (hs-cTnT), serum concentrations of pro-B-type N-terminal natriuretic peptide (NT-proBNP), hematology, and D-dimer. Furthermore, the analyses of liver function parameters [alanine aminotransferase (ALT) and aspartate transaminase (ASP)]; renal function parameters [creatinine, glomerular filtration rate (GFR) estimated by Modification of Diet in Renal Disease (MDRD)], electrolytes, inflammatory cytokine [C-reactive protein (CRP)], glucose level, lipoprotein profile: total cholesterol (TC),

low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) were performed.

Comprehensive echocardiography was performed using commercially available ultrasound systems (Vivid E95 – GE Healthcare, Chicago, IL, USA) in accordance with current guidelines [9]. Left ventricular dimensions in the end-diastole: left ventricular internal diameter (LVID d), inter-ventricular septum (IVS d) and left ventricular posterior wall (LVPW d) were calculated. Left ventricular volume (LV) and ejection fraction (EF) were measured by the quantitative 2-dimensional biplane modified Simpson method from a 4- and 2-chamber view. The 2-dimensional maximal left atrial volume (LAV) was determined based on the apical 2- and 4-chamber views at end-systole without foreshortening, using a biplane modified Simpson's method excluding the LA appendage and pulmonary vein confluences [10]. Each LAV was indexed by body surface area (LAVi). LV mass index (LVMI) was calculated by dividing LV mass (in grams) by a body size variable such as body surface area. From the pulse Doppler echocardiography of transmitral velocities, the peak early (E) and peak late (A) mitral velocities, the ratio between the peak E and A velocity (E/A), the ratio of early transmitral peak velocity to early diastolic peak annular velocity (E/E'), deceleration time (Dec), acceleration time (A_{ts}), and isovolumic relaxation time were measured. We also assessed global peak systolic strain (GLPS) based on speckle tracking echocardiography [11]. Furthermore, the ascending aorta (AA), aortic bulb (AB), main pulmonary artery (MPA), and inferior vena cava (IVC) diameters were measured. The right ventricular (RV) functional measurements included tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler echocardiography (TDE) [12]. Additionally, the right atrial volume (RA) and distal right ventricular outflow tract (RVOT d) were calculated.

Cardiopulmonary exercise testing (CPET) was performed on an electromagnetically braked upright cycle ergometer Bike M (CORTEX Biophysik GmbH, Leipzig, Germany) with a metabolic gas analyzer METALYZER 3B (CORTEX Biophysik GmbH, Leipzig, Germany) using the MetaSoft Studio application software of CORTEX Systems [13]. Basic spirometry was performed prior to exercise. Forced expiratory volume in one second (FEV₁), forced vital capacity, and FEV₁/FVC ratio (Tiffeneau index) were measured [14]. During exercise, blood pressure (BP), continuous heart rate (HR), rhythm, electrocardiogram (ECG) changes, and

oxygen saturation were monitored. Oxygen uptake (VO₂) is assessed from the difference between the volume of O₂ in the inhaled and exhaled air during exercise per unit of time and in the steady state is equal to metabolic O₂ consumption. VO₂ peak represents the highest attainable VO₂ for a subject [15]. Carbon dioxide output (VCO₂) is calculated from the difference between the volume of CO₂ in the inhaled and exhaled air during exercise per unit of time. Respiratory exchange ratio (RER) corresponds to the gas exchange ratio. We also measured the anaerobic threshold (AT) and the minute ventilation/carbon dioxide production slope (VE/VCO₂ slope) [16].

Segmental Body Composition Analyzer (Tanita Pro, Tokyo, Japan) is a tool for non-invasive body mass analysis. This device provides estimated values for each measured value using Bioelectrical Impedance Analysis (BIA method). The Tanita Body Composition Analyzer measures body composition using a constant current source with a high-frequency current (50 kHz, 90 μA). Eight electrodes are positioned so that the electric current is supplied from the electrodes to the tips of the toes of both feet, and the voltage is measured to the heel of both feet. The current flows into the upper limbs or lower limbs, depending on the body parts to be measured [17]. Total and regional fat mass (FM), fat-free mass (FFM), total body water (TBW), intracellular water (ICW), extracellular water (ECW), and ECW/TBW % ratio were measured. Additionally, we measured metabolic age and basal metabolic rate (BMR) [18, 19].

The STATISTICA 13.1 software package (StatSoft, Poland) was used for analysis. The concordance of normal distribution of all variables was calculated with the Shapiro-Wilk test. To compare the 2 groups, Student's t-test for continuous variables with normal distribution and the Mann-Whitney U test for non-normally distributed variables were used. The correlations between the analyzed parameters were determined by Spearman's test. In the analyses, a p-value < 0.05 was considered statistically significant. The parameters for which the univariate analysis indicated statistically significant results were included in the multivariate analysis. Because these parameters presented continuous variables, they were transformed into dichotomous variables based on the median calculated for the entire studied population. Subsequently, a stepwise logistic regression analysis was conducted. The statistically significant results (p < 0.05) were presented as odds ratios (OR) with 95% confidence intervals (CI).

Results

The subjects were divided into a low-risk group with low-to-moderate CVD risk in SCORE2 (70 patients) and a high-risk group with high and very high CVD risk (78 patients). The patients with high-risk presented with significantly higher age, BMI, BSA, and SBP ($p < 0.001$; $p < 0.001$; $p = 0.003$; $p < 0.001$, respectively) compared to low-risk subjects. Patients from the high-risk group significantly more frequently had arterial hypertension ($p < 0.001$), hypercholesterolemia ($p < 0.001$), arrhythmia ($p < 0.001$), and obesity ($p < 0.001$), and they more often smoked ($p < 0.001$) and drank too much alcohol ($p = 0.02$) compared to the low-risk group. Data are shown in Table 1.

The levels of hs-cTnT, NT-proBNP, creatinine, urea, glucose, ALT, ASP, D-dimer, and triglycerides were significantly higher ($p < 0.001$; $p < 0.001$; $p = 0.004$; $p < 0.001$; $p < 0.001$; $p = 0.02$; $p = 0.02$; $p = 0.001$; $p = 0.003$, respectively) in the high-risk group in comparison to low-risk group. High-risk patients also presented with decreased level of thrombocytes (PLT) and HDL ($p = 0.03$; $p = 0.04$, respectively). The results are shown in Table 2.

High-risk subjects presented with significantly greater LVID d, IVS d, LVPW d, LA, LAV, LAVi, LVMI, A, and E/E' ($p = 0.047$; $p < 0.001$; $p < 0.001$; $p < 0.001$; $p = 0.003$; $p < 0.001$; $p < 0.001$; $p = 0.008$; $p < 0.001$, respectively) compared to the low-risk group. The high-risk patients also had also larger AB, AA, and MPA and longer deceleration time than the low-risk subjects ($p < 0.001$; $p < 0.001$; $p < 0.001$; $p = 0.02$, respectively). RVOT d and E/A were lower in the high-risk group ($p < 0.001$; $p < 0.001$, respectively). The data are presented in Table 3.

The high-risk patients presented with significantly lower level of effort, HR max, FVC, RER, VO_{2max} , and VO_{2AT} ($p = 0.006$; $p < 0.001$; $p = 0.01$; $p = 0.04$; $p = 0.008$; $p = 0.02$, respectively) compared to the low-risk group. The results are shown in Table 4.

Fat content (in % and kg), FFM, TBW (in kg), ECW, $ECW/TBW \times 100\%$, and metabolic age were significantly higher in the high-risk group ($p < 0.001$; $p < 0.001$; $p = 0.008$; $p = 0.03$; $p < 0.001$; $p < 0.001$; $p < 0.001$, respectively) than in the low-risk group. Table 5 contains the results.

Parameters with a p value < 0.05 in the univariate analysis were entered into the multivariate analysis using logistic regression analysis. In a multiple logistic regression model, the following

variables were independently associated with high and very high CVD risk: E/E' > 6.75 cm/s (OR 3.9 95% CI: 1.5–10.3; $p = 0.004$) and hs-cTnT > 4.8 pg/mL (OR 6.02, 95% CI: 2.3–15.8; $p < 0.001$) (Tab. 6).

SCORE2 (%) correlated positively with metabolic age (R Spearman = 0.79; $p < 0.001$), hs-cTnT (R = 0.6; $p < 0.001$), and NT-proBNP (R = 0.5; $p < 0.001$) and negatively with GFR (R = -0.5; $p < 0.001$) and VO_{2max} (mL/min/kg) (R = -0.3; $p < 0.001$) (Fig. 1).

Discussion

SCORE2 is a tool that incorporates various factors to provide a comprehensive assessment of an individual's risk of developing CVD. Understanding the factors that influence SCORE2 is crucial for healthcare professionals to accurately estimate risk and guide preventive strategies.

In our findings, patients from the high-risk group presented with significantly more frequent obesity. This group also had significantly higher BMI, fat content, and TBW content. The relationship between obesity and cardiovascular risk is complex. Obesity is a chronic medical condition characterized by excessive accumulation of body fat, and it is often accompanied by other risk factors, such as sedentary lifestyle, poor dietary choices, and insulin resistance, which further contribute to the development of cardiovascular disease. Additionally, obesity can have detrimental effects on the structure and function of the cardiovascular system, leading to conditions like hypertension, atherosclerosis, and HF [20]. BMI is a measure of body fat based on height and weight and serves as a useful indicator of obesity [21]. The association between obesity and higher risk of CAD was demonstrated in many epidemiological studies [22–25]. The association of obesity with CAD and its independence from metabolic cardiovascular risk factors linked to excess weight has generated conflicting results. Some large prospective analyses suggest that hypertension, dyslipidemia, diabetes, and other comorbidities largely mediate the link between obesity and CAD [26]. On the other hand, other prospective studies indicate a significant residual CAD risk in obesity even after considering these risk factors [27]. Likewise, certain studies show that obesity without metabolic syndrome is not associated with incident myocardial infarction [27], unlike other studies [28]. A meta-analysis of 21 studies involving 1.8 million individuals indicates that approximately half of the connections between overweight/obesity and CAD can be explained by blood pressure, cholesterol, and

Table 1. Evaluation of basic characteristics among the investigated groups

Parameter	Low-to-moderate CVD risk in SCORE2 n = 70	High and very high CVD risk in SCORE2 n = 78	P-value
Basic characteristics			
Age	(32.00–48.00), 43.00*	(58.00–70.00), 64.00*	< 0.001
BMI, kg/m ²	(22.28–27.70), 24.76*	(23.85–32.53), 29.65*	< 0.001
BSA, m ²	(1.69–1.95), 1.83*	(1.79–2.08), 1.93*	0.003
SBP, mmHg	(121.00–135.00), 129.00*	(128.00–149.00), 136.00*	< 0.001
DBP, mmHg	(74.00–87.00), 80.00*	(68.00–78.00), 72.00*	0.14
HR	(70.00–84.00), 73.00*	(68.00–78.00), 72.00*	0.19
Arrhythmia (%)	2	23	< 0.001
Arterial hypertension (%)	25	81	< 0.001
Hypercholesterolemia (%)	25	77	< 0.001
Use of β -blockers (%)	44	74	0.001
Use of ACEIs/ARBs (%)	20	77	< 0.001
Use of CCBs (%)	12	32	0.03
Use of diuretics (%)	13	53	< 0.001
Use of statins (%)	14	77	< 0.001
Obesity (%)	10	45	< 0.001
Abuse alcohol (%)	0	8	< 0.02
Smoking (%)	0	23	< 0.001

*median; values with non-normal distribution are expressed as median (range) values. Values with normal distribution are expressed as mean \pm standard deviation (SD). ACEIs — angiotensin-converting enzyme inhibitors; ARBs — angiotensin II receptor antagonists; CCBs, calcium channel blockers; BMI — body mass index; BSA — body surface area; DBP — diastolic blood pressure; HR — heart rate; SBP — systolic blood pressure

Table 2. Evaluation of laboratory tests among the investigated groups

Parameter	Low-to-moderate CVD risk in SCORE2 n = 70	High and very high CVD risk in SCORE2 n = 78	P-value
Laboratory tests			
hs-cTnT, pg/mL	(3.00–4.70), 3.20*	(4.70–10.50), 6.85*	< 0.001
NT-proBNP, pg/mL	(31.00–96.00), 55.00*	(51.50–334.00), 115.00*	< 0.001
RBC, 10 ⁶ /uL	(4.23–5.03), 4.60*	(4.15–4.75), 4.44*	0.08
Hemoglobin, g/dL	(12.60–14.60), 13.50*	(12.80–14.50), 13.70*	(0.98)
PLT, 10 ³ /uL	230.96 (\pm 56.77)	210.47 (\pm 50.67)	0.03
Creatinine, mg/dL	(0.65–0.85), 0.72*	(0.72–0.95), 0.82*	0.004
GFR, ml/min/1.73 m ²	(89.90–107.30), 98.00*	(72.30–94.50), 82.10*	< 0.001
Urea, mg/dL	29.19 (\pm 7.89)	38.66 (\pm 11.15)	< 0.001
Glucose, mg/dL	(84.00–93.00), 89.00*	(89.00–100.00), 92.00*	< 0.001
ALT, U/L	(15.00–27.00), 20.00*	(20.00–35.00), 23.00*	0.02
ASP, U/L	(22.00–29.00), 26.00*	(25.00–35.00), 27.00*	0.02
CRP, mg/dL	(0.50–0.50), 0.50*	(0.50–0.50), 0.50*	0.42
D-dimer, ng/mL	(149.50–316.50), 261.00*	(235.00–511.00), 334.00*	0.001
TC, mg/dL	174.86 (\pm 30.80)	169.43 (\pm 50.32)	0.44
LDL, mg/dL	100.22 (\pm 26.67)	90.74 (\pm 37.59)	0.08
HDL, mg/dL	(44.00–59.00), 53.00*	(39.00–57.00), 44.00*	0.04
TG, mg/dL	(78.00–134.00), 98.00*	(89.00–175.00), 116.00*	0.003
Na, mmol/L	(138.00–140.00), 139.00*	(138.00–141.00), 139.00*	0.06
K, mmol/L	(4.20–4.50), 4.40*	(4.10–4.60), 4.30*	0.49

*median; values with non-normal distribution are expressed as median (range) values. Values with normal distribution are expressed as mean \pm standard deviation (SD). ALT — alanine aminotransferase; AST — aspartate aminotransferase; CRP — c-reactive protein; GFR — glomerular filtration rate; HDL — high-density lipoprotein; hs-cTnT — high-sensitivity cardiac troponin T; K — serum potassium; LDL — low-density lipoprotein; Na — serum sodium; NT-proBNP — N-terminal prohormone of brain natriuretic peptide; PLT — thrombocytes; RBC — red blood cells; TC — total cholesterol; TG — triglycerides. Conversion factors to SI units are as follows: for creatinine, 88.4020; urea, 0.1665; glucose, 0.05551; cholesterol, 0.02586; and triglycerides, 0.0114

Table 3. Evaluation of selected echocardiographic parameters among the investigated groups

Parameter	Low-to-moderate CVD risk in SCORE2 n = 70	High and very high CVD risk in SCORE2 n = 78	P-value
Echocardiography			
LVID d, mm	(43.00–50.50), 47.50*	(45.00–54.50), 49.00*	0.047
IVS d, mm	(8.00–9.00), 9.00*	(9.00–11.00), 10.00*	< 0.001
LVPW d, mm	(8.00–9.00), 8.00*	(9.00–11.00), 10.00*	< 0.001
LA, mm	(31.50–37.00), 34.00*	(35.50–44.00), 40.00*	< 0.001
LAV, mL	(41.50–70.00), 49.00*	(53.50–92.50), 67.50*	< 0.001
LAVi, mL/m ²	(23.00–36.50), 27.00*	(27.79–43.50), 28.65*	0.003
RA, cm ²	(12.00–17.00), 14.50*	(15.00–20.90), 17.45*	< 0.001
RVOT d, mm	29.42 (± 4.54)	32.72 (± 3.95)	< 0.001
AB, mm	(28.00–34.00), 31.00*	(31.00–37.00), 34.00*	< 0.001
AA, mm	(27.50–32.00), 29.00*	(31.00–36.00), 34.00*	< 0.001
MPA, mm	(18.00–19.00), 19.00*	(19.00–22.00), 20.00*	< 0.001
IVC, mm	(3.00–10.00), 7.00*	(5.00–9.00), 6.00*	0.85
LVMI, g/m ²	(61.00–82.00), 73.00*	(74.00–109.00), 86.50*	< 0.001
LVEF, %	(59.50–67.00), 62.00*	(55.00–65.00), 62.00*	0.11
EDV, cm ³	(75.00–103.00), 89.00*	(68.00–105.00), 90.00*	(0.98)
ESV, cm ³	(27.00–40.00), 33.00*	(24.00–44.00), 34.00*	0.90
TAPSE, mm	22.86 (± 3.21)	23.44 (± 4.36)	0.38
TDE S', cm/s	(12.00–15.00), 13.00*	(12.00–16.00), 14.00*	0.04
GLPS, %	19.86 (± 2.21)	19.63 (± 1.59)	0.56
E, cm/s	(64.00–90.00), 77.00*	(62.00–85.00), 70.00*	0.09
A, cm/s	(53.00–74.00), 67.00*	(62.00–86.00), 72.00*	0.008
E/A	(0.98–1.67), 1.25*	(0.77–1.12), 0.95*	< 0.001
E/E'	(5.50–7.00), 6.10*	(6.26–9.30), 7.55*	< 0.0001
Dec, ms	(159.50–225.00), 190.50*	(175.50–260.40), 212.00*	0.02
Ats, ms	(118.00–153.50), 135.00*	(110.00–141.00), 130.00*	0.10

*median; values with non-normal distribution are expressed as median (range) values. Values with normal distribution are expressed as mean ± standard deviation (SD). A — late diastolic filling velocity; AA — ascending aorta; AB — aortic bulb; Ats — acceleration time; Dec — deceleration time; E — early diastolic filling velocity; E/A — ratio of early to late diastolic transmitral flow velocity; E/E' — ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; EDV — end-diastolic volume; ESV, end-systolic volume; GLPS — global peak systolic strain; IVC — inferior vena cava; IVS d — interventricular septum end-diastole; LA — left atrial diameter; LAV — left atrial volume; LAVi — left atrial volume index; LVEF — left ventricular ejection fraction; LVID d — left ventricular internal diameter end-diastole; LVMI — left ventricular mass index; LVPW d — left ventricular posterior wall end-diastole; MPA — main pulmonary artery; RA — right atrial area; RVOT d — distal right ventricular outflow tract; TAPSE — tricuspid annular plane systolic excursion; TDE S' — tissue Doppler echocardiography

glucose levels [29]. However, this estimation may be lower than the actual value due to the remaining confounding factors that were evaluated at a single time point or were not directly measured in some studies.

Our next findings indicate that higher LAVI, LVMI, and E/E' were significantly increased in the high-risk group in comparison with the low-risk group. Furthermore, E/E' was independently associated with high and very high CVD risk. LAVI is a measurement that assesses the size of the left atrium relative to body surface area and can be indicative of various cardiovascular conditions, e.g.,

hypertension, atrial fibrillation, valvular heart disease, and HF [30]. Some studies demonstrated the relationship between higher LAVI and cardiovascular events [31, 32]. The study of Bombelli et al. showed that LVMI is an independent predictor of cardiovascular events [33]. E/E' is a ratio that represents the ratio of the early diastolic transmitral flow velocity (E) to the early diastolic tissue Doppler velocity of the mitral annulus (E'). It provides valuable information about left ventricular filling pressure and can help in evaluating diastolic dysfunction [34]. The prognostic significance of the E/E' ratio in patients with different cardiac

Table 4. Evaluation of spirometry among the investigated groups

Parameter	low-to-moderate CVD risk in SCORE2 n = 70	high and very high CVD risk in SCORE2 n = 78	P-value
Spirometry			
Exercise time, s	(428.50–743.00), 559.00*	(378.00–641.00), 507.50*	0.06
Level of effort, watts	(123.00–171.00), 128.50*	(86.00–150.00), 110.50*	0.006
HR max	154.35 (± 23.81)	129.56 (± 24.71)	< 0.001
Peripheral SBP max, mmHg	(140.00–180.00), 160.00*	(140.00–200.00), 175.00*	0.09
Peripheral DBP max, mmHg	(70.00–85.00), 80.00*	(75.00–90.00), 80.00*	0.31
FEV ₁ , L	(2.64–3.67), 3.15*	(2.45–3.48), 2.91*	0.06
FVC, L	4.09 (± 1.03)	3.61 (± 0.88)	0.01
FVC, %	106.38 (± 15.99)	106.81 (± 18.14)	0.89
FEV ₁ /FVC	(78.00–87.50), 83.00*	(75.00–86.00), 81.00*	0.13
FEV ₁ /FVC, %	(96.00–110.00), 105.00*	(94.50–108.50), 103.00*	0.29
FEF 25-75, L/s	3.27 (± 1.05)	2.57 (± 1.24)	0.002
RER	(1.04–1.12), 1.09*	(0.99–1.11), 1.07*	0.04
VO ₂ max, mL/min/kg	(19.00–27.50), 22.00*	(16.00–25.00), 20.00*	0.008
VO ₂ AT, mL/min/kg	(12.00–20.00), 15.00*	(10.00–17.00), 13.00*	0.02
Peak VO ₂ max, L	(1.37–2.07), 1.69*	(1.21–1.98), 1.54*	0.18
VE/VCO ₂ slope	(25.00–32.60), 29.50*	(26.70–33.90), 29.80*	0.43

*median; values with non-normal distribution are expressed as median (range) values. Values with normal distribution are expressed as mean ± standard deviation (SD). DBP — diastolic blood pressure; FEF 25–75% — forced expiratory flow over the middle one half of the forced vital capacity; FEV₁ — forced expiratory volume in one second; FEV₁/FVC — ratio of forced expiratory volume in one second to forced vital capacity; FVC — forced vital capacity; HR — heart rate; peak VO₂ — highest respiratory oxygen uptake (VO₂) achieved by the subject during the maximal exercise; RER — respiratory exchange ratio; SBP — systolic blood pressure; VE/VCO₂ slope — the minute ventilation/carbon dioxide production slope; VO₂AT — oxygen uptake at anaerobic threshold per kilogram; VO₂max — the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise

Table 5. Evaluation of body mass analysis among the investigated groups

Parameter	low-to-moderate CVD risk in SCORE2 n = 70	high and very high CVD risk in SCORE2 n = 78	P-value
Body mass analysis			
Fat, %	27.67 (± 6.95)	32.45 (± 5.66)	< 0.001
Fat, kg	(15.30–26.60), 19.05*	(23.30–31.90), 27.45*	< 0.001
FFM, kg	(45.90–58.50), 50.40*	(50.00–64.80), 57.20*	0.008
TBW, kg	(33.40–43.40), 38.10*	(36.10–45.80), 41.10*	0.03
TBW, %	52.61 (± 6.12)	48.87 (± 4.36)	< 0.001
ECW, kg	(14.00–18.90), 16.45*	(16.30–20.20), 18.30*	< 0.001
ICW, kg	(19.01–25.50), 21.65*	(20.30–26.20), 22.40*	0.29
ECW/TBW × 100%	42.34 (± 3.20)	44.64 (± 2.18)	< 0.001
Metabolic age	39.66 (± 11.80)	63.40 (± 8.31)	< 0.001
BMR, kcal	(1317.00–1668.00), 1473.00*	(1269.00–1829.00), 1517.50*	0.36

*median; values with non-normal distribution are expressed as median (range) values. Values with normal distribution are expressed as mean ± standard deviation (SD). BMR — basal metabolic rate; ECW — extracellular water; ECW/TBW% — ratio of extracellular water to total body water; FFM — fat-free body mass; ICW — intracellular water TBW, total body water

conditions has been investigated in several studies [35, 36].

In our study, lower VO₂AT and VO₂max were observed in high-risk patients compared to counterparts. VO₂max is a measurement that represents

the maximum amount of oxygen an individual can utilize during intense exercise. It is considered one of the most valid and reliable indicators of cardio-respiratory fitness and aerobic endurance [37]. VO₂max is a valuable marker for assessing overall

Table 6. Multivariate analysis — stepwise logistic regression

Variable	OR	95% CI for OR		P-value
		Lower limit	Upper limit	
E/E'	3.90	1.50	10.30	0.004
hs-cTnT	6.02	2.30	15.80	< 0.001

The following parameters were included in the multivariate analysis: $VO_{2max} < 22$ mL/min/kg, $VO_{2AT} < 14$ mL/min/kg, $E/E' > 6.75$, $LVMI > 79$ g/m², $Fat > 23.7$ kg, $ECW/TBW \times 100\% > 39.9$, $NT\text{-}proBNP > 78$ pg/mL, $hsTnT > 4.8$ pg/mL; CI — confidence interval; E/E' — ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; ECW/TBW $\times 100\%$ — ratio of extracellular water to total body water; hs-cTnT — high-sensitivity cardiac troponin T; LVMI — left ventricular mass index; NT-proBNP — N-terminal prohormone of brain natriuretic peptide; OR — odds ratio; VO_{2AT} — oxygen uptake at anaerobic threshold per kilogram; VO_{2max} — the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise

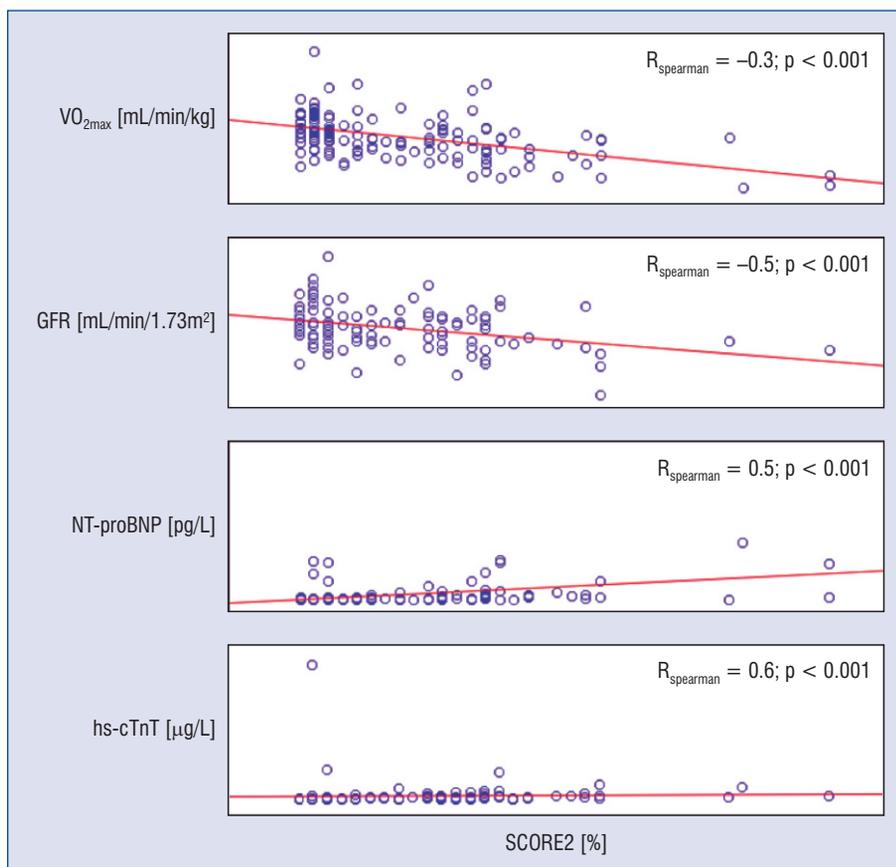


Figure 1. Significant correlations with SCORE2. GFR — glomerular filtration rate; hs-cTnT — high-sensitivity cardiac troponin T; NT-proBNP — N-terminal prohormone of brain natriuretic peptide; VO_{2max} — the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise

cardiovascular health and predicting the risk of cardiovascular disease and all-cause mortality. Low VO_{2max} levels have been associated with an increased risk of chronic conditions such as heart disease, diabetes, and obesity [38–40].

Our next findings revealed that high-risk patients presented with higher values of hs-cTnT and NT-proBNP, and lower level of GFR. In multiple logistic regression, hs-cTnT was independently associated with high and very high CVD risk. Additionally, SCORE2 correlated positively

with hs-cTnT and NT-proBNP, and negatively with GFR. hs-cTnT plays a crucial role in the diagnosis and risk stratification of patients with suspected or confirmed CAD, which encompasses a range of conditions related to the narrowing or blockage of coronary arteries. hs-cTnT is a highly sensitive biomarker that detects very low levels of cardiac troponin T, a protein released into the bloodstream following myocardial cell injury or damage [41]. Numerous studies have verified the diagnostic importance of increased troponin levels as a risk

factor for CAD [42–45]. NT-proBNP is widely used as a diagnostic marker in suspected cases of HF. Elevated levels of NT-proBNP are indicative of cardiac dysfunction and can help differentiate between cardiac and non-cardiac causes of dyspnea and other symptoms. Although NT-proBNP is not specific to CAD, it serves as an important indicator of underlying cardiac pathology. In the study of Niccoli, the authors revealed that NT-proBNP levels were higher in CAD patients experiencing major adverse cardiac events [46]. In another study, NT-proBNP was an independent predictor for patients with CAD [47]. One observational study showed that both NT-proBNP and hs-cTnT are predictors of incident CAD, independent of established risk factors and ethnicity, in a multiethnic population without known CVD [48]. We observed that the high-risk group had lower LDL cholesterol levels compared to the low-risk group, although this difference was not statistically significant. This finding underscores the effectiveness of statins in reducing LDL cholesterol, as the high-risk group used statins significantly more frequently than the low-risk group ($p < 0.001$). The lower LDL levels in the high-risk group, despite their elevated overall risk, highlight the importance of aggressive lipid-lowering therapy in reducing CVD risk. Low LDL cholesterol is a well-established protective factor against cardiovascular events, further supporting the need for intensive lipid management in high-risk individuals [49].

Chronic kidney disease (CKD) is a well-established risk factor for the development and progression of CAD. Reduced GFR is a hallmark of CKD and indicates impaired kidney function [50]. CKD is associated with a higher risk of cardiovascular complications, including CAD, due to various mechanisms such as inflammation, oxidative stress, endothelial dysfunction, and dyslipidemia [51].

Our study contributes to a better understanding of the factors influencing systemic coronary risk estimation using SCORE2 and provides valuable insights for risk stratification and management in the studied population. However, this study has some limitations, including the relatively small sample size of patients ($n = 148$). The study did not account for certain confounding variables, such as socioeconomic status, or lifestyle factors (e.g., dietary habits, physical activity), which may influence CVD risk. It is important to consider these limitations with caution. Further research with larger sample sizes, diverse populations, longitudinal design, and comprehensive assessments would be valuable in addressing these limitations and

enhancing our understanding of CVD risk estimation. These variables also need to be validated in the context of better risk stratification with c-statistic analysis in patients with long follow-up and data on CVD events and mortality.

Conclusions

In conclusion, higher left ventricular filling pressure assessed by E/E' and higher hs-cTnT level are independent predictors of high and very high-risk in SCORE2. The increasing 10-year cardiovascular disease risk correlates with higher metabolic age, higher levels of NT-proBNP and hs-cTnT, and lower level of GFR. These conclusions highlight the importance of assessing multiple factors in estimating CVD risk. Identifying these predictors can assist healthcare professionals in implementing appropriate preventive strategies and interventions to mitigate the risk of fatal and non-fatal CVD events in apparently healthy individuals with underlying risk factors. Further research and validation studies are warranted to confirm and expand upon these findings.

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