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Comparing heart risk scores to identify the most important risk factors for cardiovascular diseases

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Abstract. – OBJECTIVE: Cardiovascular disease (CVD) is the most common non-communicable disease and the leading cause of death worldwide. To reduce the global burden of CVD and related morbidity and mortality, early prediction of CVD risk is essential. Various tools are available to access the risk of cardiovascular disorders. In the present study, we evaluated four risk score calculators associated to CVD for superiority and most reliable CVD prognosis parameters.

PATIENTS AND METHODS: In the present prospective study, we investigated the probability of CVD in 150 individuals, including both men and women, using four different cardiovascular risk assessment estimators (Framingham Risk Score [FRS] Calculator, Q-RISK calculator, Reynolds score calculator, and atherosclerotic cardiovascular disease (ASCVD) risk calculator) and evaluated how closely they were related to 16 selected parameters. The four risk estimators shared several common parameters, such as age, smoking status, and blood pressure; however, each of them also used some unique parameters. We used statistical analysis to reduce the number of parameters necessary to predict CVD.

RESULTS: Statistical analysis revealed a significant correlation between the main factors responsible for CVD risk. The analysis revealed that out of the four risk calculators tested, the FRS calculator was superior to the others because it showed more significant corroboration with statistical tools and could better predict the most important prognostic factors in CVD.

CONCLUSIONS: In all four risk estimators, the parameters that affected risk most significantly and conferred the most reliable CVD prognosis were age, weight, total cholesterol, and hemoglobin levels. With that FRS calculator was superior to the others.

Key Words:
Cardiovascular disease, Coronary heart disease, Framingham heart risk calculator, Reynolds score calculator, Q-RISK heart risk calculator, ASCVD risk estimator.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. The global population with CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990 to 18.6 million in 2019[1]. CVD progresses via biological processes in the arteries and heart that eventuate in myocardial infarction (MI), stroke, heart failure, and other vascular morbid events[2]. Anxiety and associated arterial hypertension are significant risk factors for almost all cardiovascular diseases[3,4]. Because CVD has multifaceted causes, clinicians should consider all relevant risk factors when estimating a person's risk of acquiring the condition[5]. In addition to hypertension and anxiety, many other diseases are associated with higher cardiovascular mortality, such as diabetes. According to Figueroa Triana et al[6], 60% of CVD mortality is due to diabetes alone. Moreover, patients with CVD are at exceptionally high risk of mortality from COVID-19 because they are frail and carry a risk of myocardial involvement. Even the drugs used to treat COVID-19 can affect the heart and lead to CVD[6].

Early diagnosis of CVD might reduce mortality and increase the life span of patients. CVD risk is assessed using risk calculators and pre-

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diction charts to determine the incidence and severity of various risk factors. When assessing and rehabilitating CVD, clinicians use these cardiovascular disease prediction models[7]. Multiple, well-regarded, online scoring estimators are available to predict the absolute risk of future cardiovascular events using major risk factors. Because a large number of online calculators are available, we evaluated the most widely used calculators to assess superiority. The four most commonly used risk estimators are the Framingham Risk Score (FRS), Q-RISK, Reynolds score, and atherosclerotic cardiovascular disease (ASCVD) risk calculator. These calculators consider some of the most common parameters responsible for CVD, such as blood pressure, cholesterol, high-density lipoprotein (HDL) cholesterol, and total cholesterol/HDL ratio.

The Framingham risk study has been the most impactful in modern medicine's history[8]. It is a long-standing, ongoing cardiovascular study involving the inhabitants of Framingham (MA, USA). The study established the classic risk factors for CVD, such as high blood pressure, diabetes, and cigarette smoking[9,10]. The first model was the FRS, which predicted the years' risk of coronary heart disease (CHD). The second was the Q-RISK score, which was introduced in the United Kingdom and corroborated the established Framingham CVD algorithm[10]. The third was the ASCVD model, which predicts the 10-year risk of CVD[11] and the fourth was the Reynolds score, designed to predict the risk of a future heart attack, stroke, or other primary heart disease in the next 10 years[12,13]. In the present study, we used these four freely available estimators to calculate the CVD risk in a population and we compared the estimators to identify the most important predictors of heart risk and determine which predictor gives the most reliable prognosis.

Patients and Methods

Study Sample

The study population consisted of 150 consecutive, asymptomatic patients (men and women) with no prior history of clinically apparent CVD. The patients were aged between 30 and 79 years and had attended an executive cardiovascular health examination in the Subhash Parmar pathology lab. All patients were self-referred and underwent evaluation by doctors in the outpatient Department. They were informed that the information provided by them, and reports of blood examinations would be used for academic purposes only, and that anonymity would be maintained. Patients who provided consent on this basis were included in the study.

Initially, all participants completed a detailed health questionnaire to confirm the presence or absence of symptoms of heart disease (chest pain, dyspnea, palpitations at rest or with exercise) as well as to detail known risk factors for CVD (hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and family history of CVD) and medication use (aspirin, statins, anti-hypertensives, diabetic medication). The individuals were also questioned about symptoms and signs of acute infection (fever, cough, sputum production, etc.). The exclusion criteria were the presence of known heart disease (including previous MI), symptoms of cardiac disease, peripheral vascular disease, history of stroke or symptomatic cerebral ischemia, and the presence of symptoms consistent with current infection. All patients taking aspirin, statins, and/or antihypertensive medications were excluded. The FRS for hard CHD was calculated using an online calculator (https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease#creator-insights), which estimates the 10-year risk of heart attack. The model was developed by Wilson et al[12] (1998) and intended for use in non-diabetic patients with no previous history of CVD.

Physical Parameters, Blood Profile, and Cardiovascular Risk Assessment

All study subjects were subjected to cardiovascular assessment that comprised complete physical examination and recorded age, sex, smoking status, systolic blood pressure, and treatment using blood pressure medications. All blood tests (lipid profiles) were performed using fasting samples to measure total cholesterol and HDL cholesterol. The various components of blood were determined using the blood smear method in routine pathological lab procedures. Total white blood cell (WBC) count, lymphocyte count, red blood cell (RBC) count (cells/μL), monocyte count, neutrophil count, eosinophil count, platelets (cells/μL), and hemoglobin (g/dL) were determined.

Use of Various Calculators

Using the links available on the web (given separately in each section), different scores were calculated using parametric scores and tabulated.

Table I. The current version of the Framingham-risk-score calculator uses the following parameters.

Sl. No	Parameter undertaken for study
1	Age
2	Sex
3	Smoking status
4	Total cholesterol
5	HDL cholesterol
6	Cholesterol HDL ratio
7	Systolic blood pressure and the presence of diabetes

Framingham Risk Score Calculation

The risk of CHD (fatal or non-fatal) and fatal CVD (including both coronary and cerebrovascular deaths) was calculated for all patients using the FRS calculation, which was derived from the Framingham Heart Study Cohort and predicts gender-specific, 10-year risk of CHD development by assigning a weighting to each individual's age, sex, smoking status, total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, systolic blood pressure, presence of diabetes, and smoking status. The FRS was calculated using the available online link (https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease). The values of the different parameters used and resulting scores are shown in Tables I and IV, respectively.

Q-RISK Heart Risk Calculation

The United Kingdom National Institute for Health and Care Excellence guidelines recommends using the Q-RISK calculator to estimate the 10-year risk of CVD and identify high-risk individuals for primary prevention in those aged 84 years and younger. Adults aged ≥ 85 years and those with existing CVD and type I diabetes (Link for a calculator- https://qrisk.org/three- https://qrisk.org/three/) were included in the study. The values of the different parameters used and resulting scores are shown in Tables II to VI, respectively.

Reynolds score

The Reynolds score tool has been used to predict the risk of future heart attack, stroke, or other significant cardiac event in the next 10 years. In the present study, the score was calculated using available online software (https://www.mdcalc.com/reynolds-risk-score-cardiovascular-risk). The values of the different parameters used, and the resulting scores are shown in Tables III and VII, respectively.

ASCVD Score

The Reynolds score tool has been used to predict the risk of future heart attack, stroke, or other significant cardiac event in the next 10 years. The score was calculated using available online software (https://www.mdcalc.com/reynolds-risk-score-cardiovascular-risk). The values of the

Table II. The current version of the calculator (QRISK) uses the following parameters.

Sl. No.	Parameter undertaken for study
1.	Patient age (25-84).
2.	Patient sex
3.	Ethnicity
4.	Smoking status (non, ex, light, moderate, heavy)
5.	Diabetes
6.	Angina or heart attack in a first-degree relative <60 (yes/no)
7.	CKD stage 3, 4 or 5
8.	Atrial fibrillation
9.	Existing treatment with blood pressure agent (yes/no)
10.	Postcode (postcode-related Townsend score) - a geographical measure of deprivation
11.	Migraines
12.	Rheumatoid arthritis
13.	Systemic lupus erythematosus (SLE)
14.	Severe mental illness, including schizophrenia, bipolar disorder or moderate/severe depression
15.	Atypical antipsychotics
16.	Regular steroid tablets
17.	Diagnosed erectile dysfunction
18.	BMI (height and weight).
19.	Systolic blood pressure (use current not pre-treatment value)
20.	Total and HDL cholesterol
21.	Self-assigned ethnicity (should not be confused with nationality)

Table III. The current version of the calculator Reynolds Score uses the following parameters.

Sl. No	Parameter undertaken for study
1.	Age
2	Smoking status
3	Systolic blood pressure
4	Total cholesterol
5	HDL cholesterol
6	CRP

different parameters used and the resulting scores are shown in Tables IV and VIII, respectively.

Statistical Analysis

Multivariate Linear Regression Analysis

Multivariate linear regression analysis was performed for the statistical analysis. Regression analysis was performed using the software Statistical Product and Service Solutions 16 (SPSS 16, IBM, Armonk, NY, USA). The analysis was performed individually using the FRS, Q-RISK score, Reynolds score, and ASCVD score, which consider various parameters, including age, weight, systolic blood pressure, height, HDL cholesterol, total cholesterol, hemoglobin, WBC count, lymphocyte percentage, eosinophil percentage, neutrophil percentage, monocyte percentage, and RBC count. The results of the FRS, Q-RISK score, Reynolds score, and ASCVD score are depicted in Tables I, II, III, and IV, respectively. The tables are arranged with the most significant variables at the top and the least significant at the bottom.

Table IV. The current version of the ASCVD score calculator uses these parameters.

Sl. No	Parameter undertaken for study
1.	Age
2	Sex
3	Systolic blood pressure
4	Diastolic blood pressure
5	Total cholesterol, HDL cholesterol, LDL cholesterol
6	Diabetes status, on a hypertension treatment
7	Smoking status, on a statin

Backward Stepwise Regression

The backward stepwise regression analysis was performed using SPSS 16 (IBM). The analysis was performed individually using the FRS, Q-RISK score, Reynolds score, and ASCVD score, which consider various parameters, including age, weight, systolic blood pressure, height, HDL cholesterol, total cholesterol, hemoglobin, WBC count, lymphocyte percentage, eosinophil percentage, neutrophil percentage, monocyte percentage, and RBC count. The four most significant variables were determined for each score and are presented in Figure 6.

Results

Multivariate Linear Regression

Initially, multiple linear regressions were performed to assess different parameters in the entire clinical sample using an individual calculator. The statistical analyses of each calculator (regres-

Table V. Results of multivariate regression analysis for Framingham Score.

Sl. No	Variable	Slope	Error	Intercept	Error	r	p
1	Age	0.643	0.141	45.893	1.393	0.353	0.000 ***
2	Weight	0.415	0.099	63.620	0.979	0.327	0.000***
3	Diastolic blood pressure	0.173	0.051	84.437	0.508	0.269	0.001***
4	Systolic blood pressure	0.267	0.082	126.720	0.815	0.258	0.002**
5	Cholesterol/HDL ratio	0.053	0.018	3.816	0.174	0.240	0.003**
6	Height	0.204	0.096	163.300	0.951	0.173	0.036*
7	Total cholesterol	1.383	0.660	194.880	6.523	0.171	0.038*
8	Hb	0.120	0.059	8.306	0.583	0.166	0.043*
9	Eosinophil %	0.030	0.015	2.014	0.149	0.164	0.046*
10	HDL cholesterol	-0.383	0.208	56.085	2.061	-0.150	0.068
11	RBC	0.040	0.022	3.054	0.215	0.150	0.070
12	WBC	0.074	0.043	5.020	0.424	0.142	0.086
13	Neutrophil %	0.422	0.314	44.064	3.107	0.111	0.181
14	LDL cholesterol	0.881	0.695	121.250	6.869	0.104	0.207
15	Monocyte %	0.018	0.015	1.866	0.145	0.104	0.209
16	Platelets	0.001	0.015	1.795	0.149	0.005	0.954

***: $p<0.001$; **; $p<.01$; *: $p<0.05$

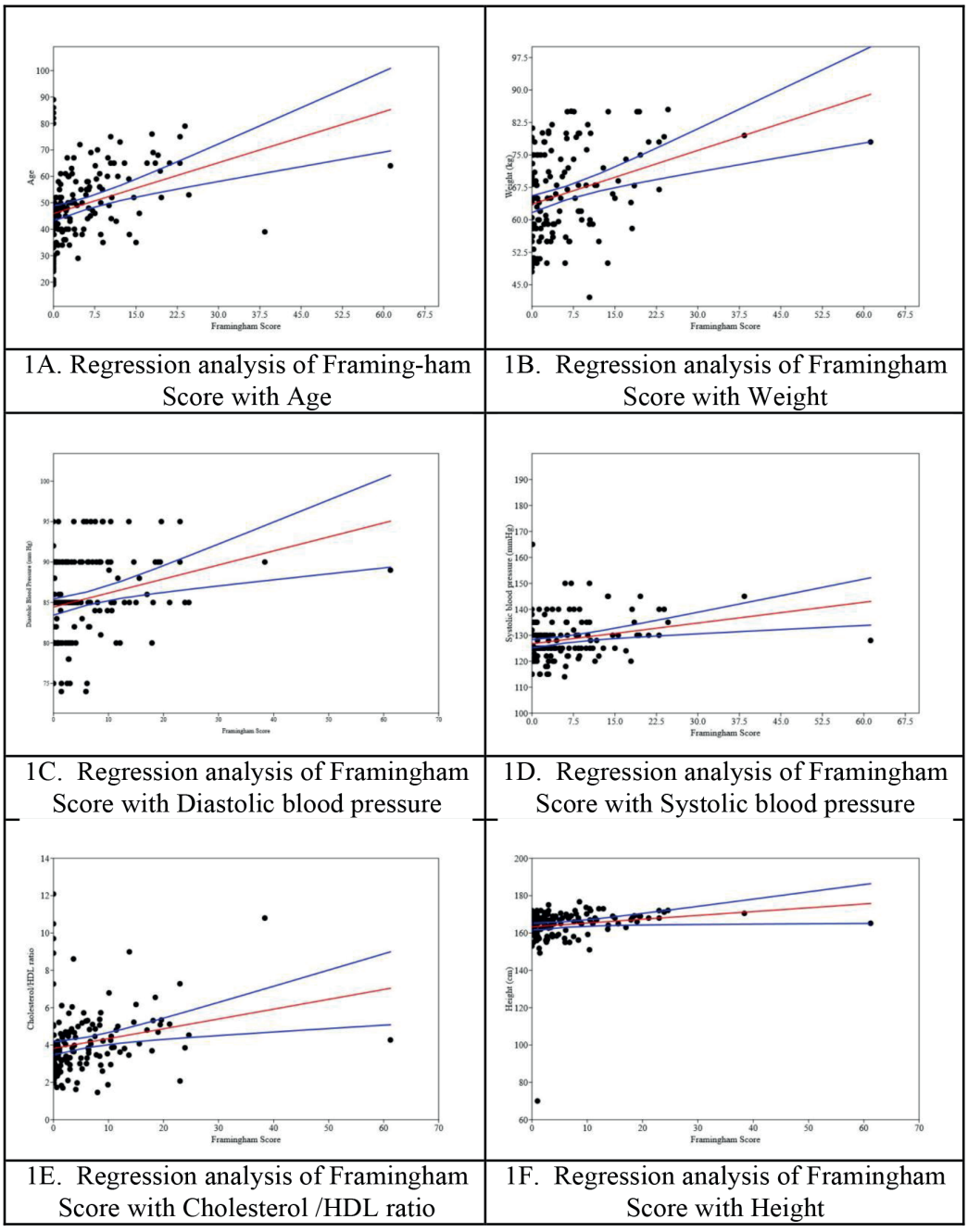
sion [r] and probability [p]) are shown in Table V (FRS), Table VI (Q-RISK Score), Table VII (Reynolds Score), and Table VIII (ASCVD score).

Multiple Regression Model of Framingham Risk Score and the 16 Parameters Calculated

Multivariate linear regression analysis between FRS and different parameters is shown in Table V. Of the 16 parameters calculated, nine had a significant correlation with the FRS. Figure 1 shows the regression analysis between the FRS and the parameters that showed significant correlation.

Multiple Regression Model of Q-RISK and the 16 Parameters Calculated

Multivariate linear regression analysis between Q-RISK score and different parameters is shown



1A. Regression analysis of Framing-ham Score with Age

1B. Regression analysis of Framingham Score with Weight

1C. Regression analysis of Framingham Score with Diastolic blood pressure

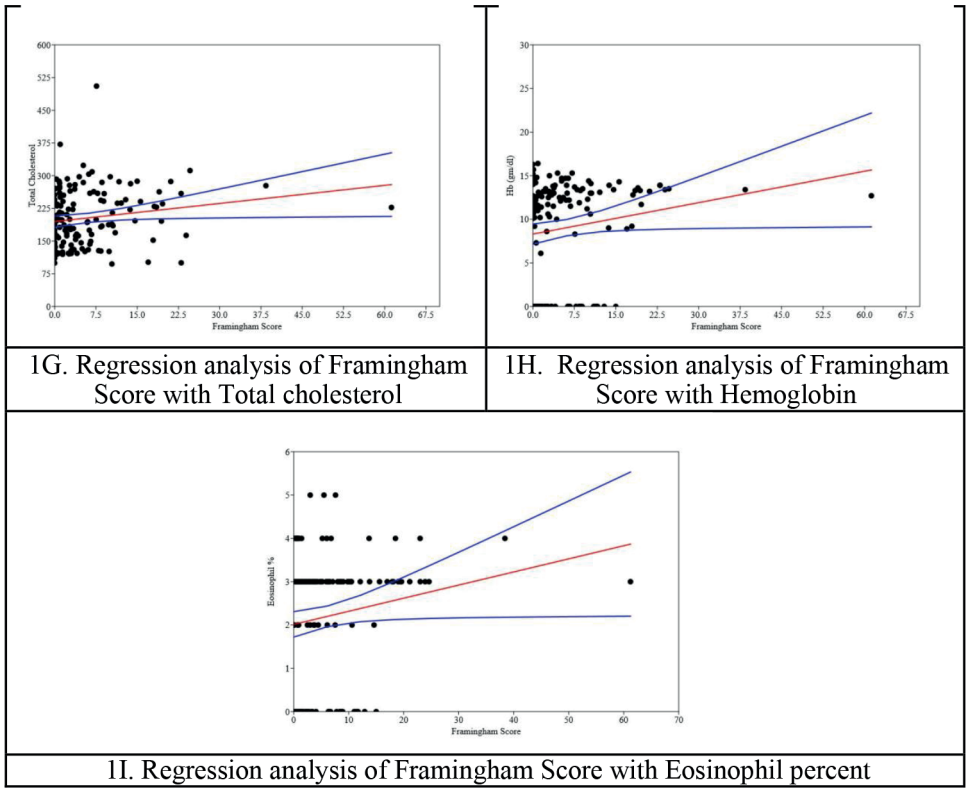
1D. Regression analysis of Framingham Score with Systolic blood pressure

1E. Regression analysis of Framingham Score with Cholesterol /HDL ratio

1F. Regression analysis of Framingham Score with Height

Figure 1. Regression analysis of Framingham Score with parameters significantly associated.

Figure continued



1G. Regression analysis of Framingham Score with Total cholesterol

1H. Regression analysis of Framingham Score with Hemoglobin

1I. Regression analysis of Framingham Score with Eosinophil percent

Figure 1. ***(Continued).*** Regression analysis of Framingham Score with parameters significantly associated.

in Table VI. Of the 16 parameters calculated, five were significantly correlated with the Q-RISK heart risk score. Figure 2 shows the regression analysis between the Q-RISK score and the parameters that showed significant correlation.

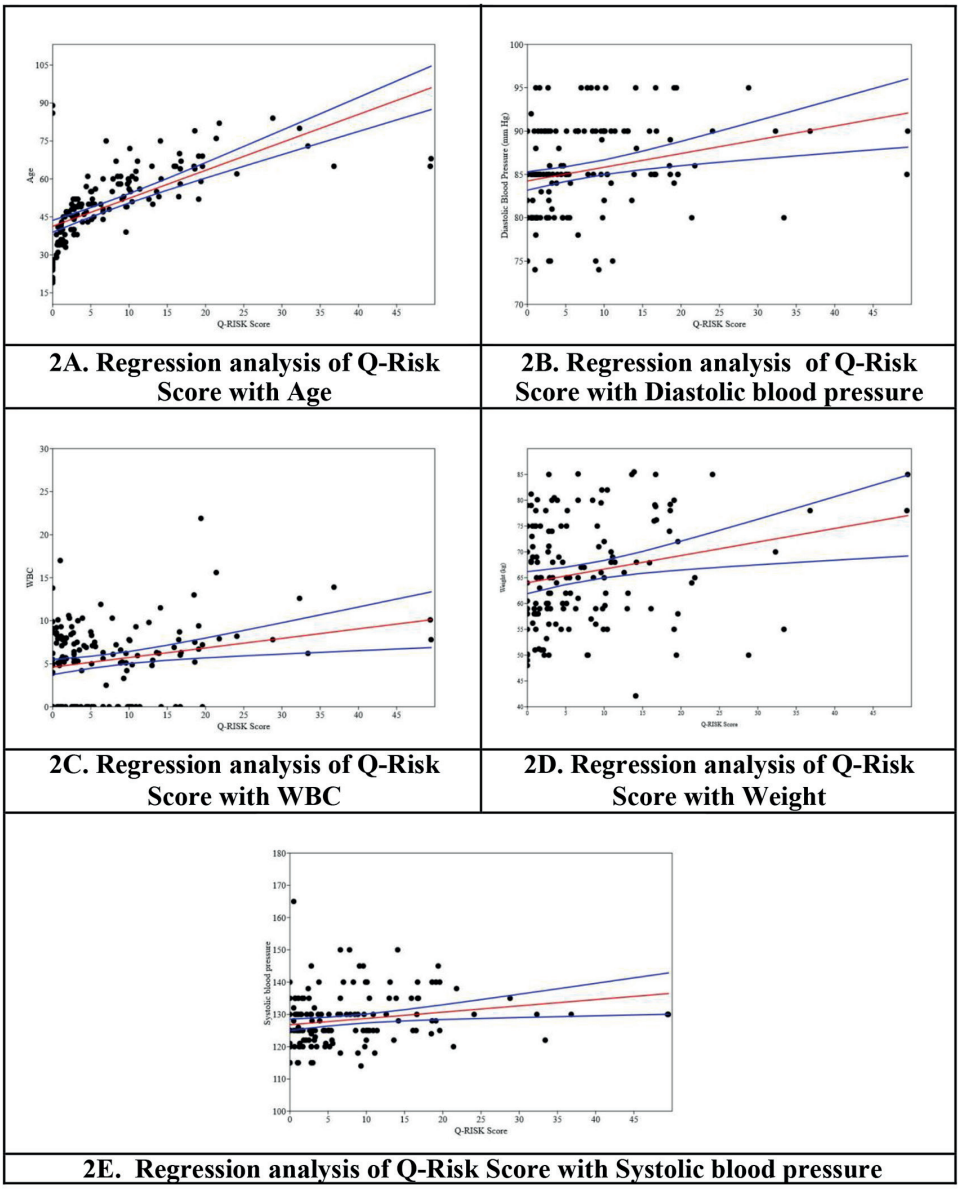
Multiple Regression Model of Reynolds Score and the 16 Parameters Calculated

Multivariate linear regression analysis between Reynolds score and different parameters is shown in Table VII. Of the 16 parameters calculated, 13

Table VI. Results of multivariate regression analysis for Q-RISK Score.

Sl. No	Variable	Slope	Error	Intercept	Error	r	*p*
1	Age	1.105	0.101	41.280	1.176	0.671	0.000***
2	Diastolic blood pressure	0.158	0.046	84.245	0.540	0.271	0.001***
3	WBC	0.111	0.038	4.611	0.444	0.234	0.004**
4	Weight	0.263	0.092	64.037	1.075	0.229	0.005**
5	Systolic blood pressure	0.195	0.076	126.790	0.879	0.209	0.011*
6	Eosinophil%	0.026	0.014	1.990	0.158	0.158	0.055
7	Cholesterol/HDL ratio	0.030	0.016	3.893	0.189	0.151	0.067
8	Total cholesterol	1.093	0.600	194.640	6.973	0.149	0.071
9	Neutrophil %	0.503	0.283	42.718	3.295	0.145	0.078
10	LDL cholesterol	0.906	0.628	119.510	7.305	0.118	0.152
11	Height (cm)	0.125	0.088	163.540	1.021	0.117	0.156
12	Hb	0.072	0.054	8.458	0.626	0.110	0.183
13	RBC	0.024	0.020	3.106	0.231	0.098	0.234
14	Monocyte%	0.013	0.013	1.875	0.155	0.080	0.332
15	HDL cholesterol	-0.156	0.191	55.042	2.215	-0.067	0.416
16	Platelets	0.008	0.014	1.739	0.158	0.049	0.550

***: $p<0.001$; **; $p<.01$; *: $p<0.05$



2A. Regression analysis of Q-Risk Score with Age

2B. Regression analysis of Q-Risk Score with Diastolic blood pressure

2C. Regression analysis of Q-Risk Score with WBC

2D. Regression analysis of Q-Risk Score with Weight

2E. Regression analysis of Q-Risk Score with Systolic blood pressure

Figure 2. Regression analysis of Q-Risk Score with parameters significantly associated.

were significantly correlated with the Reynolds heart risk score. All significantly associated parameters were positively correlated, except for HDL cholesterol. Figure 3 shows the regression analysis between Reynolds score and the parameters that showed a significant correlation.

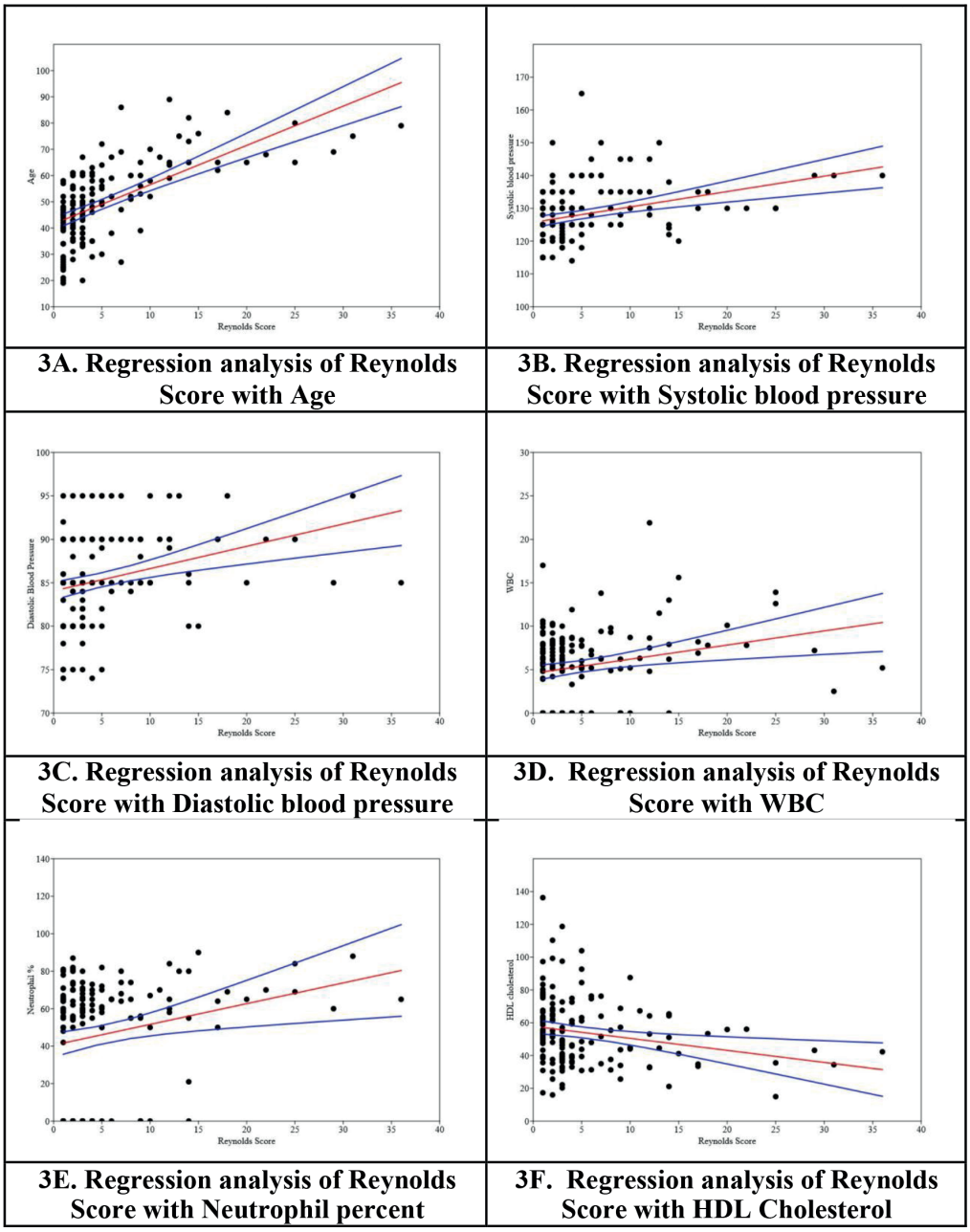
Multiple Regression Model of ASCVD Score and the 16 Parameters Calculated

Multivariate linear regression analysis between ASCVD scores and different parameters are shown in Table VIII. Of the 16 parameters calculated, five were significantly correlated with the ASCVD heart risk score. All the significant associations were positively correlated. Figure 4 shows the regression analysis between the ASCVD score and the parameters that showed significant correlation.

A heat map was drawn to see the consensus between the parameters for various scores (Figure 5).

Backward Stepwise Regression

The multiple linear analyses shown in Figure 5 indicate that the FRS, Q-RISK, Reynolds, and ASCVD scores were significantly correlated with nine, five, thirteen, and five parameters, respecti-



3A. Regression analysis of Reynolds Score with Age

3B. Regression analysis of Reynolds Score with Systolic blood pressure

3C. Regression analysis of Reynolds Score with Diastolic blood pressure

3D. Regression analysis of Reynolds Score with WBC

3E. Regression analysis of Reynolds Score with Neutrophil percent

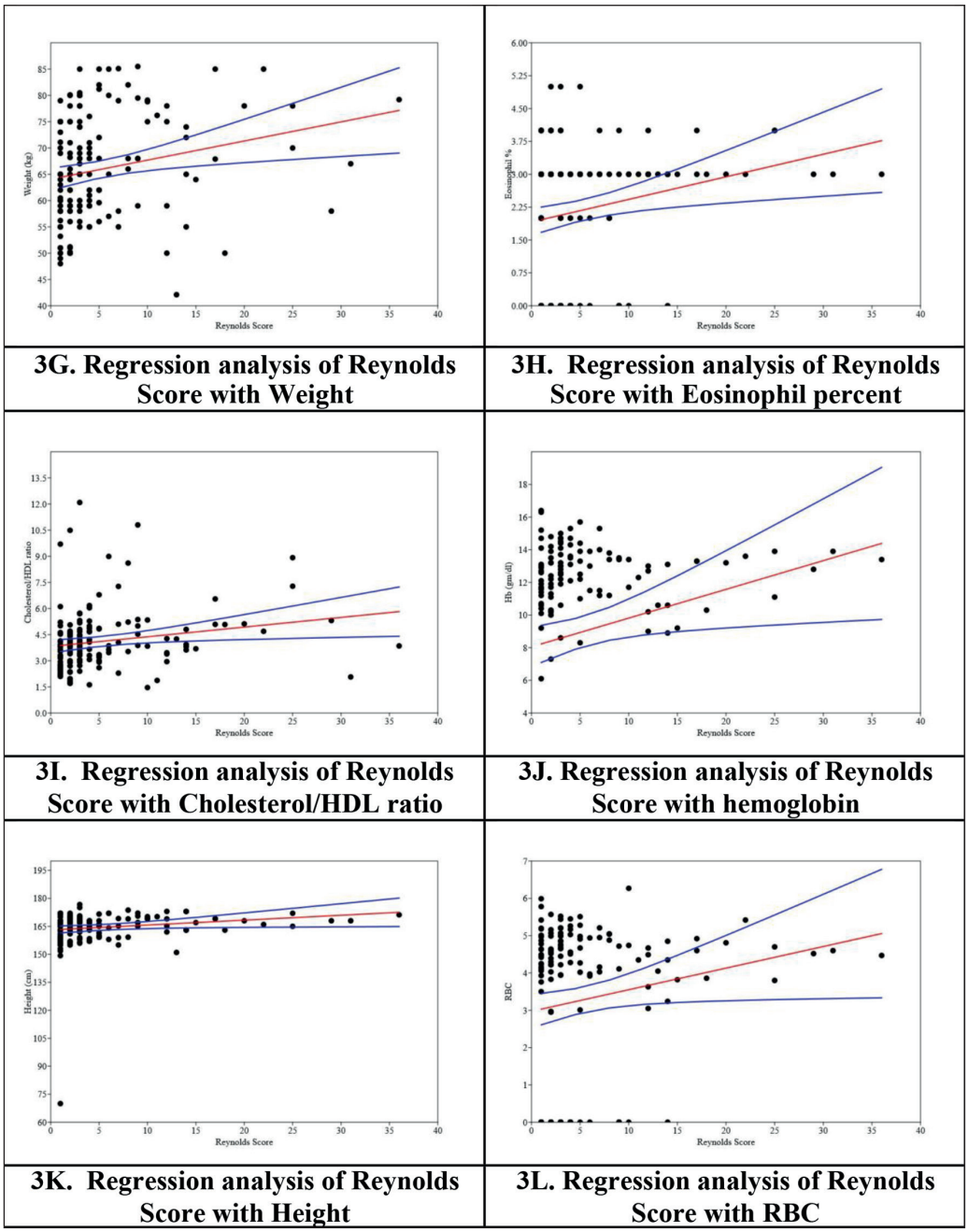
3F. Regression analysis of Reynolds Score with HDL Cholesterol

Figure 3. Regression analysis of Reynolds Score with parameters significantly associated.

Figure continued

vely. To determine the significant parameters that were common to the different risk scores and obtain the most critical parameters, backward stepwise regression was carried out on up to four of the most important parameters of each risk score. The results are depicted as heat maps in Figure 6. All four risk scores showed high association with age, while weight had an association with all risk scores except for Reynold's score. Backward stepwise regression identified five parameters as the most important risk factors for CVD: age, weight, total cholesterol, cholesterol/HDL ratio, and hemoglobin level.

After backward regression, diastolic blood pressure was eliminated and was not listed in the top four predictors, despite having highly signi-



3G. Regression analysis of Reynolds Score with Weight

3H. Regression analysis of Reynolds Score with Eosinophil percent

3I. Regression analysis of Reynolds Score with Cholesterol/HDL ratio

3J. Regression analysis of Reynolds Score with hemoglobin

3K. Regression analysis of Reynolds Score with Height

3L. Regression analysis of Reynolds Score with RBC

Figure 3. ***(Continued).*** Regression analysis of Reynolds Score with parameters significantly associated.

ficant correlation with all four predictors (p-values between 0.0001 and 0.01). Likewise, systolic blood pressure had significant association with all risk estimators and WBC count with three risk estimators (*p*-values between 0.0001 and 0.05). However, they only appeared among the top four prognostic parameters in the Reynolds and Q-RISK scores, respectively.

Discussion

CVD Risk Scores and Age

CHD is common in both men and women, and CHD risk increases with age[13]. The normal aging process is associated with progressive deterioration of the structure and function of the heart and vasculature, which likely contributes to the deve-

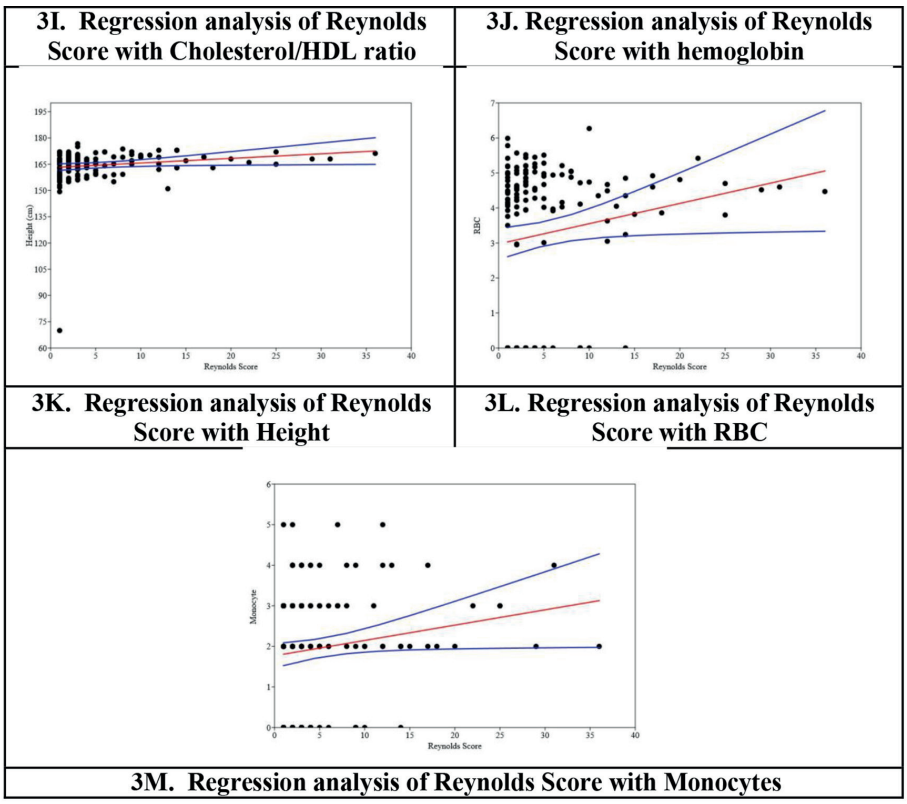


Figure 3. ***(Continued).*** Regression analysis of Reynolds Score with parameters significantly associated.

lopment of CVDs, including CHD, hypertension, and heart failure[14]. One study found that, by 2030, approximately 20% of the population would be aged 65 years or older and that CVD will rank as the leading cause of death in this age group, resulting in 40% of all deaths[15]. Our study emphasized that elderly age is a major risk factor for CVD, corroborating a cohort study conducted by Jousi-

Table VII. Results of multivariate regression analysis for Reynolds Score.

Sl. No	Variable	Slope	Error	Intercept	Error	r	*p*
1	Age	1.496	0.149	41.551	1.225	0.640	0.000***
2	Systolic blood pressure	0.469	0.103	125.740	0.846	0.354	0.000***
3	Diastolic blood pressure	0.257	0.065	84.056	0.537	0.310	0.000 ***
4	WBC	0.163	0.054	4.573	0.445	0.242	0.003**
5	Neutrophil %	1.107	0.396	40.545	3.263	0.226	0.006**
6	HDL cholesterol	-0.734	0.264	57.821	2.176	-0.224	0.006**
7	Weight	0.364	0.131	64.058	1.082	0.223	0.006**
8	Eosinophil%	0.052	0.019	1.912	0.158	0.218	0.008**
9	Cholesterol/HDL ratio	0.056	0.023	3.820	0.189	0.197	0.016*
10	Hb	0.176	0.075	8.053	0.622	0.190	0.021*
11	Height (cm)	0.263	0.124	163.070	1.019	0.173	0.035*
12	RBC	0.058	0.028	2.973	0.230	0.169	0.040*
13	Monocyte%	0.038	0.019	1.770	0.154	0.165	0.045*
14	LDL cholesterol	1.432	0.890	118.630	7.334	0.132	0.110
15	Platelets(lack/cmm)	0.013	0.019	1.730	0.159	0.055	0.503
16	Total cholesterol	0.084	0.860	202.420	7.092	0.008	0.922

***: $p<0.001$; **; $p<.01$; *: $p<0.05$

Table VIII. Results of multivariate regression analysis for ASCVD Score.

Sl. No	Variable	Slope	Error	Intercept	Error	r	p
1	Age	0.824	0.118	44.813	1.253	0.499	0.000***
2	Systolic blood pressure	0.247	0.075	126.830	0.791	0.264	0.001***
3	Weight	0.296	0.092	64.292	0.973	0.258	0.002**
4	Diastolic Blood Pressure	0.143	0.047	84.606	0.496	0.245	0.003**
5	WBC	0.085	0.039	4.954	0.409	0.179	0.029*
6	Hb	0.093	0.054	8.459	0.568	0.142	0.085
7	Height (cm)	0.133	0.088	163.700	0.930	0.124	0.132
8	Neutrophil %	0.428	0.285	44.015	3.013	0.123	0.135
9	Eosinophil%	0.020	0.014	2.073	0.145	0.120	0.147
10	Total Cholesterol	0.854	0.604	197.910	6.386	0.116	0.159
11	RBC	0.027	0.020	3.128	0.210	0.112	0.177
12	Monocyte%	0.013	0.013	1.899	0.141	0.079	0.342
13	LDL Cholesterol	0.499	0.633	123.440	6.694	0.065	0.432
14	HDL cholesterol	0.138	0.191	54.674	2.021	-0.060	0.470
15	Cholesterol/HDL ratio	0.011	0.016	4.056	0.174	0.055	0.507
16	Platelets(lack/cmm)	0.004	0.014	1.778	0.144	0.022	0.788

***: $p<0.001$; **; $p<.01$; *: $p<0.05$

lahti et al[13] and involving 14,786 Finnish men and women aged 25–64 years at baseline. Rodgers et al[16] reviewed age as a significant independent risk factor for CVD because it is associated with an increased likelihood of developing any additional cardiac risk factors, including obesity and diabetes. According to the American Heart Association, between 2013 and 2017, 77.8% of women and 70.8% of men aged 65–74 years were diagnosed with high blood pressure or hypertension. Rates for diagnosed hypertension increased drastically to 85.6% in women and 80.0% in men aged > 75 years, and hypertension is a significant risk factor for CVD[16]. In the present study, all CVD risk scores were significantly associated with age (p< 0.0001). All four bioinformatics-based scores, without any ambiguity, ranked age as the most important factor affecting heart health. In addition, in both the multiple regression and back regression analyses, age appeared as a factor impacting CVD, clearly indicating that, in the elderly population, even if the other morbidities are absent, special attention must be paid to CVD risk.

Bodyweight and CVD Risk Score

Obesity is an established risk factor for CVDs, and weight was the second factor common to the three risk scores (Q-RISK, Reynolds, ASCVD). It was significantly associated with CVD (p< 0.0001–0.01). A systematic review and dose-response meta-analysis of 23 prospective cohort studies with 1,093,337 participants demonstrated that the risk of CVD mortality was unchanged with an initial weight gain of up to 5 kg. The risk then increased sharply and linearly (p for non-linearity < 0.001). This phenomenon could be used as a supplementary approach to predict CVD[17]. According to Khosravi et al[18] risk of fatal and non-fatal cardiovascular events in middle-aged men increases to 72% if their BMI is between 25 and 29 kg/m^2. Our results were in concordance with those of Khosravi et al[18], and the bioinformatics tool data clearly corroborate the data obtained from experiment.

Prognostic Value of Cholesterol

Higher total cholesterol, LDL cholesterol, triglycerides, and lower HDL cholesterol are known risk factors for CVD[19,20]. In the present study, a strong correlation was found between high cholesterol levels and CVD risk. A significant association of $p< 0.05$ was found in three risk scores (Q-RISK, Reynolds, and ASCVD score); in one risk score (FRS), the association had a p-value of < 0.01. Similar results were obtained in a study conducted by Jeong et al[21], where the effect of total cholesterol on CVD risk was studied in 2,682,045 young adults (aged 20–39 years) who had undergone two consecutive national health check-ups provided by the Korean National Health Insurance Service between 2002 and 2005. The study concluded that increased cholesterol levels were associated with elevated CVD risk, while decreased cholesterol levels were associated with reduced CVD risk among young adults[21].

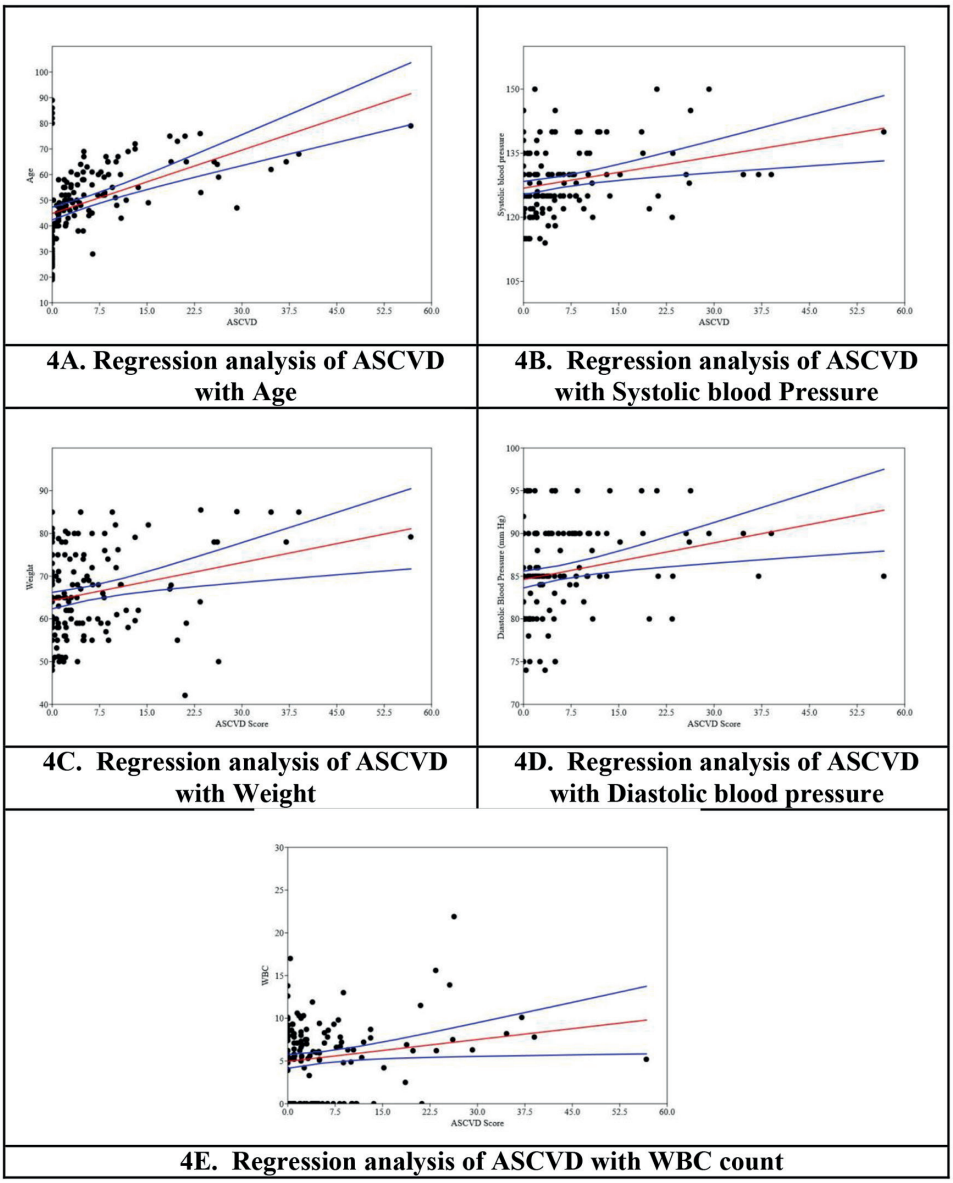


Figure 4. Regression analysis of ASCVD with parameters significantly associated.

Prognostic Value of Hemoglobin Level

Hemoglobin concentration can affect the cardiovascular system via oxygen supply and blood viscosity. Several studies have assessed the association between hemoglobin or hematocrit levels and CVD[22]. In Cox proportional hazard models, men with low or high hemoglobin levels showed higher hazard ratios (HRs) with total CVD than those with mid-levels of hemoglobin. Women with higher hemoglobin levels also showed higher HRs with CVD[22]. In the present study, a strong significant association was found between hemoglobin level and CVD risk. Of the four, the FRS and Reynolds's scores showed significant association at p-values < 0.05, while Q-RISK and ASCVD showed significant association (p-values < 0.05), probably because increased hemoglobin concentration leads to increased blood viscosity and hinders blood flow and perfusion[23]. Elevated hemoglobin levels may also activate platelets through adenosine diphosphate release. Furthermore, high iron levels may themselves be a cause of CVD, causing oxidative stress and lipid peroxidation.

Prognostic Values of Other Parameters

HDL level acts as a complementary risk factor for predicting and managing CVD risk. The

Variable	Framingham	Q-Risk	Reynolds	ASCVD
Age				
Cholesterol/HDL ratio				
Diastolic Blood Pressure				
Eosinophil				
Hb				
HDL cholesterol				
Height				
LDL Cholesterol				
Monocyte				
Neutrophil				
Platelets				
RBC				
Systolic blood pressure				
Total Cholesterol				
WBC				
Weight				

Figure 5. Heat map for significant association (p-value) between various scores and parameters. Color rule: Red 0-0.0001; Yellow 0.0001-0.01; Green 0.01-0.05; Blue Greater than 0.05 (Non-significant).

Framingham risk score	Q-Risk	Reynolds score	ASCVD
1	1	1	1
2	2	6	2
5	6	7	3
3	8	4	4

1	Red	Age
2	Orange	Weight (kg)
3	Yellow	Total Cholesterol
4	Purple	Hb (gm/dl)
5	Light green	HDL cholesterol
6	Green	Cholesterol/HDL ratio
7	Dark pink	Systolic blood pressure
8	Light pink	WBC

Figure 6. Result of backward stepwise regression. Color code given to see the consensus for a parameter among various risk scores.

association between low HDL levels and atherosclerotic CVD was first shown by the Framingham study[24,25] Low HDL is a potent marker of hypertriglyceridemia and elevated residual particle concentrations; many clinicians feel that it is linked to an increased risk of CHD[26]. A recent study also revealed that low levels of HDL are associated with CVD (FRS: $p > 0.05$, Q-RISK: $p > 0.05$, Reynolds: $p > 0.01$, ASCVD: $p > 0.05$). Roth et al[1] obtained the same results, which are in concordance with our study.

High levels of cholesterol and low levels of HDL are directly associated with risk of CVD, as found in a recent study (FRS: $p < 0.01$, Q-RISK: $p > 0.05$, Reynolds: $p < 0.05$, ASCVD: $p > 0.05$)[27,28].

A study by Gu et al[29] indicated a strong, linear, and independent relationship between blood pressure and CVD risk in Chinese adults. Systolic BP was a stronger predictor of CVD risk than diastolic BP. Increases in systolic BP were associated with a greater risk of CVD than corresponding increases in diastolic BP. A linear trend for increased CVD risk related to higher BP levels was observed in all subgroups of sex, age, body weight, and cigarette smoking[29]. In our study, systolic blood pressure had a significant association with CVD in three out of the four risk scores (ASCVD: $p < 0.001$, Q-RISK: $p < 0.01$, FRS: $p < 0.01$).

High WBC count, as well as high count of WBC subtypes (neutrophils, monocytes, lymphocytes, and eosinophils), has been linked to CHD, peripheral arterial disease, and stroke[30]. Our results were corroborated by Caerphilly and Speedwell's studies, which followed 4,860 men aged 45–63 years for 5 years. The neutrophil number is an essential biomarker for acute infection and inflammation but is not used routinely to predict cardiac risk. However, the prognostic value of neutrophils in estimating CVD cannot be ruled out. After a 10-year follow-up, ischemic heart disease increased with an increase in neutrophil count after odds adjustment for age, smoking habit, preexisting disease status, total cholesterol, diastolic blood pressure, and body mass index[31]. The results of the present study corroborated those of previous studies. In three risk scores, neutrophils were significantly associated with CVD (FRS: $p < 0.05$, Q-RISK: $p < 0.05$, ASCVD: $p< 0.05$).

In our study, two out of the four risk scores were significantly associated with eosinophil count (FRS: $p < 0.05$, Reynolds $p < 0.01$). In a cross-sectional study of 1363 consecutive participants in whom coronary artery calcification was considered a risk factor for CHD, multivariate linear regression analysis demonstrated that eosinophil count was positively correlated with coronary artery calcification[32]. A cohort of 55,004 individuals with CVD was followed up for over 3.8 years. During the initial 6 months, there was a strong association between low eosinophil count and the incidence of 12 CVDs.

Dragu et al[33] conducted a study on 1037 patients with acute MI and concluded that an elevated WBC count was associated with higher mortality in patients with acute coronary syndromes[30]. With regards to WBC count, three of the parameters measured in the present study showed a significant association (Q-RISK: $p < 0.01$, Reynolds: $p < 0.01$, ASCVD: $p < 0.05$). These results match those of a case-control study in which high CHD risk was found to be associated with high WBC count in gender-, age-, and risk-matched subjects[34]. According to Twig et al[35], WBC count is an independent risk factor for coronary artery disease and may help recognize subgroups of young men at either low or high risk of coronary artery disease.

Attempts to Screen Risk Calculators

In an attempt to shortlist risk calculators, Allan et al[36] calculated CVD and CHD risk in 128 hypothetical patients using 25 calculators. After comparing concordance in categorization with three standard risk categories (low [10%], moderate [10%-20%], and high [20%]), pairs of calculators classified the same patients into different categories. The authors pointed out that risk calculators must be chosen carefully as they have a significant impact on risk classification and absolute risk assessment[36].

In another study, Allan et al[37] studied 16 calculators chosen from six nations to estimate CVD or CHD risk using 5- and 10-year forecasts. Patients with diabetes showed a similar pattern of outcomes. Over several risk categories, specific calculators had some consistency. Although some variation in relative risk was seen among the different calculators, the 10-year CVD Framingham calculators appeared to provide the most consistently related risk increase[37].

In the present study, the most common risk factors for CVD were age, weight, total cholesterol, hemoglobin level, HDL, and LDL cholesterol. All the risk calculators performed well; however, to choose one, the FRS calculator appeared as the best CVD assessment tool in our work. A similar finding was reported by Salam et al[7]. Moreover, the results were corroborated by multiple and back regression analysis, which showed that, among the four most significant parameters, the FRS matched with three. A strong positive association was observed between FRS and the incidence of hard CHD events[14]. In addition, the study indicated that age, weight, total cholesterol, and hemoglobin level could be used as prognostic markers.

It is beneficial that these risk calculators are available as applications on smartphones. The ASCVD risk estimator was made available for free by the American College of Cardiology and American Heart Association, both on the Internet and as an application on the App Store and Google Play. On average, it is used > 11,000 times each day[11]. The Pan-American Health Organization (PAHO) officially launched the PAHO/WHO Cardiovascular Risk Calculator on World Heart Day (September 29), 2014. It is available on the PAHO website and also at the App Store and Google Play[38].

The present study had several limitations. First, only a small number of participants were included. Moreover, only parameters with numerical values could be considered, while parameters such as smoking status, diabetes status, and dependability on other medications, which are integral in some of the scores, could not be considered. The patients were chosen randomly, and follow-up data were not available.

Conclusions

In India, the burden of CVD is substantial and expanding. Models for predicting cardiovascular risk are crucial to prevent and treat the disease. Many risk-estimation techniques are available. The FRS is the most well-known and extensively used worldwide. Our study revealed that the FRS calculator was the most useful CVD risk assessment model among our samples and that it could be prioritized over other risk calculators to shorten the prognostic parameters and calculate the risk of CVD. In addition, the analysis revealed that age, weight, total cholesterol, and hemoglobin were the most significant risk-related parameters in all four risk estimators, conferring the most reliable CVD prognosis. With a reduced number of prognostic parameters, it would be easier to assess heart risk; clinicians could conduct fewer tests and the cost of medical check-ups would be lower.

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All authors contributed substantially for the manuscript.

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