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Hidden Cardiovascular Phenotypes in Apparently Low risk Cardiology Outpatients

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Abstract

Background: Patients classified as low risk in routine cardiology outpatient practice are generally assumed to have minimal cardiovascular vulnerability. However, conventional risk assessment focuses primarily on overt clinical events and may overlook early biological, electrical, functional, and structural abnormalities. Whether a limited set of clinically key associated factors can explain subclinical cardiovascular vulnerability in apparently low-risk outpatients remains unclear.

Methods: This retrospective observational study included 476 adults aged 18–75 years evaluated in a cardiology outpatient clinic. Patients with established cardiovascular disease or major cardiac comorbidities were excluded. Routine outpatient data encompassing clinical characteristics, laboratory findings, electrocardiography, exercise treadmill testing, and transthoracic echocardiography were reviewed. Subclinical cardiovascular vulnerability was defined as the presence of at least one abnormality across inflammatory, electrical, functional, or structural domains. Multivariable modeling was performed with emphasis on identifying clinically dominant determinants of subclinical cardiovascular phenotypes.

Results: Subclinical cardiovascular vulnerability was identified in 30.0% of patients. Although multiple clinical, biochemical, and functional parameters were associated with this phenotype, the majority of the clinically relevant signal was driven by a limited subset of variables. Current smoking, ischemic ST-segment depression during exercise testing, and elevated hs-CRP consistently demonstrated the strongest associations, while other factors contributed more modestly to the overall risk profile.

Conclusion: A substantial proportion of cardiology outpatients categorized as low risk exhibit subclinical cardiovascular vulnerability detectable through routine outpatient assessment. While several factors are associated with this phenotype, a small number of key associated factors appear to account for most of the clinically actionable risk. A focused, phenotype-oriented interpretation of simple outpatient markers may improve risk refinement and help identify individuals who warrant closer cardiovascular surveillance despite apparently low estimated risk.

Keywords: subclinical cardiovascular phenotypes; risk misclassification; smoking; exercise testing; inflammation; primary prevention

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Görünürde Düşük Riskli Kardiyoloji Ayaktan Hasta Popülasyonunda Subklinik Kardiyovasküler Fenotipler

Öz

Amaç: Rutin kardiyoloji poliklinik pratiğinde düşük riskli olarak sınıflandırılan hastaların kardiyovasküler açıdan minimal risk taşıdığı varsayılmaktadır. Ancak geleneksel risk değerlendirme yaklaşımları çoğunlukla belirgin klinik olaylara odaklanmakta ve erken dönemdeki biyolojik, elektriksel, fonksiyonel ve yapısal anormallikleri gözden kaçırabilmektedir. Görünürde düşük riskli hastalarda sınırlı sayıda klinik olarak baskın belirtecin subklinik kardiyovasküler kırılganlığı açıklayıp açıklayamayacağı net değildir. Bu çalışmada, düşük riskli kardiyoloji polikliniği hastalarında subklinik kardiyovasküler kırılganlığın ve bunu belirleyen baskın klinik sinyallerin değerlendirilmesi amaçlandı.

Yöntemler: Bu retrospektif gözlemsel çalışmaya, bir kardiyoloji polikliniğinde değerlendirilen 18–75 yaş arası 476 erişkin hasta dahil edildi. Önceden tanımlı kardiyovasküler hastalığı veya majör kardiyak komorbiditesi olan hastalar çalışma dışı bırakıldı. Klinik özellikler, laboratuvar bulguları, elektrokardiyografi, efor testi ve transtorasik ekokardiyografi verileri içeren rutin poliklinik kayıtları incelendi. Subklinik kardiyovasküler kırılganlık; inflamatuvar, elektriksel, fonksiyonel veya yapısal alanlardan en az birinde anormallik saptanması olarak tanımlandı. Subklinik kardiyovasküler fenotiplerin klinik olarak baskın belirleyicilerini ortaya koymak amacıyla çok değişkenli analizler yapıldı.

Bulgular: Hastaların %30,0'unda subklinik kardiyovasküler kırılganlık saptandı. Birden fazla klinik, biyokimyasal ve fonksiyonel parametrenin bu fenotiple ilişkili olduğu gözlenmekle birlikte, klinik açıdan anlamlı ilişkinin büyük bölümü sınırlı sayıdaki değişken tarafından belirlendi. Güncel sigara kullanımı, efor testinde iskemik ST-segment depresyonu ve yüksek hs-CRP düzeyleri en güçlü ilişkileri gösterirken, diğer faktörlerin genel risk profiline katkısı daha sınırlı düzeyde kaldı.

Sonuç: Düşük riskli olarak sınıflandırılan kardiyoloji polikliniği hastalarının önemli bir kısmında, rutin poliklinik değerlendirme ile saptanabilen subklinik kardiyovasküler kırılganlık mevcuttur. Bu fenotip ile çeşitli faktörler ilişkili olsa da, klinik olarak eyleme dönüştürülebilir riskin büyük kısmı sınırlı sayıdaki baskın sinyal tarafından açıklanmaktadır. Basit poliklinik belirteçlerinin fenotip odaklı yorumlanması, risk sınıflandırmasının daha hassas yapılmasına katkı sağlayabilir ve görünürde düşük tahmini riske rağmen daha yakın kardiyovasküler izlem gerektiren bireylerin belirlenmesine yardımcı olabilir.

Anahtar kelimeler: Subklinik kardiyovasküler fenotipler; Kardiyovasküler riskin yanlış sınıflandırılması; Sigara kullanımı; Efor testi; İnflamasyon; Birincil Korunma.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide despite major advances in preventive cardiology[1]. Traditional cardiovascular risk stratification tools are designed to estimate the probability of future overt clinical events and are effective at a population level; however, they primarily reflect long term epidemiologic risk and may fail to capture early biological, functional, and structural vulnerability in individual patients classified as low risk in routine clinical practice[2,3]. Accumulating evidence indicates that atherosclerosis, myocardial remodeling, and vascular dysfunction develop silently over prolonged periods before the onset of overt clinical disease[4,5]. During this latent phase, multiple abnormalities including inflammatory activation, electrical instability, functional impairment, and subtle structural remodeling may coexist despite an apparently reassuring risk profile[6]. Consequently, a subset of cardiology outpatients labeled as "low risk" may not be biologically benign and may remain unrecognized by conventional risk-based approaches[7].

In routine outpatient settings, clinicians have access to several widely available diagnostic tools, including laboratory testing, electrocardiography, exercise testing, and transthoracic echocardiography. Each of these modalities has independently been associated with adverse cardiovascular outcomes in asymptomatic or low-risk populations[8–11]. However, the simultaneous presence of multiple modest abnormalities presents a practical challenge: although numerous parameters may demonstrate statistical associations with cardiovascular vulnerability, not all contribute equally to clinically

meaningful or actionable risk[12]. Most prior studies addressing subclinical cardiovascular disease have focused on single biomarkers or advanced imaging modalities, such as coronary computed tomography angiography or cardiac magnetic resonance imaging, which are not routinely applicable in low-risk outpatient populations[13,14]. Moreover, analytical approaches emphasizing statistical significance across numerous correlated variables may dilute clinical interpretability and limit translational relevance. From a pragmatic perspective, identifying a limited number of dominant determinants that account for the majority of cardiovascular vulnerability is more informative than cataloging multiple weak predictors[15].

Accordingly, the present study aimed to evaluate subclinical cardiovascular vulnerability in a clinically low-risk cardiology outpatient population using routinely available diagnostic modalities. Rather than focusing solely on the accumulation of multiple abnormalities, we sought to identify the key signals that most strongly characterize subclinical cardiovascular phenotypes and are most likely to carry clinical relevance in everyday cardiology practice. This phenotype-oriented approach was designed to bridge the gap between statistical association and meaningful risk interpretation in real world settings.

METHODS

Study Design and Population

This retrospective observational study included 476 consecutive adults aged 18–75 years who presented to the cardiology outpatient clinic for routine cardiovascular evaluation. Patients were classified as clinically low risk at the time of assessment and had no prior diagnosis of established atherosclerotic cardiovascular disease. Clinical low-risk classification was based on the absence of established cardiovascular disease and major cardiac comorbidities at the time of outpatient evaluation rather than on formal cardiovascular risk estimation models. Individuals with documented coronary artery disease, previous myocardial infarction or coronary revascularization, clinical heart failure, moderate to severe valvular heart disease, sustained atrial arrhythmias, or cardiac implantable electronic devices were excluded. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

Table I: Baseline Characteristics of the Study Population (n = 476)

Variable	Overall
Age, years	49.8 ± 11.6
Male sex, n (%)	248 (52.1)
Current smoking, n (%)	76 (16.0)
Hypertension, n (%)	77 (16.2)
Diabetes mellitus, n (%)	20 (4.2)
Systolic blood pressure, mmHg	128 ± 14
Body mass index, kg/m²	27.4 ± 4.2
LDL cholesterol, mg/dL	132 ± 36
hs-CRP ≥2 mg/L, n (%)	167 (35.1)

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Clinical and Laboratory Assessment

Demographic characteristics, smoking status, systolic blood pressure, body mass index, and cardiovascular comorbidities were obtained from electronic medical records. Laboratory evaluation included fasting lipid profile and high sensitivity C-reactive protein (hs-CRP). hs-CRP was analyzed as a continuous variable to preserve biological gradient information and avoid arbitrary dichotomization.

Electrocardiographic, Functional, and Echocardiographic Evaluation

Standard 12-lead electrocardiography performed during routine outpatient visits was

reviewed based on official clinical reports. Documented abnormalities included left ventricular hypertrophy, ST–T segment changes, fragmented QRS complexes, and prolonged corrected QT interval. Exercise treadmill testing was performed according to standard protocols at the discretion of the treating cardiologist, and achieved metabolic equivalents (METs) as well as the presence of ischemic ST-segment depression were recorded. Transthoracic echocardiography was conducted as part of routine clinical care, with reported diastolic dysfunction or other structural abnormalities extracted from formal reports.

Definition of Subclinical Cardiovascular Vulnerability

Subclinical cardiovascular vulnerability was defined as the presence of at least one abnormality across four predefined domains: inflammatory/biochemical, electrical, functional, and structural. This domain-based framework was adopted to capture early cardiovascular perturbations detectable during routine outpatient practice. Operational definitions and domain criteria are detailed in Table 2.

Table II: Domain-Based Definition of Subclinical Cardiovascular Vulnerability

Domain	Definition
Inflammatory / Biochemical	Elevated hs-CRP (≥2 mg/L) and/or abnormal lipid profile
Electrical	LVH, ST–T abnormalities, fragmented QRS, QTc prolongation on ECG
Functional	Reduced exercise capacity and/or ischemic ST-segment depression
Structural	Diastolic dysfunction or other structural abnormality on echocardiography

Abbreviations: ECG, electrocardiography; hs-CRP, high-sensitivity C-reactive protein; LVH, left ventricular hypertrophy; QTc, corrected QT interval.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the ethics Committee (meeting date: December 3, 2025; decision number: 163). The study was conducted in accordance with the principles of the Declaration of Helsinki. This investigation was designed as a retrospective observational analysis based on routinely collected and anonymized clinical data. No additional diagnostic procedures or interventions were performed for study purposes. Informed consent was waived by the ethics committee due to the retrospective nature of the study and use of de-identified data.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as counts and percentages. Between group comparisons were performed using Student's t-test or Mann–Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. To avoid over parameterization and enhance clinical interpretability, a parsimonious modeling strategy was applied. Candidate variables were selected based on clinical relevance and univariable associations with the study outcome. Particular attention was paid to minimizing redundancy among closely related variables during model construction. The primary objective of the modelling strategy was to identify clinically relevant determinants within the predefined phenotype framework rather than to develop a prognostic prediction model. The purpose of the multivariable analysis was not to develop a predictive risk model for an external outcome but to identify the relative contribution of individual components within the predefined subclinical cardiovascular phenotype framework. Accordingly, the analysis was intended to explore the clinical prominence of phenotype-related factors rather than establish causal relationships. Adjusted odds ratios with 95% confidence intervals were reported. Results of the multivariable model are presented in Table

3, and dominant determinants are visualized using a forest plot (Figure 1). A two-sided p value <0.05 was considered statistically significant.

RESULTS

Study Population

The study population consisted of 476 consecutive cardiology outpatients classified as clinically low risk. The mean age was 49.8 ± 11.6 years, and 52.1% of patients were male. Hypertension and diabetes mellitus were present in 16.2% and 4.2% of the cohort, respectively. Elevated hs-CRP levels (≥2 mg/L) were observed in 35.1% of patients (Table 1).

Sex-Stratified Analysis

Sex-stratified analyses showed that age, hypertension, and diabetes mellitus were comparable between female and male participants. Male patients demonstrated significantly higher rates of current smoking, higher LDL cholesterol levels, and higher hs-CRP concentrations. Despite these differences in selected cardiovascular risk markers, the prevalence of subclinical cardiovascular vulnerability did not differ significantly between sexes (Supplementary Table S1).

Supplementary Table S1. Sex-stratified comparison of study participants

Variable	Female (n=228)	Male (n=248)	p-value
Age (years)	49.3 ± 11.8	50.2 ± 11.4	0.42
Hypertension, n (%)	34 (14.9)	43 (17.3)	0.49
Diabetes mellitus, n (%)	9 (3.9)	11 (4.4)	0.81
Current smoking, n (%)	22 (9.6)	54 (21.8)	<0.001
LDL-C (mg/dL)	126 ± 36	137 ± 36	0.002
hs-CRP (mg/L)	1.3 (0.7–2.6)	1.8 (0.9–3.5)	0.004
Subclinical cardiovascular vulnerability, n (%)	67 (29.4)	76 (30.6)	0.77

Prevalence of Subclinical Cardiovascular Vulnerability

Overall, 143 patients (30.0%) exhibited subclinical cardiovascular vulnerability, defined by the presence of at least one abnormal finding across inflammatory, electrical, functional, or structural domains (Table 2). Patients with subclinical vulnerability were older and more frequently male and demonstrated higher systolic blood pressure, body mass index, low-density lipoprotein cholesterol, and hs-CRP levels compared with those without vulnerability (all p<0.05).

Domain-Specific Findings

Electrical abnormalities and functional impairment were disproportionately represented among patients with subclinical cardiovascular vulnerability. Reduced exercise capacity and ischemic ST-segment depression during treadmill testing were significantly more prevalent in this group. Structural abnormalities, most commonly reported diastolic dysfunction, were also observed more frequently in vulnerable patients, albeit at a lower overall prevalence (Table 2).

Determinants of Subclinical Cardiovascular Phenotypes

Although multiple demographic, clinical, biochemical, and functional variables demonstrated associations with subclinical cardiovascular vulnerability, the strength of these associations was not uniform. In parsimonious multivariable analysis, a limited subset of variables emerged as clinically dominant determinants. Current smoking status, ischemic ST-segment depression during exercise testing, and elevated hs-CRP demonstrated the strongest independent associations with subclinical cardiovascular vulnerability (Table 3, Figure 1). Other variables, including age, blood pressure, lipid

parameters, body mass index, exercise capacity, and reported diastolic dysfunction, contributed more modestly to the overall risk profile.

Table III: Parsimonious Multivariable Logistic Regression Model Outcome: Subclinical Cardiovascular Vulnerability

Variable	Adjusted OR	95% CI	p value
Ischemic ST-segment depression	2.75	1.80–4.20	<0.001
Current smoking	2.10	1.45–3.05	<0.001
hs-CRP (per 1 mg/L)	1.22	1.12–1.34	<0.001

Odds ratios are adjusted for age and sex (data not shown). Variables were selected based on clinical relevance and effect size rather than statistical significance alone.

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

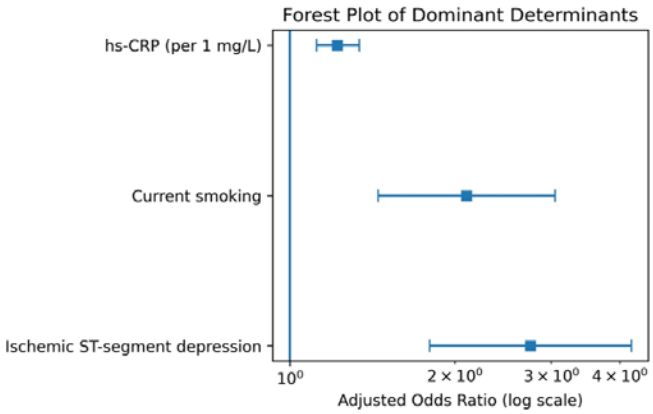

Figure 1. Forest Plot of Dominant Determinants of Subclinical Cardiovascular Vulnerability

CCTA Subgroup Analysis

Coronary computed tomography angiography was performed in a clinically selected subgroup of 32 patients. Among these individuals, those with elevated hs-CRP levels demonstrated a higher median Agatston coronary calcium score compared with patients with normal hs-CRP levels, providing an anatomic correlate of inflammatory activation. This analysis was considered exploratory and hypothesis generating.

DISCUSSION

In this real-world outpatient cohort, nearly one-third of patients classified as clinically low risk demonstrated evidence of subclinical cardiovascular vulnerability detectable using routine diagnostic tools. This observation reinforces prior epidemiological and imaging-based studies showing that atherosclerotic and myocardial disease processes begin long before the onset of overt clinical events and may remain clinically silent for extended periods (14–16). Importantly, our findings highlight that low estimated clinical risk does not necessarily exclude the presence of subclinical cardiovascular vulnerability.

A key finding of the present study is that although multiple demographic, biochemical, functional, and structural parameters were statistically associated with subclinical cardiovascular vulnerability, the magnitude and clinical relevance of these associations were not uniform. From a pragmatic clinical perspective, the critical issue is not the enumeration of numerous statistically significant predictors, but the identification of a limited number of key associated factors that capture the majority of clinically actionable vulnerability[17]. In our cohort, current smoking status, ischemic ST-segment depression during exercise testing, and elevated high-sensitivity C-reactive protein (hs-CRP) consistently emerged as the strongest contributors to the subclinical phenotype.

These key associated factors may reflect different but potentially complementary pathways of early cardiovascular vulnerability. Cigarette smoking is a well-established driver of endothelial dysfunction, oxidative stress, and inflammatory activation, accelerating both functional ischemia and atherosclerotic progression even in individuals without overt cardiovascular disease[18,19]. Exercise induced ischemic ST-segment depression reflects impaired coronary flow reserve and reduced myocardial functional reserve, which has been shown to predict adverse cardiovascular outcomes independent of traditional risk factors[20,21]. Elevated hs-CRP serves as an integrated marker of systemic inflammation

and has been repeatedly linked to early plaque development, endothelial dysfunction, and future cardiovascular events across diverse populations[22–24]. Notably, other variables commonly included in multivariable risk models such as age, blood pressure, lipid levels, body mass index, and mild diastolic dysfunction remained associated with subclinical cardiovascular vulnerability but contributed incrementally rather than dominantly to overall risk expression. While these factors are biologically relevant, their individual modification may not yield the same proportional clinical impact as targeted intervention in the dominant domains identified above. This distinction underscores the value of a parsimonious, phenotype oriented analytical framework in low-risk outpatient populations[25].

The exploratory coronary computed tomography angiography (CCTA) analysis provides supportive anatomic context for these observations. Although limited by small sample size and indication driven selection, patients with elevated hs-CRP demonstrated higher coronary calcium burden, consistent with prior reports linking systemic inflammation to subclinical coronary atherosclerosis[26,27]. These findings should be interpreted as biological validation rather than justification for routine imaging in low-risk individuals.

Several prior studies have emphasized the prognostic relevance of individual biomarkers or advanced imaging techniques in asymptomatic populations. However, such approaches may inadvertently promote exhaustive variable centered analyses that obscure clinical prioritization. By contrast, the present study emphasizes clinical dominance and interpretability over comprehensive statistical enumeration, aiming to identify signals most likely to influence real world preventive decision making[28].

This study has limitations that warrant consideration. Exercise treadmill testing and transthoracic echocardiography were performed according to routine clinical indications rather than a predefined study protocol. Consequently, a degree of selection bias cannot be excluded. Furthermore, the retrospective nature of the study may have resulted in incomplete availability of certain diagnostic data, which should be considered when interpreting the findings. Its retrospective design introduces potential residual confounding, and electrocardiographic and echocardiographic findings were derived from routine clinical reports without centralized adjudication. The CCTA findings are exploratory and hypothesis-generating. Additionally, external validation in independent cohorts will be required to confirm the generalizability of the identified dominant determinants. Nevertheless, the internal consistency of associations across biological, functional, and anatomic domains supports the coherence of the proposed subclinical cardiovascular phenotype framework. In addition, hs-CRP levels may be influenced by non-cardiovascular inflammatory or infectious conditions that could not be systematically assessed because of the retrospective study design. Therefore, residual confounding related to inflammatory status cannot be completely excluded[29].

In summary, our findings suggest that in patients traditionally classified as low risk, subclinical cardiovascular vulnerability is common and heterogeneously distributed across multiple domains. A small number of dominant, clinically actionable signals appear to account for a disproportionate share of this vulnerability. Incorporating phenotype-oriented interpretation of routine outpatient assessments may enhance early risk refinement and inform more targeted preventive strategies in contemporary cardiology practice[30].

CONCLUSION

In a routine cardiology outpatient population classified as clinically low risk, subclinical cardiovascular vulnerability is common and detectable using simple, widely available diagnostic assessments. The present study demonstrates that although numerous clinical, biochemical, functional, and structural variables may be associated with this vulnerability, their contribution is not uniform. A limited number of key clinically relevant factors particularly current smoking status, exercise-induced ischemic ST-segment depression, and elevated high sensitivity C-reactive protein appear to account for a disproportionate share of subclinical cardiovascular risk. Other associated factors contribute incrementally but do not meaningfully alter the overall vulnerability profile when considered in isolation. These findings support a phenotype-oriented, parsimonious approach to cardiovascular risk interpretation in low-risk outpatient populations. Focusing on a small number of key associated factors rather than exhaustive multivariable profiling may enhance clinical interpretability, improve early risk refinement, and help identify individuals who warrant closer preventive attention despite apparently reassuring traditional risk estimates.

Adjusted odds ratios (ORs) with 95% confidence intervals for dominant determinants of subclinical cardiovascular vulnerability. Odds ratios are adjusted for age and sex. The vertical line indicates an odds ratio of 1.0.

Ethics Committee Approval: The study protocol was reviewed and approved by the ethics Committee (meeting date: December 3, 2025; decision number: 163). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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