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Subclinical Myocardial Injury Identified by Cardiac Infarction/ Injury Score and the Risk of Mortality in Men and Women Free of Cardiovascular Disease

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Abstract

Previous studies have explored the ability of the Cardiac Infarction/Injury Score (CIIS) to identify individuals who are high-risk for cardiovascular disease (CVD) mortality. However, its prognostic significance among those without CVD in the United States general population has not been established. This analysis included 6,298 participants (mean age: 59 ± 13 years; 53% female; 51% non-whites) from the Third National Health and Nutrition Examination Survey (NHANES III), excluding participants with a history of CVD or electrocardiographic evidence of old myocardial infarction or ischemic ST depression at baseline. Subclinical myocardial injury was defined as CIIS ≥ 10. Mortality data were ascertained using the National Death Index. Cox proportional-hazards regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for association between subclinical myocardial injury with CVD and all-cause mortalities. Subclinical myocardial injury was detected in 1,376 (22%) participants. A total of 1,928 deaths occurred during a median of 14 years follow-up, of which 765 (40%) were due to CVD. In a multivariable model adjusted for demographics, traditional CVD risk factors, and other medical comorbidities, subclinical myocardial injury was associated with an increased risk of CVD (HR=1.26, 95% CI=1.02, 1.56) and all-cause (HR=1.42, 95% CI=1.23, 1.63) mortalities. In conclusion, subclinical myocardial injury in persons without manifestations of CVD is associated with an increased risk of CVD and all-cause mortalities. These findings highlight the important role of

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Disclosures

None.

CIIS to identify subclinical myocardial injury and its association with mortality among men and women in the United States.

Keywords

electrocardiography; mortality; epidemiology

INTRODUCTION

The Cardiac Infarction/Injury Score (CIIS) was developed as an electrocardiogram-based score to identify patients with previous myocardial infarction.¹ This score uses electrocardiogram features that often are missed with conventional criteria for the diagnosis of myocardial infarction/injury, such as abnormal T wave amplitude and direction. Previous studies have explored the ability of CIIS to identify individuals who are high-risk for cardiovascular disease (CVD) mortality.^{2–7} However, the prognostic significance of subclinical myocardial injury, as detected by CIIS, among individuals without apparent CVD in the general United States population has not been established. Therefore, the purpose of this study was to examine the risk of mortality associated with subclinical myocardial injury using data from the Third National Health and Nutrition Examination Survey (NHANES III).

METHODS

NHANES is a periodic survey of a representative sample of the civilian non-institutionalized United States population. The purpose is to determine estimates of disease prevalence and the overall health status of the United States population. All participants gave written informed consent at the time of study enrollment. Participant characteristics, electrocardiogram methodology, and ascertainment of mortality in NHANES III have been previously published.^{8,9} Briefly, NHANES III baseline data were collected during an in-home interview and a subsequent visit to a mobile examination center between 1988 and 1994. Data collected during the in-home interview included demographic and medication information. Blood samples were obtained at mobile centers and basic laboratory values were recorded for each participant (total cholesterol, high-density lipoprotein (HDL) cholesterol, and plasma glucose). The present analysis included 6,298 participants who were free of baseline CVD and who had available baseline demographic, laboratory, medication, and mortality data. Exclusion of participants with CVD was determined by a self-reported history of heart attack and/or stroke, or electrocardiographic evidence of myocardial infarction or major ST/T depression by Minnesota Electrocardiogram Classification.¹⁰

Participant characteristics recorded during NHANES III were used in this analysis. Age, sex, race/ethnicity, and smoking history were self-reported. Medication history, including the use of antihypertensive agents and lipid-lowering therapies also were self-reported. Smoking was defined as current or former smoker. Blood pressure measurements were obtained and values used were average readings from 3 in-home measurements and 3 mobile center measurements. Body mass index was computed as the weight in kilograms divided by the

square of the height in meters. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, glycosylated hemoglobin A1c values ≥ 6.5 , or a history of diabetic medication use.

Standard 12-lead electrocardiograms were recorded using a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin) by trained technicians during each participants' visit to a mobile examination center. Computerized automated analysis of the electrocardiographic data was performed with visual inspection of outlier values by a trained technician in a central electrocardiogram core laboratory. The calculation of the CIIS and methodology have been previously described.¹ Briefly, the score is defined by a set of 11 discrete features in combination with 4 features measured in continuum and provides a simple scoring scheme suitable for both visual and computer classification of the conventional 12-lead electrocardiogram. By design, CIIS values were multiplied by a factor of 10 in NHANES III to avoid using decimal points. We divided the reported CIIS values by 10. Subclinical myocardial injury was defined as CIIS values ≥ 10 , representing the limit for borderline abnormal CIIS.¹

Mortality data for NHANES III participants were available through December 31, 2006 and methods for mortality ascertainment have been described.¹¹ A probabilistic matching algorithm based on 12 identifiers was used to link participants with death information captured in the National Death Index. Matching identifiers included social security number, gender, and date of birth. Follow-up was defined as the interval between the NHANES III examination and either of the following, depending on whichever came first: date of death, date of censoring, or December 31, 2006. The end-points of CVD and all-cause mortalities were examined and analyzed using data from the NHANES III Linked Mortality File. International Classification of Diseases, Tenth Revision codes were used to identify each endpoint. CVD mortality was defined by codes 100–178. When censoring at the time of death occurred and did not include CVD, participants were grouped as all-cause mortality. Participants who were unable to be matched with a death record were considered to be alive through the entire follow-up period.

Continuous variables were reported as mean $\pm$ standard error while categorical variables were reported as frequency and percentage. Statistical significance for continuous variables was tested using the t-test procedure and the Rao Scott chi-square method for categorical variables. Unadjusted CVD and all-cause mortality rates (per 1,000 person-years) were calculated. Kaplan-Meier estimates were used to compute unadjusted survival estimates for CVD and all-cause mortalities and the differences in estimates were compared using the log-rank procedure.¹² Cox proportional-hazards regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between subclinical myocardial injury and CVD and all-cause mortalities. Additionally, CIIS scores were analyzed as a continuous variable per 5-unit increase in CIIS. Multivariable models were constructed with incremental adjustments as follows: Model 1 adjusted for age, sex, race/ethnicity; Model 2 adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, antihypertensive medication use, and lipid-lowering medication use. We tested for interactions between our main effect variable and age (dichotomized at 65 years), sex, and race/ethnicity (whites vs. non-white). We also constructed a restricted cubic spline model to examine the graphical relationship between

each endpoint and CIIS, and incorporated knots at the 5th, 50th, and 95th percentiles.¹³ The proportional hazards assumption was not violated in our analysis. Statistical significance was defined as $p \leq 0.05$. Data were analyzed using SAS Version 9.3 (Cary, NC). All analyses accounted for the complex sampling design of NHANES by including recommended sample weights.⁹

RESULTS

A total of 6,298 study participants (mean age 59 ± 13 years; 53% female; 49% white; 22% black; 24% Mexican; 4.3% other) were included in this analysis. Baseline characteristics for study participants stratified by subclinical myocardial injury are shown in Table 1. Participants with subclinical myocardial injury were more likely to be older, white, a current or former smoker, diabetic, and to take antihypertensive medications compared with those without subclinical myocardial injury. Additionally, subclinical myocardial injury was associated with higher values for body mass index, systolic blood pressure, and total cholesterol.

Over a median follow-up of 14 years, there were 1,928 all-cause and 765 (40%) CVD deaths. Incidence rates stratified by subclinical myocardial injury are shown in Table 2. As shown, the incidence rates for CVD and all-cause mortalities were higher among participants with subclinical myocardial injury ($p < 0.0001$). Unadjusted Kaplan-Meier survival estimates are shown for CVD (Figure 1A) and all-cause (Figure 1B) mortalities.

In an unadjusted Cox proportional-hazard regression analysis, subclinical myocardial injury was associated with more than double the risk of CVD and all-cause mortalities. The increased risk of mortality persisted after adjustment for demographics and potential confounders. The presence of subclinical myocardial injury was associated with a 26% ($p = 0.030$) and 42% ($p < 0.0001$) increased risk of CVD and all-cause mortalities, respectively (Table 3). When CIIS was examined as a continuous variable, each 5-unit increase was associated with an 8% ($p = 0.0036$) and 12% ($p < 0.0001$) increased risk of CVD and all-cause mortalities, respectively (Table 3). We observed a dose-response relationship between CIIS and the risk of CVD and all-cause mortalities. Figure 2 shows the association of CIIS with CVD (Figure 2A) and all-cause (Figure 2B) mortalities across the continuum of CIIS values. The risk of both endpoints was noted to increase with increasing CIIS values.

These results were generally consistent across subgroups of age, sex, and race/ethnicity. There was a significant interaction between subclinical myocardial injury and age for all-cause mortality in the fully adjusted model, with the strength of association being relatively stronger in younger compared with older participants (interaction $p = 0.0010$) (Table 4).

DISCUSSION

In this nationally representative sample from NHANES III, subclinical myocardial injury, defined by CIIS values (CIIS ≥ 10), was associated with an increased risk of CVD and all-cause mortalities among individuals without CVD. This association persisted despite rigorous adjustment for confounders. The association of subclinical myocardial injury and

CVD mortality also was consistent across subgroups of age, race, and sex, thereby underscoring the importance of the nationally representative cohort of NHANES.

The association between subclinical myocardial injury and all-cause mortality was higher in younger compared with older participants. The differential prediction of CIIS by age has been reported. In the Zutphen Study, CIIS was shown to predict incident angina and myocardial infarction among middle-aged but not elderly men.³ Additionally, coronary artery calcium, a marker of subclinical atherosclerosis, in younger individuals is associated with a higher risk of all-cause mortality when compared with older persons.¹⁴ Increased CIIS scores, similar to increased levels of coronary artery calcium, in younger persons likely represent aggressive subclinical atherosclerosis that increase one's susceptibility to adverse outcomes.

Previous epidemiologic studies have shown the association of CIIS with mortality.²⁻⁷ However, few studies have examined this association among individuals who are free of CVD or among populations with racial diversity. For example, 2 studies from the Netherlands have shown that CIIS is associated with CVD events (e.g., coronary heart disease and CVD mortality) among healthy men and women.^{2,3} Another study has shown that CIIS is associated with an increased risk of sudden cardiac death among patients who are treated for hypertension.⁴ Our examination of CIIS using NHANES III data shows the utility of CIIS to predict CVD and all-cause mortalities among individuals without apparent CVD in a diverse population that is representative of the general United States population. To our knowledge, this has not been previously reported.

The CIIS may be a more sensitive indicator of myocardial injury than other electrocardiogram markers that only rely on 1 or 2 data points, such as QRS duration or minor Q waves, which also are associated with increased mortality.^{15,16} Although many individual electrocardiogram variables predict mortality, a large number of persons with subclinical myocardial injury will be missed if abnormalities are examined separately. The application of a scoring system, such as CIIS, to identify at-risk individuals was shown in this study as a large group of persons without clinical CVD had an increased risk of CVD and all-cause mortalities.

The CIIS system improves the accuracy of the standard 12-lead electrocardiogram to identify persons with subclinical myocardial injury.⁵ With the increasing prevalence of comorbid conditions in the general population and improvement in cardiac imaging techniques, the importance of identifying subclinical myocardial injury and silent ischemia has become more apparent.¹⁷⁻¹⁹ Those identified to have subclinical myocardial injury likely have clinically undetectable atherosclerosis and warrant more aggressive medical and lifestyle interventions. Also, the increased risk of mortality associated with these electrocardiographic abnormalities may have public health implications as we target appropriate interventions to reduce the burden of CVD in the United States.

Due to its low-cost and widespread availability, the electrocardiogram potentially is a cost-effective tool for identifying individuals with subclinical myocardial injury who do not have known heart disease. With the increasing cost of cardiac imaging, techniques such as CIIS

need to be further examined as they are non-invasive and do not expose patients to harmful radiation.²⁰ Additionally, the electrocardiogram and scores similar to CIIS may soon regain popularity as clinicians strive for more cost-effective ways to identify patients who are high-risk for CVD outcomes instead of perpetuating the overutilization of high-cost imaging modalities.²¹

This study has several limitations. We examined the association of baseline electrocardiogram data with mortality over a relatively long period. Potentially, changes in participants' health behaviors (e.g., smoking, exercise) and overall health influenced their mortality. We adjusted for several covariates that are known to influence survival, however residual confounding remains a possibility. Several covariates included in our model are time-dependent and may change with time (e.g., improvement in systolic blood pressure with lifestyle modification). Also, covariates such as smoking were self-reported and subjected our analysis to recall bias. Furthermore, although CVD mortality was confirmed by International Classification of Diseases codes, misclassification of the primary cause of death remains a possibility.

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Figure 1. Unadjusted Kaplan-Meier Survival Estimates for Mortality by Subclinical Myocardial Injury*

*Kaplan-Meier estimates presented for CVD (A) and all-cause (B) mortalities were significantly different (log-rank $p < 0.0001$). Subclinical myocardial injury defined by CIIS 10.

CIIS=cardiac infarction/injury score; CVD=cardiovascular disease.

Figure 2.

Risk of Mortality by Cardiac Infarction Injury Score*

*Hazard ratios for CVD (A) and all-cause (B) mortalities are shown. Each hazard ratio was generated with the median CIIS value of 2.2 as the reference and was adjusted for age, sex, and race/ethnicity. Dotted-lines represent the 95% confidence interval.

CIIS=cardiac infarction/injury score; CVD=cardiovascular disease.

Table 1

Baseline Characteristics by Subclinical Myocardial Injury

Variable	Subclinical Myocardial Injury*		P-value [†]
	Absent (n=4,922)	Present (n=1,376)	
Age, mean (SE) (years)	54 (0.32)	59 (0.64)	<0.0001
Male Sex	2,239 (45%)	690 (50%)	0.94
Race/Ethnicity			
White	2,369 (48%)	745 (54%)	
Black	1,080 (22%)	309 (22%)	
Mexican	1,230 (25%)	294 (21%)	
Other	243 (4.9%)	28 (2.0%)	<0.0001
Current or former smoker	2,594 (53%)	825 (60%)	<0.0001
Body mass index, mean (SE) (kg/m ²)	27 (0.11)	28 (0.36)	<0.0001
Diabetes mellitus	641 (13%)	261 (19%)	<0.0001
Systolic blood pressure, mean (SE) (mm Hg)	126 (0.33)	131 (0.95)	<0.0001
Total cholesterol, mean (SE) (mg/dL)	216 (0.94)	220 (2.0)	0.0003
HDL-cholesterol, mean (SE) (mg/dL)	51 (0.50)	51 (0.75)	0.69
Antihypertensive medication use	892 (18%)	353 (26%)	<0.0001
Lipid-lowering medication use	147 (3.0%)	39 (2.8%)	0.20
CVD Mortality	516 (11%)	249 (18%)	<0.0001
All-Cause Mortality	1,325 (27%)	603 (44%)	<0.0001

* Subclinical myocardial injury defined by CIIS 10.

[†] Statistical significance was tested for continuous variables using the t-test procedure and for categorical variables using the Rao-Scott Chi-square method.

CIIS=cardiac infarction/injury score; CVD=cardiovascular disease; HDL=high-density lipoprotein; SE=standard error.

Table 2

Incidence Rates for Mortality by Subclinical Myocardial Injury*

	Events/No. at risk	Incidence Rate per 1,000 person-years (95%CI)	Incidence Rate Ratio (95%CI) †
Cardiovascular Disease Mortality			
No Subclinical Myocardial Injury	516/4,922	7.88 (7.23, 8.59)	1.0
Subclinical Myocardial Injury	249/1,376	14.90 (13.16, 16.87)	1.89 (1.63, 2.20)
All-Cause Mortality			
No Subclinical Myocardial Injury	1,325/4,922	20.23 (19.17, 21.35)	1.0
Subclinical Myocardial Injury	603/1,376	36.09 (33.32, 39.08)	1.78 (1.62, 1.96)

* Subclinical myocardial injury defined by CIIS = 10.

† Incidence rate ratios calculated with no subclinical myocardial injury as the reference group.

CIIS=cardiac infarction/injury score; CI=confidence interval.

Table 3

Risk of Mortality by Subclinical Myocardial Injury*

	Events/No. at risk	Model 1 [†] HR (95%CI)	Model 2 [‡] HR (95%CI)
Cardiovascular Disease Mortality			
No Subclinical Myocardial Injury	516/4,922	1.0	1.0
Subclinical Myocardial Injury	249/1,376	1.38 (1.12, 1.69)	1.26 (1.02, 1.56)
CIIS per 5-unit increase	765/6,298	1.10 (1.05, 1.16)	1.08 (1.03, 1.14)
All-Cause Mortality			
No Subclinical Myocardial Injury	1,325/4,922	1.0	1.0
Subclinical Myocardial Injury	603/1,376	1.52 (1.31, 1.76)	1.42 (1.23, 1.63)
CIIS per 5-unit increase	1,928/6,298	1.14 (1.09, 1.18)	1.12 (1.08, 1.17)

* Subclinical myocardial injury defined by CIIS ≥ 10 .

[†] Adjusted for age, sex, and race/ethnicity.

[‡] Adjusted for Model 1 covariates plus systolic blood pressure, body mass index, total cholesterol, HDL-cholesterol, diabetes, smoking, antihypertensive medication use, and lipid-lowering medication use.

CIIS=cardiac infarction/injury score; CI=confidence interval; HR=hazard ratio.

Table 4

Risk of Mortality Stratified by Age, Sex, and Race/Ethnicity*

Events/No. at risk		Model 1 [†] HR (95%CI)	Model 2 [‡] HR (95%CI)	Interaction P-value ^{//}
Cardiovascular Disease Mortality				
Age				
65 years	221/4,318	1.78 (1.17, 2.71)	1.29 (0.84, 1.98)	0.41
>65 years	544/1,980	1.44 (1.14, 1.82)	1.35 (1.06, 1.72)	
Sex				
Female	393/3,369	1.30 (1.01, 1.67)	1.22 (0.92, 1.61)	0.78
Male	372/2,929	1.48 (1.04, 2.10)	1.34 (0.92, 1.94)	
Race/Ethnicity				
White	450/2,664	1.33 (1.05, 1.69)	1.22 (0.96, 1.55)	0.30
Non-White	315/3,184	1.62 (1.18, 2.23)	1.49 (1.09, 2.05)	
All-Cause Mortality				
Age				
65 years	660/4,318	2.13 (1.71, 2.64)	1.78 (1.42, 2.23)	0.0010
>65 years	1,268/1,980	1.45 (1.25, 1.68)	1.34 (1.17, 1.53)	
Sex				
Female	921/3,369	1.53 (1.27, 1.85)	1.43 (1.18, 1.74)	0.64
Male	1,007/2,929	1.50 (1.22, 1.85)	1.43 (1.17, 1.74)	
Race/Ethnicity				
White	1,086/3,114	1.53 (1.30, 1.80)	1.43 (1.22, 1.66)	0.56
Non-White	842/3,184	1.41 (1.13, 1.76)	1.32 (1.05, 1.65)	

* HR presented for subclinical myocardial injury defined by CIIS = 10.

[†] Adjusted for age, sex, and race/ethnicity.[‡] Adjusted for Model 1 covariates plus systolic blood pressure, body mass index, total cholesterol, HDL-cholesterol, diabetes, smoking, antihypertensive medication use, and lipid-lowering medication use.^{//} Interactions tested using Model 2.

CIIS=cardiac infarction/injury score; CI=confidence interval; HR=hazard ratio.