

# Predictive Value of Global Plaque Burden Nomograms Estimated by Conventional Computed Tomography Scan

*Valor pronóstico de los nomogramas de carga global de placa coronaria estimada por tomografía computada convencional*

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## ABSTRACT

**Background:** Coronary artery calcification, of established predictive value, can be assessed by conventional chest computed tomography (CT).

**Objective:** To assess the prognostic value of nomograms for global plaque burden applied to data obtained by conventional chest CT scan.

**Methods:** Consecutive patients between 40 and 74 years undergoing clinically indicated conventional chest CT scan at our institution were included between August and December 2012. The presence and extent of coronary artery calcifications was evaluated and the patients were grouped according to age- and sex-adjusted percentiles of segment involvement score (CACSIS).

**Results:** A total of 1,194 patients were included in the study. After a mean follow-up of  $3.7 \pm 0.5$  years, 53 (4.4%) patients died. There was a significant association between sex- and age-adjusted survival rates and CACSIS (RR 1.27; 95% CI, 1.01-1.60,  $p=0.040$ ).

**Conclusions:** Age-adjusted nomograms for global atherosclerotic plaque burden applied to conventional chest CT scan were predictors of mortality.

**Keywords:** Computed tomography - Vascular Calcification - Atherosclerosis - Chest

## RESUMEN

**Introducción:** La calcificación coronaria, de valor pronóstico establecido, puede valorarse por tomografía computada (TC) de tórax convencional.

**Objetivo:** Explorar el valor pronóstico de los nomogramas de carga global de placa aterosclerótica aplicados a datos obtenidos de la TC de tórax convencional.

**Material y métodos:** Incluimos pacientes consecutivos de 40 a 74 años que se sometieron a una TC de tórax en nuestra institución entre agosto y diciembre de 2012 por diversas indicaciones. Se evaluó la presencia y extensión de calcificaciones coronarias y los pacientes fueron clasificados según el percentil de la puntuación de afectación de segmento (CACSIS) por edad y sexo.

**Resultados:** Se incluyeron 1194 pacientes. Tras un seguimiento medio de  $3.7 \pm 0.5$  años, 53 (4.4%) pacientes fallecieron. Se identificó una relación significativa entre las tasas de sobrevida ajustadas según sexo y edad y el percentil de la puntuación de afectación de segmento [RR 1.27 (95% IC 1.01-1.60),  $p=0.040$ ].

**Conclusiones:** Los nomogramas de carga de placa aterosclerótica global ajustados por edad aplicados a la TC de tórax convencional fueron predictores de mortalidad.

**Palabras clave:** Tomografía computarizada - Calcificación vascular - Aterosclerosis - Tórax

## Abbreviations

|        |  |     |                           |
|--------|--|-----|---------------------------|
| CTCA   | Computed tomography coronary angiography           | SIS | Segment involvement score |
| CAC    | Coronary artery calcification                      | TC  | Computed tomography       |
| CACSIS | Coronary artery calcification assessment using SIS |     |                           |

## INTRODUCTION

The relevance of global atherosclerotic plaque burden over the severity of coronary artery stenosis has gained considerable interest due to the evidence provided by studies using invasive coronary angiography

and computed tomography coronary angiography (CTCA). Several studies have identified a group of high-risk patients previously overlooked, defined as those patients with extensive nonobstructive coronary artery disease. (1-4) Multiple scores, mostly calculated

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using CTCA, have been reported since the seventies to evaluate the extent of coronary artery disease reflecting a risk continuum. The segment involvement score (SIS) has emerged as the best score of global atherosclerotic burden based on CTCA, and has been identified as a robust predictor of adverse events. (2, 3, 5-7) Coronary artery calcification (CAC) is strongly associated with atherosclerotic burden, age and sex, and can be determined by visual estimation using non-gated conventional chest computed tomography (CT) which has similar prognostic value as gated calcium score. (8) In a recent study, we demonstrated the feasibility and prognostic value of CAC using SIS (CACSIS) in patients undergoing clinically indicated conventional chest CT scan. (9) However, the prognostic value of age- and sex-adjusted CACSIS remains unclear. The aim of this study was thus to explore the prognostic value of recently developed age- and sex-specific SIS nomograms (10) to the CACSIS estimated by conventional chest CT scan.

## METHODS

We included consecutive patients aged between 40 and 74 years undergoing clinically indicated non-enhanced conventional chest CT scan between August and December 2012 due to non-malignant pulmonary disease, respiratory symptoms of unknown etiology, nonmalignant nonrespiratory disease and nonrespiratory symptoms of unknown etiology. Patients with malignancies, metal devices implanted in the thorax, previous revascularization and multiple trauma were excluded from the analysis. In case of repeated scans, only the first one was included. There was no information about the presence of coronary risk factors as the patients were referred for chest CT scans due to symptoms not related with coronary artery disease. All-cause mortality was evaluated until September 2016, and those patients lost to follow-up were excluded. The details about the methods of image acquisition and analysis have been previously reported. (9) Briefly, the CACSIS was evaluated according to the modified classification of the American Heart Association. (7) Patients were classified using the following recently published age- and sex-adjusted CACSIS percentiles: CACSIS 0; ≤50th percentile CACSIS; 50–74th percentile CACSIS and >75th percentile CACSIS (10).

## Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical package for Windows (Armonk, NY) and MedCalc Software (Ostend, Belgium). Continuous variables with normal

distribution were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The differences between groups were compared using the chi-square test. Cox proportional hazard models were used to analyze survival adjusted for sex and age. A p value < 0.05 was considered statistically significant.

## Ethical considerations

All the procedures were performed following the 1975 recommendations of the Declaration of Helsinki. An Ethics Committee's approval was separately obtained for the waiver of habeas data and for corroboration of death occurrence.

## RESULTS

A total of 1,194 patients were included in the study. Mean age was  $58.1 \pm 8.8$  years and 44% were men. The presence of coronary artery calcifications (CACSIS > 0) was identified in 594 (50%) patients. Mean extent of calcifications (number of segments with calcifications, CACSIS) was  $2.0 \pm 2.8$ . The population was divided into tertiles according to age (T1: 40-53 years; T2: 54-63 years; and T3: 64-74 years). Male patients presented evidence of CAC earlier than women and more frequent CAC in multiple vessels (Table). According to pre-established nomograms, 273 (23%) patients were in the > 75th percentile CACSIS and 120 (10%) in the 90th percentile CACSIS. After a mean follow-up of  $3.7 \pm 0.5$  years, 53 (4.4%) patients died. There was a significant association between sex- and age-adjusted survival rates and CACSIS [Figure, relative risk (RR) 1.27; 95% CI, 1.01-1.60,  $p=0.040$ ].

## DISCUSSION

The present study, which included patients with clinical indication of conventional chest CT scan, identified age- and sex-adjusted CACSIS (a surrogate of global atherosclerotic plaque burden) as predictor of all-cause mortality.

The identification of patients with extensive atherosclerotic burden, independently of the severity of coronary artery stenosis, has gained clinical relevance over the past 10 years due to consistent findings in several investigations using invasive and non-invasive methods demonstrating that extensive nonobstructive coronary artery disease is associated with significant risk of adverse events, similar to the one of extensive obstructive coronary artery disease. (1, 2)

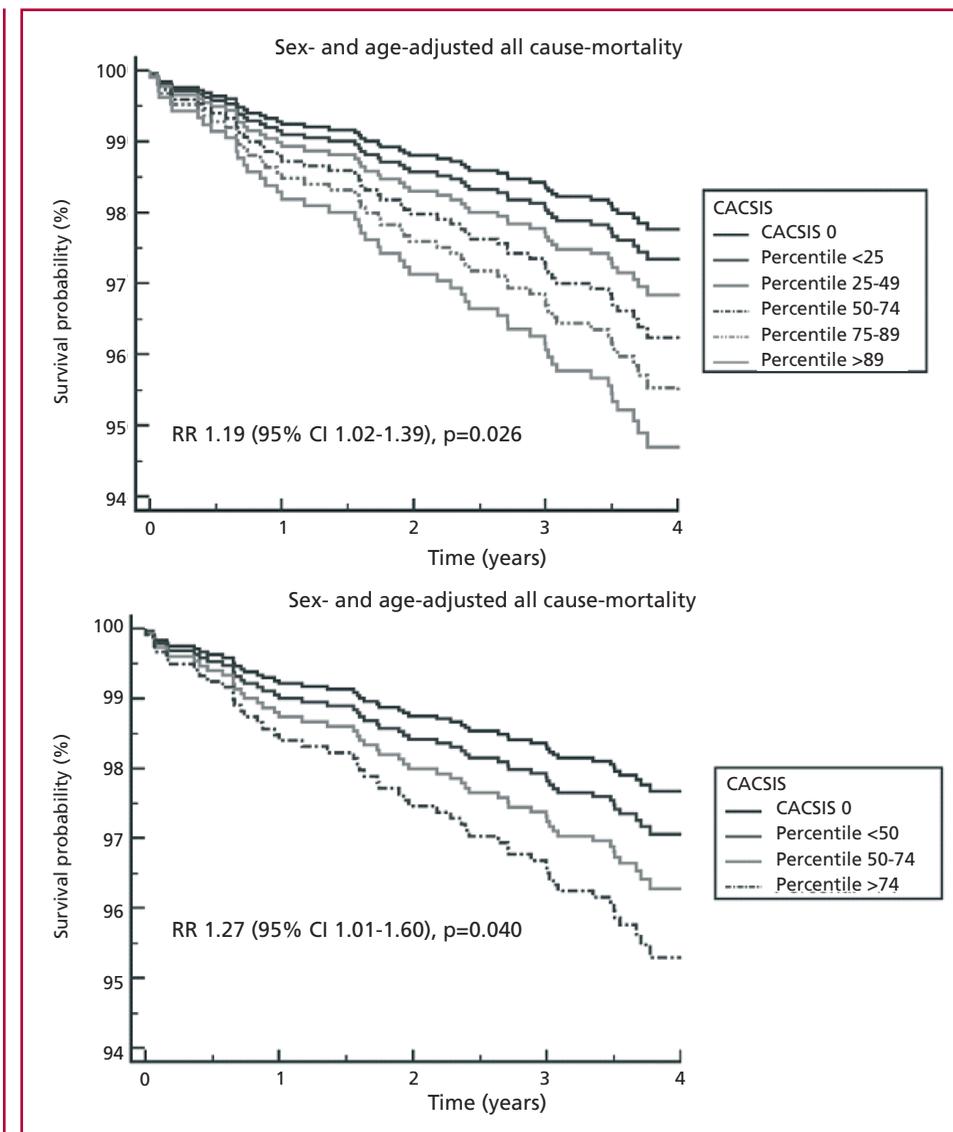
|                 | 45-53 years | 54-63 years | 64-74 years  |
|-----------------|-------------|-------------|--------------|
| Men (n = 528)   | n = 163     | n = 205     | n = 160      |
| CACSIS > 0      | 61 (37%)*   | 140 (68%)*  | 134 (84%)*   |
| CAC ≥ 2 vessels | 36 (22%)*   | 99 (48%)*   | 110 (69%)*   |
| Women (n = 666) | n = 208     | n = 242     | n = 216      |
| CACSIS > 0      | 27 (13%)    | 96 (40%)    | 136 (63%) 73 |
| CAC ≥ 2 vessels | 6 (3%)      | 49 (20%)    | (34%)        |

\* $p < 0,0001$  between sexes

CAC: Coronary artery calcification CACSIS: Extent of coronary artery calcification according to sex and age group.

**Table 1.** Presence of coronary artery calcification and extent of coronary calcification according to sex and age group.

**Fig. 1.** Survival curves according to sex- and age-adjusted percentile number of segments with calcifications (CAC SIS).



We have recently reported an association between CACSIS >5 evaluated with conventional chest CT scan and mortality. (9) However, as the extent of coronary artery disease is closely related with age and sex, CACSIS should be reported in percentiles, same as the CAC score. Despite our findings are hypothesis generators, they suggest the feasibility of extrapolating the data of nomograms derived from CTCA to those obtained with conventional chest CT in terms of prognostic value, and the importance of evaluating and reporting CAC in patients undergoing a conventional chest CT scan.

It should be pointed out that CACSIS, a surrogate of calcific atherosclerotic burden, might not indicate the likelihood of obstructive coronary artery disease assessed by CTCA. (6, 11) Despite our institution lacks the software to calculate CAC from non-gated scans, the National Lung Screening Trial did not find significant predictive differences between the Agatston score and a simple visual analysis. (8)

In conclusion, in this large cohort of consecutive patients with clinical indication of conventional chest CT scan, age- and sex-adjusted nomograms of global plaque burden derived from CTCA and applied to conventional chest CT scan were predictors of all-cause mortality.

#### Conflicts of interest

Dr. Patricia Carracosa is Consultant of GE Healthcare. None of the other authors have conflicts of interest to declare (See authors' conflicts of interest forms on the web/Supplementary material).

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