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Research Article

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Prospective History of Long-Term Mortality and Modes of Death in Patients Discharged After Acute Coronary Syndrome: The ABC-2* Study on Acute Coronary Syndrome

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Abstract

Background: The aim of this study was to examine the prognostic value of several clinical characteristics on long-term mortality and causes of death after acute coronary syndrome.

Methods: The ABC-2 study is a prospective investigation comprising 557 patients with acute coronary syndrome. During hospitalization, 33 clinical variables, including demographics, cardiovascular risk factors, in-hospital characteristics, and blood components, were examined. "Acute models" were survival models containing the variables accrued within 72 h from admission, and "sub-acute models" contained data accrued over a 7-day period. Cox regression models were used for the survival analysis.

Results: The 12-year follow-up study revealed that 51.2% of the patients died (15.8% of the patients died from coronary artery disease and/or heart failure, 12.6% of the patients experienced sudden death, 8.3% of the patients died from other-cardiovascular diseases, and 14.5% of the patients died from non-cardiovascular causes. The following factors were independently associated with all-cause mortality in both the acute and sub-acute models: age, left ventricular ejection fraction (negative), body mass index (non-linear), previous myocardial infarction, diabetes mellitus, blood glucose (non-linear), Killip class>1, albumin/creatinine ratio, and pre-hospital time delay. The variables associated with coronary artery disease and/or heart failure included age, left ventricular ejection fraction (negative), body mass index (non-linear), previous myocardial infarction, Killip class>1, albumin/creatinine ratio, and pre-hospital time delay, while the variables associated with sudden death included age, hypertension (negative), uric acid, left ventricular ejection fraction (negative), and pre-hospital time delay, and those associated with other- cardiovascular causes included age, hypertension, and albumin/creatinine ratio. The only variable associated with non- cardiovascular mortality was age. The C-statistic of the predictive models was 0.86 for all-cause mortality, whereas the C-statistic ranged from 0.74 to 0.80 for cardiovascular causes.

Conclusions: The ABC-2 study revealed clinical predictors of long-term mortality after acute coronary syndrome that might help prognostication, patient education, and risk modification. Furthermore, the results showed that the modes of death are independently associated with different baseline clinical features.

Keywords

Acute coronary syndrome; Mortality; Risk prediction; Survival analysis (*ABC is acronym for Adria, Bassano, Conegliano, and Padova Hospitals)

Introduction

Although the treatments used in the last decades have improved the prognosis of patients with acute coronary syndrome (ACS), major adverse events, and death have been observed in many of these patients [1-4]. Furthermore, much of the increased cardiovascular (CV) risk associated with ACS remains unexplained [2,5]. Several studies have contributed to our understanding of the characteristics that predict death. However, most of them focused on predictors of death during index hospitalization or the first year after ACS, and few ones have examined long-term mortality [6-8]. Furthermore, most of these studies assessed only a few clinical factors simultaneously [7]. To achieve broad applicability and avoid emphasis on individual risk factors rather than the overall risk, the risk assessment should consider a reasonable number of potentially relevant prognostic indicators derived from unselected samples of patients [9]. Indeed, the examination of the causes of death could be useful for risk stratification and pathophysiological inferences [10,11]. To our knowledge, there have been no other studies concerning the long-term causes of death in patients after ACS.

The aim of the present study was to examine the prognostic value of baseline clinical characteristics associated with long-term mortality and causes of death in an unselected sample of ACS patients discharged alive after index hospitalization.

Methods

Patients

The Adria, Bassano, Conegliano, and Padova Hospital Study on Acute Coronary Syndrome (the ABC-2 Study on ACS) is an ongoing an ongoing, prospective investigation reflecting an unbiased population of ACS patients. The sample includes Caucasian patients with definite ACS (ST elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina [UA], admitted to the intensive care units at Adria, Bassano, and Conegliano Hospitals between June 21, 1995 and January 19, 1998. The original aim of the ABC study was to examine the natural history of a sample of unselected, consecutive ACS patients and evaluate the prognostic value of a number of baseline clinical features. The criteria for the diagnosis of ACS included the clinical presentation, electrocardiogram (ECG) findings, and the identification of serum biochemical necrosis markers. Specifically, acute myocardial infarction is defined as the typical rise and gradual decline of creatine kinase MB expression, accompanied by at least one of the following conditions: ischemic symptoms, development of pathologic ECG Q waves, and ECG changes indicative of ischemia (i.e., ST segment

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elevation or depression). UA is considered as the occurrence of one or more episodes of angina at rest during the preceding 48 h, corresponding to Braunwald class III, with ECG changes indicative of ischemia [2]. The ACS type was examined as a dichotomic variable, based on absence/presence of ST elevation ACS. A total of 778 eligible patients were considered upon admission (Figure 1). Among these, 47 patients had diseases other than coronary artery disease (CAD), and 53 patients had CAD, but not ACS; these patients were excluded from the study. Forty-five patients were excluded from the study for concomitant conditions potentially affecting the investigated variables (Figure 1). Thirty-four additional patients were excluded for other reasons, as shown in Figure 1. Forty-two of the enrolled patients died during index hospitalization and were excluded from the present analysis. Hence, the post-discharge follow-up study included 557 patients (Figure 1). Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. Written informed consent was obtained from all enrolled patients, and the study was approved through the hospital ethics committee.

Measurements

Upon enrollment, a thorough patient history was obtained from medical records and patient interviews. All baseline clinical and laboratory data reported in the present study were obtained during

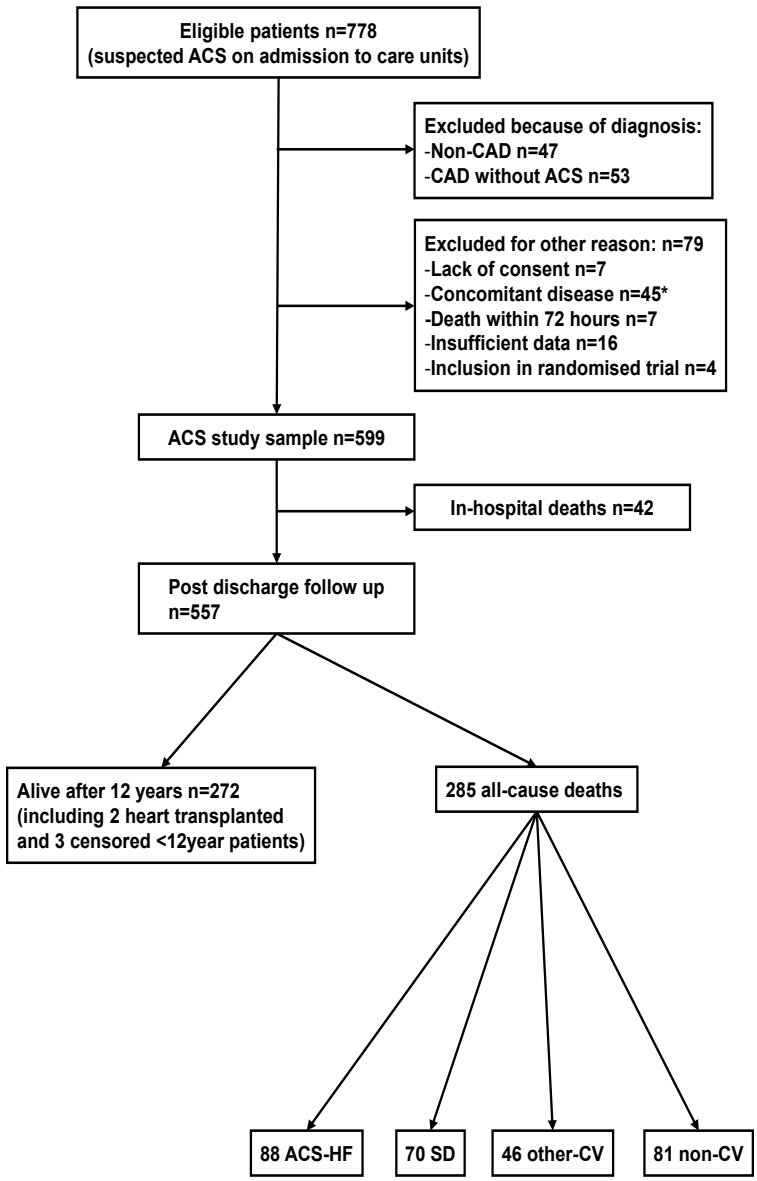

Figure 1: Flow diagram of subject progress during follow-up. ACS indicates Acute Coronary Syndrome, CAD indicates Coronary Artery Disease, CV, cardiovascular, HF indicates Heart Failure, and SD indicates Sudden Death.
*The exclusion criteria included chronic renal failure, with a documented history of estimated glomerular filtration rate (eGFR) <1.0 mL/s/1.73 m² for 3 months, with or without kidney damage, or dialysis treatment (n=7); nephrotic proteinuria (n=2); concomitant acute infection (n=19); myocardial re-infarction within 3 days of admission (n=5); surgical treatment for bone fractures (n=3); recent surgery (n=2); systemic lupus erythematosus (n=1); menstrual flow (n=1); neoplastic disease (n=5); death within 3 days of admission (n=7); or insufficient data (n=16).

the first 7 days of hospitalization in the Intensive Coronary Care Unit. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher diastolic blood pressure of 90 mm Hg or higher the use of at least one class of anti-hypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dL or higher the use of insulin or at least one oral hypoglycemic agent. Patients with cholesterol levels of 240 mg/dL or higher those taking lipid-lowering agents were classified as hyperlipidemic. The body mass index was calculated as kg body weight/m^2 body height. Upon admission, and every 4 h thereafter, the serum enzyme levels were recorded, and a 12-lead ECG test was performed. The venous blood was drawn for biochemical determinations. The blood pressure and heart rate were measured between 7 and 8 a.m., and the mean value of three recordings was used in the analyses. The presence and degree of heart failure were assessed according to the Killip classification [12]. The presence of atrial fibrillation/flutter, ventricular tachy- and brady-arrhythmias was recorded during the first week of hospitalization. Left ventricular ejection fraction (LVEF) was assessed using two-dimensional echocardiography according to Simpson's method [13]. The LVEF was not obtained for 81 patients who underwent echocardiography after discharge from the intensive care units or possessed technically inadequate echocardiographic images. Two physicians, with no knowledge of the patient clinical data, examined the records. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [14]. The albumin excretion was measured in 24-h urine samples using a radioimmunoassay, and the data were expressed as the ratio of albumin to creatinine (ACR) [15].

Follow-up and outcomes

At one, three, five, seven, ten, and twelve years after recruitment, each patient underwent a clinical check-up. At each recruitment hospital, 2 cardiologists carefully performed a 12-year follow-up on the surviving cohort. The primary aim of this study was to determine the 12-year all-causes mortality and modes of death associated with ACS. Two researchers, with no knowledge of baseline patient data, examined the modes of death, which were classified into the following categories:

1) CAD and/or heart failure progression (CAD-HF).

2) Sudden death (SD) defined as witnessed, out-of-hospital death within 1 h after the onset of acute symptoms or unwitnessed, unexpected death (e.g., during sleep) in patients within the 24 h prior to the onset of symptoms [16].

3) Other cardiovascular (CV) causes and

4) non-CV causes. All data were obtained from scheduled examinations, public administrations, hospital records, family doctors, postmortem examinations, and death certificates. The medications administered during index hospitalization and follow-up treatments were also recorded. If a patient underwent heart transplantation, he/she was excluded from the primary survival analysis. He/she was only included in a secondary sub-analysis to verify the general results.

Statistical analysis

The measured variables were analyzed as both continuous variables in table and increasing quartile values (in other analyses) (Table 1). Log transformations were used to correct for positive-skewed distributions, as appropriate. Unpaired Student's t-test and Pearson's chi-square (χ^2) test were used to analyze measured and categorical variables, respectively. The Cox proportional hazard regression analysis was used to describe the influence of the variables on mortality during follow-up. If a patient dropped out before completing 12 years of follow up, her/his data were censored at that time. Scaled Schoenfeld residuals were used to test the proportionality assumption. The proportional-hazards assumption was verified for all variables ($p>0.30$). To avoid the exclusion of potentially significant predictors, the excluded variables were retested in the final model. Because ACS is a pathophysiologically dynamic process operating over time, the surviving models including variables accrued within 72 h after admission, were referred to as "acute models", and those including variables accrued at 7 days after admission were called "sub-acute models". The variables were tested for co linearity. All variables were assessed for conformity to increasing (or decreasing) gradients to determine whether the association between a variable and an outcome produced a non-linear, J/U-shaped trend. If a variable showed a J/U shape, the non-linear hazard was estimated by adding to the Cox model the quadratic term of the variable, beside the untransformed variable [11]. The discriminative power of the final parsimonious models was determined as the area under the receiver operating characteristic curve, also called the C-statistic, which evaluates the ability of a model to accurately classify events. The Hosmer-Leme show test was used to assess model calibration. The baseline characteristics were summarized using median values and interquartile ranges for continuous variables and numbers and percentages for categorical variables. The International System of Units was used throughout the text. Unless otherwise indicated, two-tailed p values <0.05 were considered significant. The statistical analyses were performed using STATA 12 (College Station, Texas, USA) and JMP 8.0 (SAS Institute, Cary, NC, USA).

Results

Death rate

The 557 patients included in this study underwent a 12-year follow up, unless preempted by death, and three patients were excluded (two patients withdrew consent and one patient moved overseas). Among these, two patients underwent heart transplantation. After 12 years, 285 patients died (51.2%), and the entire sample represented 4587.2 person-years of follow-up. Among the deceased patients, 88 (15.8%) patients died from CAD-HF (reinfarction, n=31, heart failure, n=29, acute pulmonary edema, n=13, cardiogenic shock, n=5; in-hospital arrhythmic death, n=6; other cardiac cause, n=4). Seventy (12.6%) patients died from SD. Forty-six (8.3%) patients died from other CV causes (stroke, n=28; pulmonary embolism, n=5; fatal complication of coronary bypass surgery, n=3; other causes, n=10), and 81 (14.5%) patients died from non-CV causes (neoplastic disease, n=46; respiratory infection, n=7; non-neoplastic cachexia, n=5, other non CV causes, n=23).

The median (IQ) time to death was 4.2 (1.4-7.8) years for all-cause mortality, 3.1 (0.9-7.8) years for CAD-HF, 2.9 (0.8-5.1) years for SD, 3.3 (2.3-6.3) years for the other CV mortality, and 6.3 (3.1-9.5) years for non-CV mortality. Table 1 shows the clinical features of the patients, their primary treatments and the differences between deceased and surviving patients. Death was more frequently observed in older female patients. Most of the clinical characteristics were significantly different in dead patients compared with the survivors (Table 1).

Potential predictors of mortality, causes of death and influence of age and gender

Among the 33 clinical variables tested (Table 1), 26 variables were associated with all-cause mortality at univariable level. After adjusting for age and gender, only the following 10 variables were associated with all-cause mortality in both acute and sub-acute

Table 1: Baseline characteristics of the patients with acute coronary syndrome

Variable name	Overall Population (N=557)	Survivors (N=272)	Dead patients (N=285)	P value
Demographics				
Age (years)	67(58-74)	60(52-67)	72(66-78)	<0.0001
Gender (female)	29	20	37	<0.0001
Education (high school or above)	26	33	19	<0.0001
Coexisting conditions				
Current smoking	38	47	28	<0.0001
Physical activity	7	11	4	0.002
Hypertension	46	38	54	<0.0001
Hypercholesterolemia	27	29	25	0.19
Diabetes mellitus	21	14	29	<0.0001
Body mass index (Kg/m²)	26(24-28)	26(24-28)	25(23-28)	0.003
Alcohol use	74	77	72	0.12
Coffee use	88	91	84	0.008
Medical history				
Family coronary heart disease	26	30	23	0.03
History of angina	25	18	32	<0.0001
Previous myocardial infarction	24	16	32	<0.0001
In-hospital characteristics				
Pre-hospital time delay* (min) (n=465)	185(120-517)	175(110-311)	235(120-660)	<0.0001
Systolic blood pressure (mmHg)	117(106-127)	115(107-128)	122 (112-139)	0.002
Diastolic blood pressure (mmHg)	78(70-84)	80(71-83)	74(68-80)	0.43
Heart rate (beats/min)	70(60-78)	67(58-75)	72(64-83)	<0.0001
ST-elevation myocardial infarction	61	66	57	0.05
CK MB-peak (U/L)*	103(43-207)	106(40-228)	99(44-193)	0.86
Killip class > 1	32	18	46	<0.0001
Tachy-arrhythmias † ‡	20	17	22	0.15
Brady-arrhythmias † ‡	7	8	6	0.18
Atrial fibrillation/flutter †	10	5	15	<0.0001
LVEF (%) (n=476)	52(45-60)	59(50-64)	39(49-57)	<0.0001
Thrombolysis	35	47	25	<0.0001
Blood components				
Hemoglobin (g/L)	137(126-147)	138(129-148)	135(124-146)	0.01
Blood glucose (mmol/L)	6.6(5.5-8.8)	6.5(5.5-8.1)	6.9(5.7-10.2)	<0.0001
Total cholesterol (mmol/L)	5.4(4.6-6.3)	5.5(4.8-6.4)	5.3(4.4-6.1)	<0.0001
Uric acid (µmol/L)	327(274-393)	315(256-369)	345(285-416)	<0.0001
Potassium (mEq/L)	4.1(3.8-4.4)	4.1(3.8-4.4)	4.1(3.8-4.4)	0.009
Sodium (mEq/L)	140(138-142)	140(138-142)	140(138-142)	0.78
Kidney and endothelial function				
eGFR (mL/s x 1.73 m²) *	1.2(1.0-1.4)	1.3(1.2-1.5)	1.1(0.9-1.3)	<0.0001
ACR (mg/mmol) *	0.6(0.3-1.7)	0.4(0.2-0.9)	1.1(0.4-2.9)	<0.0001
Follow-up treatments				
ß-receptor blocker	49	66	34	<0.0001
Calcium channel-blocker	54	61	48	0.002
Long-acting nitrate	82	76	88	<0.0001
ACE-inhibitor/Angiotensin II receptor blocker	71	74	68	0.09
Diuretic	58	45	70	<0.0001
Antiplatelet	90	96	83	<0.0001
Anticoagulant	20	16	23	0.04
Digitalis	25	11	38	<0.0001
Antiarrhythmic	16	13	18	0.13
Lipid-lowering drug	41	63	19	<0.0001
Coronary artery bypass graft surgery	19	27	11	<0.0001
Percutaneous coronary angioplasty	19	31	7	<0.0001

The values are presented as medians and interquartile ranges or percentages. Pre-hospital time delay indicates the time from the onset of symptoms to the arrival at the coronary care unit for patients with definite myocardial infarction; CK-MB, creatine kinase-MB isoenzyme; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; ACR, albumin to creatinine excretion ratio; CV, cardiovascular. *P values were calculated for log-transformed data. † During the first 7 days of hospital stay. ‡ Tachy-arrhythmia and brady-arrhythmia, excluding the perithrombolytic period..

models: diabetes mellitus, previous myocardial infarction, pre-hospital time delay, ST-elevation myocardial infarction, atrial fibrillation/flutter, LVEF (negative), Killip class>1, heart rate, blood glucose (non-linear association), and ACR. Diabetes mellitus, previous myocardial infarction, pre-hospital time delay, atrial fibrillation/flutter, LVEF (negative), Killip class>1, heart rate, blood glucose (non-linear association), ACR, uric acid, sodium (negative), eGFR (negative), plasma albumin (negative), alcohol use (negative), and blood hemoglobin (negative), were associated with one or more causes of death. History of hypertension and/or systolic and diastolic blood pressures were negatively associated with sudden death and positively associated with other CV causes (data not shown).

Predictive models for all-cause mortality

The variables independently associated with all-cause mortality are reported in Table 2. When LVEF was included in the analysis, the following factors remained significantly associated with all-cause mortality in both acute and sub-acute models: age, LVEF (negative), body mass index (non-linear), previous myocardial infarction, diabetes mellitus, blood glucose (non-linear), Killip class>1, ACR, and pre-hospital time delay (Table 2 and Figure 2). Notably, body mass index and blood glucose level in the acute model showed a non-linear association with outcome (J or U curve association), and mortality was associated with the first and 4th quartiles (external quartiles) (Table 2). Heart rate, uric acid, and

Table 2: Multivariable Cox regression models for all cause mortality versus 12-year survivors.

	Acute model			Sub-acute model		
Variable	**β ± SE**	**Hazard ratio (95% CI)**	**P value**	**β ± SE**	**Hazard ratio (95% CI)**	**P value**
All Patients	**(n=557, deaths n=287)**			**(n=499, deaths n=255)**		
Age	0.69 ± 0.07	8.0(5.3-12.0)	<0.0001	0.73 ± 0.07	8.9(5.8-13.7)	<0.0001
Gender (female)	-0.17 ± 0.14	0.8(0.6-1.1)	0.21	-0.29 ± 0.14	0.7(0.6-0.9)	0.04
Body mass index	0.13 ± 0.06	1.3(1.1-1.6)	0.03*	0.16 ± 0.06	1.4(1.1-1.8)	0.01*
Previous myocardial infarction	0.77 ± 0.14	2.2(1.6-2.8)	<0.0001	0.89 ± 0.15	2.4(1.8-3.3)	<0.0001
Diabetes mellitus †	0.55 ± 0.14	1.7(1.3-2.3)	0.0002	0.77 ± 0.15	2.2(1.6-2.9)	<0.0001
Blood glucose †	0.18 ± 0.06	1.4(1.1-1.8)	0.002*	0.32 ± 0.06	2.6(1.8-3.7)	<0.0001
Heart rate	0.18 ± 0.06	1.7(1.2-2.4)	0.003	0.16 ± 0.06	1.6(1.1-2.4)	0.01
Killip class>1	0.37 ± 0.15	1.4(1.1-1.9)	0.01	0.43 ± 0.20	1.5(1.1-2.7)	0.03
ACR	0.26 ± 0.06	2.1(1.5-3.1)	<0.0001	0.23 ± 0.06	2.0(1.4-2.8)	<0.0001
Diastolic blood pressure	-0.18 ± 0.09	0.6(0.3-0.9)	0.04			
Uric acid	0.16 ± 0.06	1.6(1.1-2.2)	0.005			
Potassium	0.12 ± 0.05	1.4(1.1-2.0)	0.02			
Sodium				-0.18 ± 0.06	0.6(0.4-0.8)	0.001
Atrial fibrillation/flutter				0.43 ± 0.20	1.5(1.1-2.2)	0.03
Pre-hospital time delay	0.16 ± 0.06	1.6(1.1-2.3)	0.007	0.14 ± 0.06	1.6(1.1-2.4)	0.02
Patients with LVEF	**(n=476, deaths n=229)**			**(n=424, deaths n=201)**		
Age	0.64 ± 0.08	6.8(4.3-10.9)	<0.0001	0.73 ± 0.08	9.0(5.6-14.7)	<0.0001
Gender (female)	0.01 ± 0.15	1.0(0.7-1.4)	0.69	-0.13 ± 0.17	0.9(0.6-1.2)	0.44
LVEF	-0.21 ± 0.07	0.5(0.3-0.8)	0.002	-0.24 ± 0.07	0.5(0.3-0.7)	0.0005
Body mass index	0.14 ± 0.07	1.3(1.1-1.7)	0.04*	0.18 ± 0.07	1.4(1.1-1.9)	0.01*
Previous myocardial infarction	0.62 ± 0.16	1.9(1.4-2.5)	<0.0001	0.79 ± 0.17	2.2(1.6-3.1)	<0.0001
Blood glucose †	0.16 ± 0.07	1.4(1.1-1.8)	0.02*	0.31 ± 0.07	2.6(1.7-3.9)	<0.0001
Diabetes mellitus †	0.66 ± 0.16	1.9(1.4-2.6)	<0.0001	0.76 ± 0.16	2.1(1.3-2.9)	<0.0001
Killip class>1	0.41 ± 0.17	1.5(1.1-2.1)	0.01	0.57 ± 0.23	1.8(1.1-2.7)	0.01
ACR	0.25 ± 0.07	2.1(1.4-3.2)	0.0004	0.20 ± 0.07	1.8(1.2-2.8)	0.003
Diastolic blood pressure	-0.21 ± 0.10	0.5(0.3-0.9)	0.03			
Uric acid	0.15 ± 0.06	1.6(1.1-2.3)	0.01			
Heart rate				0.18 ± 0.07	1.7(1.1-2.6)	0.01
Sodium				-0.19 ± 0.06	0.6(0.4-0.8)	0.003
Pre-hospital time delay	0.16 ± 0.06	1.6(1.1-2.3)	0.01			
Patients with LVEF, models including reperfusion treatments and medications through follow-up time as confounders						
Age	0.64 ± 0.08	6.8(4.3-10.9)	<0.0001	0.73 ± 0.08	9.0(5.6-14.7)	<0.0001
Gender (female)	0.01 ± 0.15	1.0(0.7-1.4)	0.69	-0.13 ± 0.17	0.9(0.6-1.2)	0.44
LVEF	-0.21 ± 0.07	0.5(0.3-0.8)	0.002	-0.24 ± 0.07	0.5(0.3-0.7)	0.0005
Previous myocardial infarction	0.62 ± 0.16	1.9(1.4-2.5)	<0.0001	0.79 ± 0.17	2.2(1.6-3.1)	<0.0001
Diabetes mellitus †	0.66 ± 0.16	1.9(1.4-2.6)	<0.0001	0.76 ± 0.16	2.1(1.3-2.9)	<0.0001
ACR	0.25 ± 0.07	2.1(1.4-3.2)	0.0004	0.20 ± 0.07	1.8(1.2-2.8)	0.003
Uric acid	0.15 ± 0.06	1.6(1.1-2.3)	0.01			
Blood glucose				0.31 ± 0.07	2.6(1.7-3.9)	<0.0001
Sodium				-0.19 ± 0.06	0.6(0.4-0.8)	0.003

*Non-linear association (U/J-shaped relationship); † Excluding reciprocally blood glucose and diabetes mellitus from the model;
Abbreviations as shown in Table 1

plasma sodium (negative) were independently associated in acute or sub-acute models. When medications (β-blocker, ACE-inhibitor/anti angiotensin II receptor blocker, and lipid lowering treatment) and reperfusion treatments (thrombolysis, percutaneous coronary angioplasty, and coronary artery by-pass surgery) were included in the final models as confounders, the variables body mass index, Killip class>1, and pre-hospital time delay were most affected, and the association of these variables was no longer significant (Table 2 and Figure 2). The figure summarizes the variables (including age, gender and LVEF) independently associated with all-cause and/or cause of death in both acute and sub-acute models (Figure 2).

Predictive models based on cause of death

The variables independently associated with CAD-HF are shown in Table 3. When LVEF was included in the model, the following variables remained significantly associated in both acute and sub-acute models: age, LVEF (negative), body mass index (non-linear), previous myocardial infarction, Killip class>1, ACR, and pre-hospital

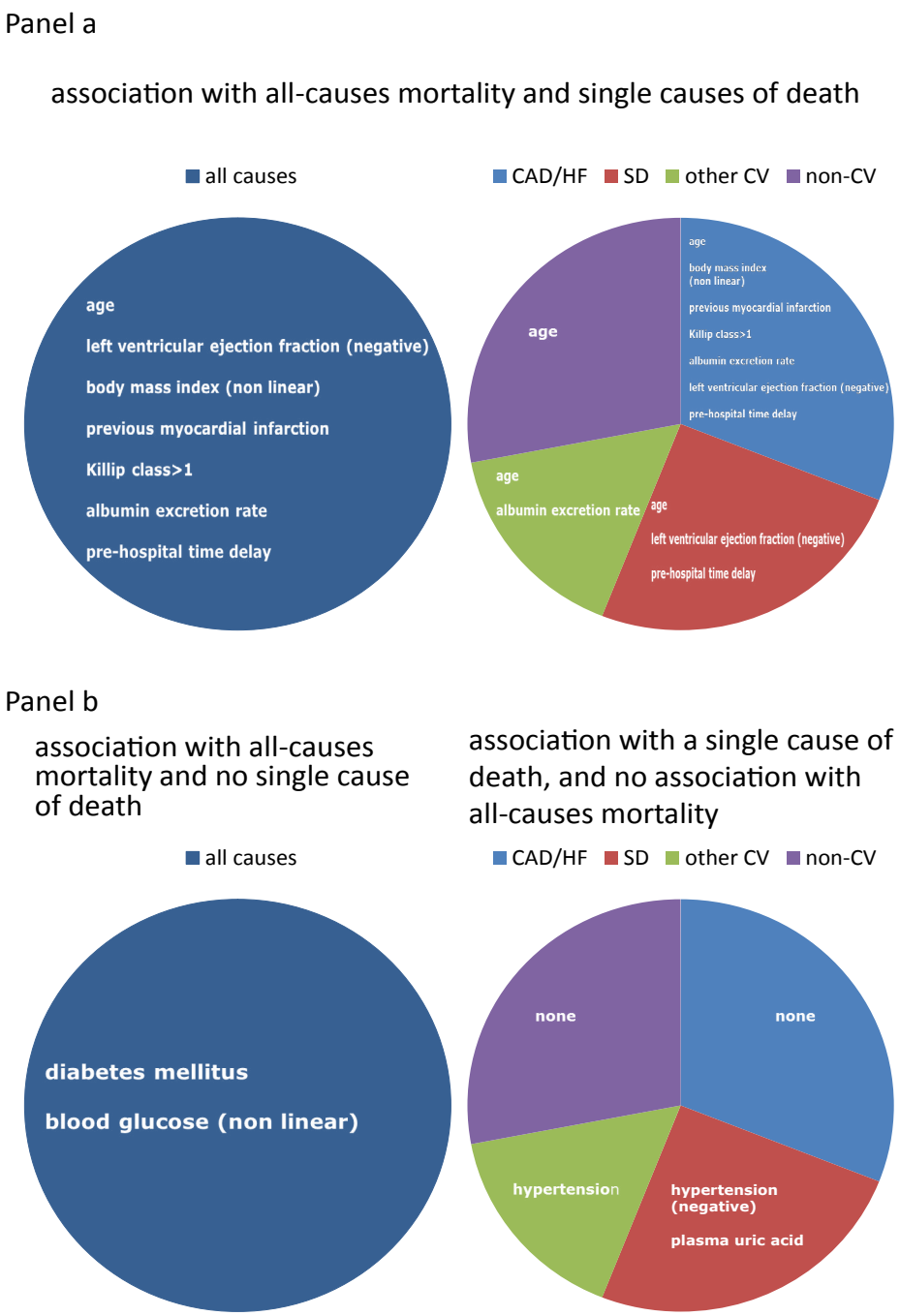

Figure 2: Summary of the independent predictors of 12-year mortality and modes of death after ACS in both acute and sub-acute models.

time delay (Table 3 and Figure 2). SD was associated with age, hypertension (negative), uric acid, LVEF (negative), and pre-hospital time delay (Table 3 and Figure 2). Other CV mortality was associated with age, hypertension, and ACR. LVEF was not independently associated with other CV mortality (Table 3 and Figure 2). Non-CV causes of death were primarily associated with age, and the association with LVEF (negative) was only slightly significant (Table 3 and Figure 2).

Predictive accuracy of the parsimonious models

The multivariable models of Table 2 were well calibrated for all-cause mortality in acute and sub-acute models, with and without

Table 3: Multivariable Cox regression models for mortality by modes of death versus 12-year survivors.

	Acute model			Sub-acute model		
Mode of death: coronary artery disease–heart failure progression						
All Patients (n=557)	**(n=557, deaths n=90)**			**(n=499, deaths n=80)**		
Age	0.64 ± 0.12	6.8(3.3-14.1)	<0.0001	0.70 ± 0.13	8.3(3.8-18.3)	<0.0001
Gender (female)	-0.02 ± 0.24	1.0(0.6-1.6)	0.93	-0.30 ± 0.26	0.7(0.4-1.2)	0.24
Body mass index	0.24 ± 0.11	1.6(1.1-2.5)	0.02*	0.32 ± 0.12	1.9(1.2-3.0)	0.006*
Previous myocardial infarction	1.29 ± 0.23	3.6(2.3-5.7)	<0.0001	1.31 ± 0.26	3.7(2.2-6.1)	<0.0001
Blood glucose †	0.21 ± 0.11	1.5(1.1-2.4)	0.04*	0.43 ± 0.11	3.6(1.9-7.1)	<0.0001
Diabetes mellitus †	0.74 ± 0.24	2.1(1.3-3.3)	0.002	0.92 ± 0.25	2.5(1.5-4.1)	0.0005#
ACR	0.38 ± 0.11	3.1(1.6-6.0)	0.0005	0.48 ± 0.12	4.2(2.2-8.5)	<0.0001
Killip class>1	0.80 ± 0.24	2.2(1.4-3.5)	0.001	0.76 ± 0.35	2.1(1.1-4.1)	0.04T
Heart rate				0.40 ± 0.12	3.3(1.7-6.7)	0.0005
Pre-hospital time delay	0.25 ± 0.10	2.1(1.1-3.9)	0.01	0.23 ± 0.10	2.0(1.1-3.8)	0.02
Patients with LVEF	**(n=476, deaths n=74)**			**(n=424, deaths n=65)**		
Age	0.64 ± 0.13	6.7(3.1-15.1)	<0.0001	0.61 ± 0.15	6.2(2.7-15.0)	<0.0001
Gender (female)	0.06 ± 0.26	1.1(0.6-1.8)	0.81	-0.25 ± 0.30	0.8(0.4-1.4)	0.39
LVEF	-0.24 ± 0.12	0.5(0.2-0.9)	0.03	-0.18 ± 0.13	0.6(0.3-1.2)	0.14
Body mass index	0.28 ± 0.12	1.8(1.1-2.9)	0.01*	0.30 ± 0.13	1.8(1.1-3.1)	0.02*
Previous myocardial infarction	0.96 ± 0.26	2.6(1.6-4.3)	0.0003	1.05 ± 0.30	2.9(1.6-5.1)	0.0007
ACR	0.35 ± 0.12	2.8(1.4-6.0)	0.003	0.48 ± 0.13	4.3(2.0-9.7)	0.0001
Diabetes mellitus †	0.88 ± 0.26	2.4(1.4-4.0)	0.001			
Killip class>1	0.67 ± 0.28	1.9(1.1-3.3)	0.01	0.59 ± 0.26	1.8(1.1-3.0)	0.02
Blood glucose †				0.38 ± 0.12	3.2(1.6-6.6)	0.001
Heart rate				0.35 ± 0.13	2.8(1.3-6.1)	0.007
Pre-hospital time delay	0.25 ± 0.12	2.1(1.1-4.3)	0.02	0.25 ± 0.12	2.1(1.1-4.3)	0.03
Mode of death: sudden death						
All Patients	**(n=557, deaths n=70)**			**(n=499, deaths n=65)**		
Age	0.51 ± 0.13	4.7(2.2-10.0)	<0.0001	0.61 ± 0.14	6.2(2.8-13.9)	<0.0001
Gender (female)	-0.21 ± 0.29	0.8(0.4-1.4)	0.45	-0.56 ± 0.32	0.6(0.3-1.1)	0.07
Previous myocardial infarction	0.64 ± 0.27	1.9(1.1-3.2)	0.02	1.14 ± 0.27	3.1(1.8-5.3)	<0.0001
Diastolic blood pressure §	-0.31 ± 0.11	0.4(0.2-0.8)	0.006	-0.23 ± 0.11	0.5(0.3-0.9)	0.04
Hypertension §	-0.64 ± 0.26	0.5(0.3-0.9)	0.01	-0.79 ± 0.27#	0.4(0.3-0.8)	0.003
Uric acid	0.28 ± 0.12	2.3(1.2-4.8)	0.01	0.26 ± 0.12	2.2(1.1-4.4)	0.02
Killip class>1	0.73 ± 0.29	2.1(1.2-3.6)	0.01			
Heart rate	0.36 ± 0.12	2.9(1.4-6.1)	0.002			
Blood glucose †				0.50 ± 0.12	4.4(2.2-9.2)	<0.0001
Diabetes mellitus †				0.71 ± 0.29	2.0(1.1-3.5)	0.02
Hemoglobin				-0.32 ± 0.13	0.4(0.2-0.8)	0.01
Sodium				-0.30 ± 0.11	0.4(0.2-0.8)	0.006
Atrial fibrillation/flutter				0.98 ± 0.33	2.7(1.3-5.0)	0.006
Pre-hospital time delay	0.38 ± 0.12	3.2(1.5-6.7)	0.001	0.39 ± 0.12	3.2(1.5-6.8)	0.001
Patients with LVEF	**(n=476, deaths n=54)**			**(n=424, deaths n=50)**		
Age	0.43 ± 0.15	3.6(1.5-8.7)	0.003	0.47 ± 0.16	4.1(1.6-10.5)	0.02
Gender (female)	0.05 ± 0.32	1.0(0.5-2.0)	0.86	0.31 ± 0.35	1.4(0.7-2.7)	0.38
LVEF	-0.61 ± 0.15	0.2(0.1-0.4)	<0.0001	-0.63 ± 0.16	0.2(0.1-0.4)	<0.0001
Hypertension §	-0.81 ± 0.31	0.4(0.2-0.8)	0.006	-0.92 ± 0.33	0.4(0.2-0.7)	0.003
Uric acid	0.42 ± 0.13	3.5(1.6-8.1)	0.001	0.31 ± 0.14	2.5(1.1-5.7)	0.02
Killip class>1	0.65 ± 0.32	1.9(1.1-3.6)	0.04			
Diastolic blood pressure §	-0.51 ± 0.22	0.2(0.1-0.8)	0.02			
Heart rate	0.26 ± 0.13	2.2(1.1-4.8)	0.04			
Blood glucose				0.55 ± 0.14	5.1(2.3-12.4)	<0.0001
Previous myocardial infarction				0.66 ± 0.32	1.9(1.1-3.6)	0.04

Pre-hospital time delay	0.30 ± 0.14	2.4(1.1-5.6)	0.02	0.29 ± 0.14	2.4(1.1-5.5)	0.03
Mode of death: other CV causes						
All Patients (n=557)	**(n=557, deaths n=46)**			**(n=499, deaths n=41)**		
Age	0.77 ± 0.19	10.2(3.5-32.9)	<0.0001	0.82 ± 0.19	11.8(3.9-38.5)	<0.0001
Gender (female)	0.19 ± 0.31	1.2(0.6-2.2)	0.54	-0.17 ± 0.34	0.8(0.4-1.7)	0.62
Hypertension	0.73 ± 0.35	2.1(1.1-4.3)	0.02	0.74 ± 0.36	2.1(1.1-4.5)	0.03
Blood glucose	0.31 ± 0.16	1.9(1.1-2.5)	0.04*	0.52 ± 0.18	2.8(1.4-5.9)	0.002*
ACR	0.67 ± 0.17	7.4(2.8-21.7)	<0.0001	0.46 ± 0.16	4.0(1.6-10.5)	0.002
eGFR (MDRD)	-0.36 ± 0.16	0.3(0.1-0.8)	0.01			
Killip class>1				0.91 ± 0.41	2.5(1.1-5.4)	0.04
Patients with LVEF	**(n=476, deaths n=37)**			**(n=424, deaths n=33)**		
Age	0.84 ± 0.20	12.5(4.0-42.9)	<0.0001	0.88 ± 0.21	14.1(4.2-51.2)	<0.0001
Gender (female)	0.04 ± 0.35	1.0(0.5-2.1)	0.91	-0.15 ± 0.38	0.9(0.4-1.8)	0.69
LVEF	-0.06 ± 0.15	0.8(0.3-2.0)	0.68	0.06 ± 0.17	1.2(0.4-3.4)	0.70
Hypertension	0.80 ± 0.37	2.2(1.1-4.8)	0.02	0.76 ± 0.39	2.1(1.1-4.8)	0.04
ACR	0.71 ± 0.19	8.4(2.9-27.5)	<0.0001	0.42 ± 0.18	3.6(1.3-10.7)	0.01
Blood glucose				0.44 ± 0.19	2.4(1.2-5.3)	0.01*
Mode of death: non-CV causes						
All Patients	**(n=557, deaths n=81)**			**(n=424, deaths n=65)**		
Age	0.86 ± 0.12	13.3(6.5-28.4)	<0.0001	0.82 ± 0.13	11.8(5.5-25.9)	<0.0001
Gender (female)	-0.24 ± 0.25	0.8(0.5-1.3)	0.33	-0.27 ± 0.28	0.8(0.4-1.3)	0.32
Family coronary heart disease				-0.75 ± 0.36	0.5(0.2-0.9)	0.02
School Education				-0.69 ± 0.35	0.5(0.2-0.9)	0.03
Total cholesterol				-0.23 ± 0.12	0.5(0.2-0.9)	0.04
Patients with LVEF	**(n=476, deaths n=64)**			**(n=424, deaths n=53)**		
Age	0.90 ± 0.14	14.9(6.6-35.1)	<0.0001	0.84 ± 0.15	12.6(5.3-31.3)	<0.0001
Gender (female)	-0.08 ± 0.28	0.5(0.5-1.6)	0.76	-0.07 ± 0.31	0.9(0.5-1.7)	0.82
LVEF	-0.23 ± 0.12	0.5(0.2-0.9)	0.04	-0.25 ± 0.13	0.5(0.2-1.0)	0.05
Family coronary heart disease				-0.72 ± 0.39	0.5(0.2-0.9)	0.04
School Education				-0.85 ± 0.41	0.4(0.2-0.9)	0.02
Total cholesterol	-0.22 ± 0.11	0.5(0.3-0.9)	0.04			

*Non-linear association (U/J-shaped relationship); † Excluding reciprocally blood glucose and diabetes mellitus from the model; § Excluding reciprocally hypertension and blood pressure from the models.
Abbreviations as shown in Table 1

LVEF (Hosmer-Lemeshow test p=0.87, p=0.57, p=0.56, and p=0.34, respectively). The models for all-cause and causes of death showed significant fits to the data (p<0.0001 for all models). The models for all-cause mortality showed elevated discriminant power, and the C-statistic was 0.86 in for acute and sub-acute measurements with or without the inclusion of LVEF (Table 4). The highest C-statistic values were observed for other-CV causes, while the lowest values were observed for non-CV causes, and the C-statistic values were similar for CAD-HF causes and SD (Table 4).

Discussion

The major findings of this prospective long-term study indicate that:

1) Long-term mortality after ACS is independently associated with a number of clinical features, beyond traditional CV risk factors;

2) Different modes of death are associated with different clinical features; and

3) Some predictors are not linearly associated with the outcomes. Adjustment for medications and coronary mechanical reperfusion during the follow up study did not substantially affect the results obtained herein.

According with other analysis, even carried out in patients treated with primary angioplasty, we found that patients with ST-elevation myocardial infarction tend to have worse long-term prognosis, even if in the final parsimonial models this feature resulted no longer significant [17]. In the present study, age was the only clinical variable independently associated with 12-year overall mortality and all single-cause mortality, even when LVEF was included in the models. These results suggest that age, *per se*, might influence patient outcomes after ACS, regardless of the mode of death [18]. BMI showed an independent, non-linear (U-shaped) association with the overall mortality. Previous studies have shown that BMI is non-linearly associated with outcomes in patients with first myocardial infarction; however, this study provides the first information for the association of BMI with increased CAD-HF mortality [19]. The presence of diabetes mellitus and blood glucose levels were independently associated with all-cause-mortality. While the presence of diabetes mellitus was more strongly associated with CAD-HF mortality than other causes of death, the blood glucose levels were associated with all CV causes of mortality. Notably, the blood glucose levels showed an independent non-linear (J/U-shaped) association in acute models and a linear relationship in sub-acute models. Several studies have shown that hyperglycemia during ACS is associated with poor patient outcomes, but much less is known about the influence of low glucose levels [20]. Indeed, the present study suggests that in ACS patients, therapeutic efforts should be aimed at both lowering and maintaining glycemic levels in a range approximating central quartiles [21]. In

Table 4: Predictive models for 12-year all-cause mortality and causes of death determined using the C-statistic analysis.

	Acute model	Sub-acute model
	C-statistic value	C-statistic value
Predictive model for:		
ALL-CAUSE MORTALITY		
All Patients	0.86	0.86
Patients with LVEF	0.86	0.86
CORONARY ARTERY DISEASE–HEART FAILURE PROGRESSION		
All Patients	0.75	0.78
Patients with LVEF	0.76	0.78
SUDDEN DEATH		
All patients	0.75	0.74
Patients with LVEF	0.78	0.78
OTHER CV CAUSES		
All patients	0.80	0.80
Patients with LVEF	0.80	0.79
NON-CV CAUSES		
All patients	0.69	0.73
Patients with LVEF	0.71	0.72

Abbreviations as shown in Table 1

the present study, history of hypertension and actual blood pressure values were not associated with all-cause mortality. Moreover, the present results suggest a positive association of these variables with other-CV causes and a negative association with SD. A blood pressure "paradox" in early outcome was observed in non-ST elevation ACS, thus lower blood pressure was associated with an increased risk of in-hospital CV events [22]. Indeed, the Thrombolysis in Myocardial Infarction (TIMI)-22 trials showed a J/U-shaped association between blood pressure and the risk of CV events after ACS [23]. It has been suggested that subjects with severe stenosis of the coronary arteries have a poor coronary flow reserve, making the myocardium vulnerable to low coronary perfusion pressures tolerated in patients without ischemia [24]. It has been recently shown that the elevated levels of uric acid are an independent predictor of 1-year mortality across the entire spectrum of ACS patients treated with percutaneous coronary intervention [25]. The results of the present study showed that plasma uric acid levels are associated with long-term mortality, and the predicted increased mortality primarily reflected SD. Even if uric acid causes endothelial dysfunction, leading to reduced nitric oxide levels, the mechanism of association between uric acid levels and SD remains unknown [25].

The TIMI study showed that history of angina and/or myocardial infarction is associated with short-term adverse events [26]. However, the present study showed that history of angina did not significantly influence mortality, while previous myocardial infarction highly influenced 12-year mortality after ACS. The presence of heart failure and LVEF has been strongly associated with all-cause mortality [27]. Indeed, although LVEF has been associated with both CAD-HF mortality and SD, the presence of heart failure has primarily been associated with CAD-HF mortality, suggesting that long-term SD was more affected by structural ventricular modifications than hemodynamic changes during ACS [18,19]. The present study showed that albumin excretion is one of the strongest factors associated with all-cause mortality after ACS. Indeed, albumin excretion has been primarily associated with an excess of CAD-HF and other-CV mortality, while no association with SD and non-CV mortality was observed. As albumin excretion is typically considered a marker of acute endothelial dysfunction during ACS, the degree of endothelial dysfunction might dictate different modes of death [28]. This observation might have implications for either prognostic purposes or pathophysiological interpretations of the vascular changes occurring during ACS [29,30]. Renal function has been implicated as an independent predictor of mortality in patients with ACS, and we recently showed a strong association between eGFR and 10-year event-free survival [3,31]. This evidence suggests that in the long term, variables other than eGFR might be more informative on mortality risk. The delay between the onset of symptoms and admission to the coronary care unit is important for the outcome of patients with acute myocardial infarction [32]. The results of the present study confirmed that time delay was strongly associated with all-cause mortality, and the predicted risk primarily affects CAD-HF and SD.

Limitations of the study

A major limitation of the ABC study on ACS was that, at the time of patient enrollment, percutaneous coronary angioplasty was not currently in use for reopening coronary arteries in patients with STEMI. Thus, it remains uncertain whether early mechanical reperfusion modified the predictive models. However, we observed that the results of the predictive model were similar for patients with STEMI and NTEMI. Furthermore, the data adjustment for thrombolytic treatment, percutaneous coronary angioplasty and coronary artery bypass graft surgery did not modify the results of the study. Furthermore, the design and analysis of the present study did not consider the extent and severity of coronary disease, as the anatomic burden is an important determinant of prognosis. Because this study was conducted in Caucasian patients, we cannot generalize these findings to other populations and ethnic groups.

Conclusion

The ABC-2 study identified clinical predictors of long-term mortality after ACS that might help prognostication, patient education, and risk modification. Furthermore, the present study showed that the analysis of the modes of death might improve the risk assessment.

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Contributors

Dr. Berton and Dr. Palatini designed the study. Dr. Cordiano and Dr. Palmieri contributed to the original data collection. Dr. Cavuto and Dr. Cordiano contributed to data handling and patient follow-up. Dr. Cordiano and Dr. Pellegrinet contributed to the creation of the dataset and preparation of the tables and figures. Dr. Berton contributed to the analysis and interpretation of the data and the preparation of the manuscript. All authors contributed to the accuracy of the data analysis.

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