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RESEARCH ARTICLE

Single Spot Albumin to Creatinine Ratio as An Independent Predictor of 12 Years Follow-Up Mortality in Acute Coronary Syndromes without ST-Segment Elevation

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ABSTRACT

Background: Up to date there is no evidence of the association between microalbuminuria, measured as single spot urine albumin to creatinine ratio (ACR), with very long-term mortality in patients with non-ST segment Elevation Acute Coronary Syndromes.

Aim: To evaluate the association between admission ACR and very long-term all-cause mortality in an unselected cohort of non-ST-segment elevation acute coronary syndromes patients.

Methods: A prospective cohort study was conducted, including patients with non-ST-segment elevation acute coronary syndromes admitted in the Intensive Care Unit. The ACR was determined in spontaneous urine samples during the first 24 hours after admission and analyzed by immunoturbidimetry. The primary endpoint was all-cause mortality during the follow-up. Actuarial survival curves were compared by log rank test and a logistical Cox regression analysis was performed to identify variables independently associated with mortality in the follow-up. Statistics were calculated using the IBM Statistics program SPSS version 26.

Results: 600 patients were analyzed. The overall average ACR value was 7 mg/gr (95% CI 4-26). 76% had normoalbuminuria (ACR 0-30 mg/gr), 22% had microalbuminuria (ACR 30-300 mg/gr), and 1.5% had macroalbuminuria (ACR > 300 mg/gr). The median and interquartile range of follow-up was 12 years (95% IC 11-14). The average ACR among those who met the primary endpoint was 59.15 mg/gr (95% CI 52-66) and among the survivors, 27.66 mg/gr (95 % CI 63-77), p > 0,003. ACR terciles were defined by 33th and 66th percentiles: tercile 1: patients with ACR of 0 to 4 mg/gr, tercile 2: ACR from 4 to 17 mg/g and tercile 3 values greater than 17mg/gr. Strong associations were observed between ACR with age, hypertension, stroke and history of COPD, previous use of angiotensin II converter/blocking enzyme inhibitors, systolic blood pressure at admission, ST segment deviation, left ventricle ejection fraction and elevation of serum Troponin T and CPK MB. All cause-mortality during the follow-up was 14% (CI 95% 11-17). Elevation of ACR was significantly associated with long term mortality risk: log rank test chi square: 133.936, p = 0.0001. By multivariate Cox regression analysis adjusted by age, gender, diabetes, hypertension, serum creatinine, troponin T elevation, ST segment deviation, previous AMI, prior use of aspirin, statins and percutaneous coronary intervention after hospitalization, the ACR was independently associated with a 12-year follow-up mortality: OR 13 (95% IC 5-35; p < 0.0001).

Conclusion: Single spot urine ACR at admission is a strong predictor of 12-year follow-up mortality in an unselected cohort of patients with non-ST-segment elevation acute coronary syndromes.

Keywords: microalbuminuria, acute coronary syndrome, prognosis, follow-up study

Introduction

WHO top ten causes of death states that the world's biggest killer is ischemic heart disease, responsible for 16% of the world's total deaths [1]

Ischemic heart disease is caused by atherosclerotic plaques in the coronary arteries. [2-3] Endothelial dysfunction is a process present during the development of atherosclerotic disease, from its onset time until the plaque disruption phase that activates the thrombotic mechanisms that ultimately lead to myocardial ischemia, acute coronary syndromes and sudden death. [4]. Risk factors such as hypertension, diabetes, smoking, hypercholesterolemia and hypercholesterolemia are strongly associated with this multifactorial and dynamic process. [5]

Acute coronary syndromes are classified according to their electrocardiographic pattern into those with ST-segment elevation, which are generally secondary to a total occlusion of the coronary arteries, and acute coronary syndromes without ST-segment elevation, which are caused by severely damaged arteries generally without total coronary occlusion. [6]

Non-ST-segment elevation acute coronary syndromes has been characterized by its high prevalence and a wide spectrum of heterogeneity regarding its short- and long-term prognosis in the real world. [7-9]

This scenario leads to the fact that the appropriate medical decision requires a case by case risk stratification assessment in order to decide either a conservative approach with pharmacological treatment or an invasive approach through a coronary angiography followed by revascularization by percutaneous coronary angioplasty or coronary by pass surgery.

Serum myocardial necrosis markers, mainly high-sensitivity troponins, are actually useful tools for identifying patients at high clinical risk associated with the degree of cardiac injury.

In the recent years, other novel risk markers have been studied, such as neurohormonal, inflammatory, plaque disruption and endothelial dysfunction markers such as microalbuminuria.

The albumin to creatinine ratio (ACR) in a single spot urine sample, is a simple, accessible and validated method for microalbuminuria measurement, as an early renal disfunction predictor, several studies proved that is an independent risk marker of total and cardiovascular mortality in both diabetic and hypertensive patients, as well as in the high-cardiovascular risk population and also a long-term mortality predictor in patients with non-fatal acute myocardial infarction. [10-26]

In the previous study published by our group, ACR was associated independently with adverse events in a 18-month follow-up. [27]

The objective of present analysis is to assess the very long-term (median of 12 years) association of ACR with all-cause mortality in our cohort of non-selected non-ST-segment elevation acute coronary syndromes patients.

Methods

Detailed information on the design and methodology of the study has been published previously. [27]

The study was approved by our institutional Review Board and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All the authors assume responsibility for the completeness and accuracy of the data.

During the development of the study, we applied the WHO, ACC, AHA and ESC third redefinition of myocardial infarction, mainly based on a 99th percentile limit of more sensitive and specific necrosis markers like serum troponins. [28-29]

The principle of the ACR measurement test is immunoturbidimetry. The COBAS 6000 analyzer (ROCHE) was used for sample processing. The analytical detection limits of the assay were 3 mg/g and 400 mg/g. The test variation coefficient was 3.8%.

The endpoint in this remote follow-up was all-cause mortality.

Patients' follow-up assessments were conducted using personal interviews, telephone or video-call interviews, review of visit records, and lead physician reports. All patients gave their written informed consent before their inclusion in the study.

Analysis of distribution of continuous variables was performed using the Kolmogorov-Smirnov test and analysis of kurtosis-skewness. Continuous data were expressed as mean and standard deviation, or as its median and its 25th and 75th interquartile. Comparison was made using the Student's T-test or the Mann-Whitney-Wilcoxon test for independent groups, according to its parametric or

nonparametric distribution, respectively. Discrete variables (proportions) were expressed as percentages, and chi square test were used for their comparison.

Sample calculation: Based on a 95% confidence level, and an 80% power, estimated odds ratio: 2, an estimated long-term follow-up mortality incidence between 10% to 20%, the sample size range calculated for this cohort study was between 500 to 550 cases.

Case actuarial survival curves were compared by Log rank Test and a logistical COX regression analysis was carried out to identify variables independently associated with mortality in the follow-up. ACR was analyzed as a continuous variable delineated by percentiles 33 and 66 values.

For statistical analysis SPSS program IBM Statistics version 26 was used. MedCalc software version 11.6.1. (Mariakerke, Belgium) was used for both construction and comparison (using DeLong test) of ROC curve areas. Two-tailed $p < 0.05$ was considered significant.

Results:

A total of 600 patients with non-ST-segment elevation acute coronary syndromes were analyzed. Patients were admitted consecutively to our Coronary Care Unit from June 2008 to December 2011 with long-term follow-up complete data. Dropout rate as 14.2% (100 cases) due to changes in their health insurance (33%), changes to their place of residence (35%), changes in their telephone or email contacts (22%) and other causes (10%), most of cases during the COVID-19 pandemic. A contingency analysis was performed comparing baseline variables between those cases with complete follow-up and those with follow-up drop-out. Differences were detected in the prevalence of previous arterial hypertension and previous IAM: 64% and 24.3% vs. 70% and 13% in those without follow-up, $p = 0.003$ and 0.02 respectively. Loss to follow-up and missing data can threaten the internal validity of a study, however these two variables: arterial hypertension and previous AMI, as described in Results, were not associated with mortality at 12 years follow-up.

Baseline demographic data, risk factors, prior history, hospitalization information and follow-up treatment and procedures are shown in Table 1.

Table 1. Demographic, cardiovascular risk factors, previous history, in-hospitalization data and follow-up treatment and interventions.

	Global	Tercile 1	Tercile 2	Tercile 3	P -value
	n= 600	n: 200	n: 199	n: 201	
Age (years) *	64 (68-73)	61 (55-68)	63 (56-72)	69 (59-70)	0.0001
Female gender, n(%)	195 (32,5)	50 (25)	50 (25)	72 (36)	0.34
Diabetes Mellitus, n(%)	109 (18,1)	24 (12)	38 (19)	48 (24)	0.21
Hypertension, n(%)	384 (64)	108 (54)	129 (65)	151 (75)	0.002
Dyslipidemia, n(%)	325 (54,2)	108 (54)	103 (52)	44 (52)	0.89
Active smoking, n(%)	260 (43,3)	84 (42)	84 (42)	45 (45)	0,93
BMI *	26 (24-29)	26 (24-28)	27 (24-29)	26 (24-29)	0.093
Pre-hospital					
AMI, n(%)	146 (24,3)	46 (23)	44 (22)	27 (27)	0.82
CABG, n(%)	43 (7,2)	8 (4)	10 (5)	18 (9)	0.09
PCI, n(%)	92 (15,3)	26 (13)	36 (18)	32 (16)	0.9
Stroke, n(%)	26 (4,3)	4 (2)	10 (5)	12 (6)	0.04
COPD, n(%)	30 (5)	6 (3)	12 (6)	14 (7)	0,04
ACE-I/ARB, n(%)	238 (39,7)	66 (33)	74 (37)	98 (49)	0,01
Beta blockers, n(%)	239 (39,9)	74 (37)	70 (35)	94 (47)	0,1
Aspirin, n(%)	251 (41,8)	74 (37)	84 (42)	74 (37)	0.10
In-hospital					
Admission Systolic blood pressure, mmHg *	139 (120-150)	130 (120-149)	140 (120-150)	140 (120-160)	0.01
Admission heart rate, beats/minute *	70 (63-80)	70 (62-80)	70 (64-80)	75 (64-85)	0.15

	Global	Tercile 1	Tercile 2	Tercile 3	P -value
	n= 600	n: 200	n: 199	n: 201	
ST segment elevation, n(%)	129 (21,5)	38 (19)	50 (25)	40 (20)	0.15
ST segment depression, n(%)	224 (37,4)	24 (12)	36 (18)	40 (20)	0.01
T wave inversion, n(%)	143 (23,9)	42 (21)	48 (24)	52 (26)	0,61
LV ejection fraction (%) *	55 (54-56)	55 (54-56)	56 (54-58)	59 (57-61)	0,001
Elevated Troponin T, n(%)	269 (44,9)	70 (35)	94 (47)	111 (55)	0,0001
Elevated CK MB Mass, n (%)	192 (32)	46 (23)	62 (31)	70 (35)	0,001
Serum creatinine (mg/dl) *	0.91 (0.8-1,1)	0.90 (0.7-1)	0.90 (0.80-1)	1 (0.80-1.2)	0.0001
Admission glycaemia (mg/dl) *	109 (98-128)	107 (96-120)	107 (98-125)	115 (100-147)	0.25
ACR (mg/gr) *	7 (4-28)	4 (3-5)	9 (4-13)	43 (29-85)	0.001
Follow-up treatment and Interventions					
PCI n(%)	48 (8)	10 (5)	26 (13) #	14 (7)	0.07
CABG n(%)	7 (1,1)	1 (0,7)	2 (1) #	14 (7)	0,77
Beta-blockers n(%)	419 (69,9)	144 (72)	125 (63) #	141 (70)	0.31
ACEIs n(%)	336 (56)	120 (60)	109 (55) #	103 (51)	0,33
Antiplatelets n (%)	480 (80)	168 (84)	54 (64) #	151 (75)	0.001
Statins n(%)	400 (66,7)	136 (68)	137 (69) #	145 (72)	0.42

ACEI: Angiotensin converting enzyme inhibitors, ACR: Albumin to creatinin ratio, AMI: Acute myocardial infarction, COPD: Chronic Obstructive Pulmnary Disease, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery By-pass Grafting

Mean admission ACR was 7 (95% IC 4-26), 76% of cases had normoalbuminuria (ACR from 0 to 20 mg/gr), 22% had microalbuminuria (between 20 and 300 mg/g) and 1.5% had macroalbuminuria (more than 300 mg / g). All-cause mortality during the follow-up was 14% (IC 95% 11-17). Mean ACR among non-survivors was 59.15 mg/gr (95% CI 52-66) and 27.66 mg/gr (95% IC 63-77) among survivors, p > 0,003. Median and interquartile range $^{25\text{-}75}$ of post-hospitalization follow-up was 12 years (range interquartile $^{25\text{-}75}$ 11-14). Analyzed as a quantitative variable, ACR significantly correlated with: age (Pearson coefficient 0,099, p 0,01), admission glycemia (Pearson coefficient 0.18, p 0.0001), ejection fraction (Pearson coefficient = - 0.130, p= 0.002).

ASSOCIATION OF ACR TERCILES VERY LONG-TERM MORTALITY

Study population was divided into terciles according to ACR 25 and 75 percentiles: tercile 1: cases with ACR between 0 to 4 mg/gr, tertiary 2: ACR values between 4 to 17 mg/g and, tercile 3: those with values greater than 17 mg/gr. In Table 1, significant associations were observed between ACR levels with age, hypertension, stroke and COPD history, previous use of angiotensin II converter/blocking enzyme inhibitors, admission systolic blood pressure, ST segment deviations, left ventricle ejection fraction and elevated cardiac markers (troponin T and CPK-MB mass).

Figure 1 outlines the ACR terciles Kaplan Meier survival curves during the follow-up, detecting strong and significant differences between the 3 terciles, observing greater mortality in the tercile 3 (Log Rank Test chi square: 133.936, p < 0.0001). The average survival time to the first event during the 12-year follow-up of the total sample was 209,68 months (95% IC 204,81-214,55), while the mean average time in tercile 1 was 230 (95%, IC 228-233), 173 months (96% IC 171-176) in tercile 2 and, of 139 months (93% IC 132-147) in tercile 3.

Table 2 shows the Cox univariate and multivariate regression analysis for association with the 12-year follow-up all-cause mortality. By multivariate COX (input method) regression analysis adjusted by age, gender, diabetes mellitus, arterial hypertension, serum creatinine, troponin T elevation, ST segment deviation, previous AMI, previous use of aspirin, use of statins in the follow-up, ACR terciles were independently associated with mortality at 12-year follow-ups: OR 13 (95% IC 5-35; p < 0.0001).

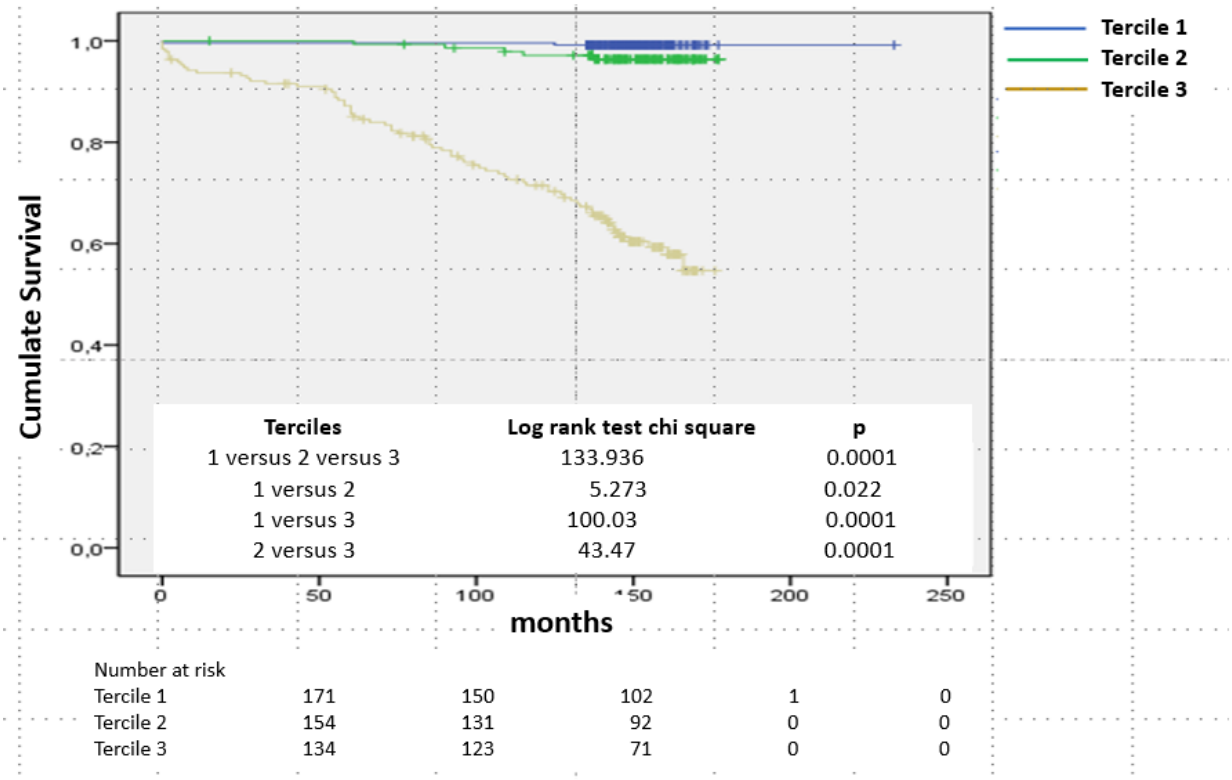

Table 2. Cox univariate and regression analysis for association with 12 years follow-up all-cause mortality

Variables	Univariate Cox Analysis		Multivariate Cox Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per year)	1.15 (1.0-2)	0.0001	1.03 (0.79-2.9)	0.007
Female sex	1.1 (0.94-1.08)	0.64	0.93 (0.5-1.7)	0.88
Diabetes mellitus	1.08 (0.8-1.4)	0.07	1.03 (0.9-2.4)	0.97
Hypertension	1.23 (0.9-1.99)	0.89	0.85 (0.3-1.8)	0.69
Creatinine (per each unit)	1.5 (2-3.7)	0.008	1.23 (0.68-2.2)	0.48
Troponin T Elevation	9.5 (7.2-10.1)	0.002	1.7 (0.95-3.1)	0.07
ST segment deviation	1.1 (0.8-2.3)	0.92	1.2 (1.1-2)	0.05
Previous AMI	1.1 (0.8-1.9)	0.24	0.9 (0.8-1.2)	0.78
Previous Aspirin	1.4 (0.69-3.04)	0.32	1.01 (0.9-1,7)	0.87
Statins in follow up	1.02 (0.55-1.8)	0.93	0.98 (1-1.1)	0.45
Beta blockers in follow up	1.6 (0.94-3.2)	1.41	0.94 (0.89-0.99)	0.25
PCI in follow-up	2.6 (1.1-6.2)	0.01	2 (1.9-2.9)	0.07
ACR	21 (13-39)	0.0001	13 (5-35)	0.0001

ACR Albumin to creatinin ratio
PCI Percutaneous Coronary Intervention

LONG-TERM MORTALITY PREDICTION VALUE OF ACR AS A CONTINUOUS AND AS A DICHOTOMIZED VARIABLE.

By a multivariate Cox regression analysis adjusted by age, gender, diabetes mellitus, arterial hypertension, serum creatinine, troponin T elevation, ST segment deviation, previous AMI, prior aspirin use, statins during the follow-up, ACR analyzed as a continuous variable was independently associated with mortality at 12-year follow-ups: OR 1.1 (per mg/gr) (95% CI 1.1-1.3; p < 0.006).

By ROC curve analysis, the best ACR cut value associated with follow-up mortality was 54 mg/gr (75% sensitivity and 97% specificity), Area under the ROC curve of 0.81 (95% IC 0.77-0.86). ACR adjusted by the above-mentioned significant confounders, as a dichotomous variable (ACR 0-54 mg/gr versus ACR > 54 mg/gr) also remained an independent predictor of long-term mortality: OR 3 (IC 95% 1.9-4.8), p= 0,001.

Discussion

We highlight the following strengths of the present study: 1- The results confirm our initial results in a short term follow-up: ACR is a strong and independent predictor of a very long-term follow-up all-cause mortality. 2- This association with determined through a simple, reliable and worldwide accessible method for the detection of microalbuminuria. 3- The timing of ACR determination (at admission) reflects the ongoing activity of endothelial dysfunction. 4- Our results provide prognostic information of ACR from a non-selected real-world cohort of non-ST-segment elevation acute coronary syndromes patients.

It is remarkable that our findings are consistent with previous studies regarding the prognostic value of microalbuminuria, in a broadening spectrum across non-ST-segment elevation acute coronary syndromes cases.

Akerblom and colleagues from the TRACER study (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) demonstrated that patients with acute coronary syndrome without elevation of the ST segment, microalbuminuria was associated with an increased risk of cardiovascular mortality 1.82 (95% CI 1.37–2.42) and total mortality 1.47, 95% CI 1.08–1.98) at 12 years follow-up. Microalbuminuria in this study was analyzed within the first 24 hours with a semiquantitative dipstick or reactive strip method. It should be taken into account the selection bias (controlled and randomized study comparing vorapaxar versus placebo) that should limit the real word setting transferability of their results. [30]

Recently, the work of Mahmud et al has been published, (ABC study), who have demonstrated the predictive power of microalbuminuria for mortality at 22 years, especially secondary to sudden death, in 449 patients with acute coronary syndrome admitted to three hospitals in the region of Véneto, Italy. Their contributions are several: they conducted serial protocolized determinations of microalbuminuria, analysis of mortality based on cause of death (heart, sudden death, non-heart) and its multicentric character. It is important to remark that in our study, the measurement of microalbuminuria was carried out by 24-hour urine and, that they did not have the availability of the dosage of troponins as a marker of cardiac necrosis. [31]

Nazer et al. (post hoc substudy of the PROVE IT TIMI 22) did not detect independent prognostic association of microalbuminuria. It should be noted that the multiple combined primary endpoint of this study was death, infarction, unstable angina requiring urgent revascularization and stroke and, on the other hand, the sample collection was carried out at day 10 of hospitalization, reflecting the influence from another mechanisms such as invasive procedures, arterial hypertension crisis or acute heart failure, beyond an inflammatory process from the endothelial dysfunction. Also, the study population was selected because of it was a controlled randomized study [32]

In a previous publication, our group demonstrated that ACR was associated with the development of contrast-induced nephropathy. By a multivariable regression analysis model, the association of ACR with contrast induced nephropathy development had an OR of 3.2 (0,7-6,2); p = 0.01. [33]. This finding is consistent with other previous reports on this topic. [34-39]

Association between microalbuminuria detection on early stages of endothelial dysfunction, intrinsic pathophysiologic mechanism on atherosclerotic plaque and its vulnerability, explains the strong association with cardiovascular events and mortality. [40-46]

In contrast to previous studies, our work was able to detect a robust association between microalbuminuria and all-cause mortality at very long-term follow-up, through a spontaneous sample determination at admission and in a non-selected non-ST-segment elevation acute coronary syndromes.

Microalbuminuria measurement is a world-wide available and accessible tool: it is used by clinicians, endocrinologists, nephrologists, general practitioners as an early predictor of renal dysfunction in diabetic or hypertensive patients, so it.

The collection and determination from spontaneous samples makes it more practical and simpler than 24-hour urine collection. Based on our results, microalbuminuria may become a widely available and useful prognostic tool for stratifying patients with non-ST-segment elevation acute coronary syndromes. and prove to be helpful in making behavioral decisions based on the patient's initial clinical risk.

A negative correlation was detected between ACR levels and left ventricle systolic function, as Jin et al described in metabolic syndrome and microalbuminuria. [46]

The presence of elevated microalbuminuria may detect patients with ischemic heart disease who should benefit with specific class of drugs.

In this sense it is well known that ACE inhibitors and angiotensin receptor blockers improve endothelial dysfunction in diabetic patients with microalbuminuria and on the development of nephropathy. [47-48]

In recent years, very interesting trials testing sodium-glucose cotransporter-2 inhibitors (empagliflozin, dapagliflozin and canagliflozin) have demonstrated their robust impact on the excretion of albuminuria in a wide setting of patients: diabetic, non-diabetic patients, as well as in those with renal dysfunction and in patients with heart failure. [49-56]

Conclusion

According to our results, admission single spot urine ACR is an independent and strong predictor of mortality at 12-years in an unselected cohort of patients with non-ST-segment elevation acute coronary syndromes.

The results of the present study are consistent with other previous trials, generating a relevant and attractive hypothesis to be tested through a multicenter, prospective, international study.

Limitations

Some limitations of the present study must be taken into account and the interpretation of the results should be interpreted with caution: 1) In our study detection of microalbuminuria was through a single sample at admission without a serial analysis during the hospitalization. Even though there is evidence that at admission, ACR represents an active and acute endothelial dysfunction, subsequent samples may be under the influence of other factors as mentioned above 2) We did not performed an analysis of the mechanism of death (eg sudden death or non-sudden death, cardiovascular and non-cardiovascular death) 3) Risk on beta error bias: taking into account that the sample size calculated was based in an estimated mortality range between 10 to 20% and an estimated OR of 2, according to the observed mortality of 14% and the ACR odds ratio for the clinical end-point of 13, the results of our analysis may be considered reliable with our final sample size: 600 patients. 4) We did not have an independent endpoint committee 5) Probable selection bias due to a dropout loss of follow-up. 5) Our study was unicenter, limiting the transferability of the results to the real wide-world.

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Data availability: The study data from this analysis cannot be shared, but we encourage to contact the corresponding author for future warranted collaboration.

Co Authors Contribution: Dr C Higa, F Novo, MJ Gambarte, MG Ciambrone and MS Donato contributed to the design of the study, methodology, data analysis and interpretation of the results. Dr E Korolov, R Montoya and S Castro Ortega contributed to the original data collection, data handling, patient follow-up, tables, figures, and manuscript preparation. All authors contributed to ensuring the accuracy of the data analysis and critical revision of the manuscript.

Statement of the use of Artificial Intelligence technologies: Co-authors declare that they do not use any artificial intelligence technology for the manuscript writing, introduction, statistics analysis neither for image creation.

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