Prognostic Value of Serum Creatinine in Non-ST-Elevation Acute Coronary Syndrome

Lorenzo Fácila,[a] Julio Núñez,[a] Vicent Bodí,[a] Juan Sanchís,[a] Vicente Bertomeu-González,[a] Luciano Consuegra,[a] Mauricio Pellicer,[a] Ángel Ferrero,[a] Rafael Sanjuán,[b] and Ángel Llácer[a]

[a]Servicio de Cardiología, Hospital Clínico Universitario, Valencia, Spain.
[b]Servicio de Cuidados Intensivos, Hospital Clínico Universitario, Valencia, Spain.

Introduction and objectives. Cardiovascular disease is the main cause of death in patients with kidney failure. Moreover, the presence of impaired renal function is an important prognostic factor in patients with heart disease, and is a determinant of outcome during follow-up. The main aim was to investigate the relationship between kidney failure at admission and one-year mortality in patients with non-ST-elevation acute coronary syndrome.

Patients and methods. We studied 1029 consecutive patients admitted to our institution. The serum creatinine level and glomerular filtration rate were determined at admission, and classical risk factors and biochemical markers were assessed. The primary endpoint was all-cause mortality at one year.

Results. Patients who died were older, more frequently had a history of diabetes or coronary artery disease, were more likely to have heart failure at admission, had higher troponin-I, myoglobin and creatinine levels, and were less likely to have dyslipidemia or to be a smoker. Multivariate analysis showed that the independent predictors of all-cause mortality at one year were age, diabetes, troponin-I level, Killip class >1, male gender, creatinine level, and glomerular filtration rate. There was a linear correlation between increased risk and creatinine level.

Conclusions. Creatinine level at admission is one of the most important covariates in early prognostic stratification in these patients. A high serum creatinine level (or a low glomerular filtration rate) increases the probability of death due to all causes. The serum creatinine level is, moreover, an inexpensive, easy-to-use, and widely available prognostic marker.

Key words: *Prognosis. Myocardial ischemia. Kidney failure.*

Valor pronóstico de la creatinina sérica en el síndrome coronario agudo sin elevación del segmento ST

Introducción y objetivos. Las enfermedades cardiovasculares son la principal causa de muerte en los pacientes con insuficiencia renal. La presencia de fallo renal es un factor pronóstico muy importante en los pacientes cardiópatas, y es determinante en el seguimiento. El objetivo es determinar la asociación entre la presencia de insuficiencia renal en el momento del ingreso y la mortalidad a 1 año en los pacientes con síndrome coronario agudo sin elevación del segmento ST.

Pacientes y método. Estudiamos a 1.029 pacientes consecutivos, en los que se determinaron la creatinina y el filtrado glomerular en el momento del ingreso, junto con los factores de riesgo clásicos y los marcadores bioquímicos. El criterio de evaluación principal fue la muerte por todas las causas a 1 año.

Resultados. Los pacientes fallecidos eran mayores, con más antecedentes de diabetes y cardiopatía isquémica, y con un mayor porcentaje de insuficiencia cardiaca en el momento del ingreso, junto con unas concentraciones más altas de troponina I, mioglobina y creatinina, y un menor porcentaje de dislipémicos y fumadores. En el análisis multivariable, los predictores independientes de muerte a 1 año fueron: edad, diabetes, troponina, clase Killip > 1, sexo masculino, creatinina y filtrado glomerular. El incremento de riesgo con respecto a las concentraciones de creatinina fue lineal.

Conclusiones. La determinación de la creatinina en el momento del ingreso es una de las variables importantes en la estratificación pronóstica inicial de estos pacientes. Las concentraciones de creatinina más elevadas (o un filtrado glomerular menor) aumentan la probabilidad de muerte por todas las causas. Se trata, por tanto, de un marcador de obtención inmediata, fácil y disponible en todos los centros.

Palabras clave: *Pronóstico. Isquemia miocárdica. Insuficiencia renal.*

INTRODUCTION

Cardiovascular diseases are the main cause of death in patients with terminal renal failure; therefore, such diseases are very common in this type of patient. On the

other hand, renal failure is a very strong prognostic factor in patients with heart disease and represents a determinant of mortality in the follow-up of those who have undergone coronary artery bypass grafting[1] or a percutaneous coronary intervention,[2,3] and those who have suffered an acute myocardial infarction (AMI).[4-11] Most of the studies that found renal failure was a prognostic factor for ischemic heart disease were done in selected patients (clinical trials, seriously ill patients, etc),[1,2,4,7,12,13] and so the findings cannot be readily generalized. Furthermore, few studies have been performed with the new definitions of acute coronary syndrome[14] or that use glomerular filtration rate (GFR) to define renal failure.[15]

In addition, prognostic stratification of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) have changed a number of times over the last decade.[16] Both epidemiological factors (such as age, sex, medical history) and biochemical markers (such as homocysteine, C-reactive protein, fibrinogen, and troponin) have been used.[17-19]

This study aimed to determine the strength of the association between renal failure—quantified by measuring serum creatinine levels or estimating the GFR—and overall long-term mortality in patients on admission to hospital for NSTE-ACS (early prognostic stratification).

PATIENTS AND METHODS

Patients

The study population comprised 1029 consecutive patients who were admitted to our hospital between November 2000 and May 2003 for ischemic chest pain and who met at least one of the following criteria: *a)* electrocardiography (ECG) suggestive of acute ischemic heart disease (ST-segment depression or T-wave inversion); *b)* elevated markers of myocardial damage (troponin I); *c)* positive findings in an exercise test (done in patients with no electrocardiographic findings and without elevated markers of myocardial damage).

Patients who failed to meet the first 3 criteria could also be included if they had a very suggestive clinical history, that is, chest pain at rest or, in the event of pain during exercise, of at least 1 week duration, or pain with a clear decrease in the appearance threshold (in patients with chronic angina). Final diagnosis of the myocardial infarction was made if troponin I was elevated (>0.5 ng/mL). The treatment administered consisted of aspirin, low-molecular weight heparin, nitrates, and beta-blockers (or calcium antagonists if beta-blockers were contraindicated). The patients were treated according to a conservative strategy. Coronary angiography was done in the event of recurrent chest pain (despite treatment), heart failure, or positive findings in the exercise test done before discharge. All clinical and biochemical data used in the analysis were recorded at the time of admission.

Renal Failure

Serum creatinine levels were measured during the first 24 hours in the emergency room. The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula[15,20] presented below:

$$\text{Estimated GFR (mL/min per 1.73 m}^2 \text{ of body surface)} = 186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{age [in years]})^{-0.203}$$

For women, the value was multiplied by 0.742.

The population was divided into 2 subgroups according to the creatinine concentrations at the moment of admission (greater than or less than 1.3 mg/dL, which is the upper limit of this test in our hospital) and into 5 categories according to the estimated GFR obtained (<15, 15-29, 30-59, 60-89, and ≥90 mL/min/1.73 m²), in accordance with international guidelines,[21] and each category was analyzed separately. The remaining prognostic variables used in the analysis were also collected at the moment of admission.

Other Analytical Measurements

Troponin I and myoglobin (immunometric method, DPC, Los Angeles, California, USA) were analyzed on arrival at the emergency room and after 6 hours (for patients who arrived within 2 hours of the onset of symptoms), and then after 8, 12, 18, and 24 hours (until the maximum was reached). In accordance with the recommendations of our laboratory, cutoff points of 0.5 ng/mL for troponin I and 70 ng/mL for myoglobulin were established.

Episodes Analyzed

We defined all-cause mortality as the primary endpoint in the 1-year follow-up.

TABLE 1. Characteristics of the Study Population, Stratified According to Creatinine Levels at the Time of Admission: Univariate Analysis*

	Creatinine ≤1.3 mg/dL (n=812)	Creatinine >1.3 mg/dL (n=217)	P
Men, %	64.0	71.4	.044
Years, mean age±SD,	67.1±11.7	73.8±10.8	<.001
Smokers, %	23.6	16.6	.02
Ex-smokers, %	30.0	39.6	.009
Hypertension, %	62.3	78.8	<.001
Dyslipidemia, %	45.7	41.0	NS
Diabetes mellitus, %	30.2	37.3	.049
Family history of IHD, %	10.6	3.2	<.001
History of IHD, %	46.0	53.0	NS
ST-segment depression, %	26.4	30.9	NS
Killip >1, %	13.2	40.1	<.001
Mean±SD troponin I, ng/mL	9.2±20.8	17.2±29.0	<.001
Mean±SD myoglobin, mg/mL	103.7±150.8	214.5±230.7	<.001
Mean±SD creatinine (on admission), mg/dL	0.98±0.19	2.25±1.55	<.001
Mean±SD EGFR, mL/min/1.73 m2	76.7±26.1	36.3±13.9	<.001

*IHD indicates ischemic heart disease; EGFR, estimated glomerular filtration rate; NS, not significant.

Follow-Up

All patients were monitored for at least 1 year or until the primary endpoint was reached (median follow-up lasted 54 weeks). Follow-up was by telephone, visits to outpatient clinics, and by review of the databases and medical records of the hospital.

Statistical Analysis

Continuous variables with a Gaussian distribution were described as means ±SD and compared with the Student t test for independent samples, or with ANOVA. Variables not normally distributed were represented as medians and interquartile range (IR) and compared by the Mann-Whitney test. Discrete variables were expressed as percentages and comparisons made with the χ^2 test.

A Cox multiple regression analysis was used to assess the independent role of the clinical and biochemical risk factors, as well as the Killip class, on admission, in predicting all-cause mortality according to whether or not renal failure was present. In this multivariate analysis, variables traditionally recognized as prognostic were included (age, sex, troponin concentrations, Killip class at the time of admission, and diabetes mellitus), as well as those with a P value greater than .20 in the univariate analysis provided they were collected within 24 hours of admission (early prognostic stratification). Two models were constructed, one with creatinine levels (for each 0.1 mg/dL) and the other with the estimated GFR, and the C statistic was determined for each. This parameter measures the predictive capacity of each model and determines how much information the model provides.[22] The same models were applied to the population divided into subgroups according to the presence of heart failure at the time of admission (Killip >1).

We investigated the proportionality of risk with the Schoerrfeld residuals analysis and the functional form of the quantitative variables (log-linear ratio) was determined by fractional polynomials. The coefficients estimated were expressed as hazard ratios (HR), with the corresponding 95% confidence intervals (CI). In all cases, P values below .05 were considered significant.

All statistical calculations were done with the SPSS software package, version 10.0 (Chicago, IL, USA) and STATA 8.2.

RESULTS

Baseline Characteristics

The study included 1029 patients who were admitted consecutively to our hospital and who met the inclusion criteria. Of these, 65.3% were men, the mean age was 68.6 ±11.8 years, 47.3% had a history of ischemic heart disease (27.4% had suffered a previous infarction), 44.7% had dyslipidemia, 31.7% were diabetic, 12.2% were insulin-dependent, 22.2% were smokers, and 65.8% had a history of hypertension. Myocardial infarction was finally diagnosed (troponin I >0.5 ng/mL) in 58.7% of the patients (n=604).

Dynamic ST-segment depression was reported in 27.3% of the patients, whereas T-wave inversion appeared in 9%. Signs of pump failure were observed in 19% of the patients (Killip class II in 13.5%, class III in 5%, and class IV in 0.1%) on admission. Troponin I concentrations were 10.94 ng/mL (interquartile range [IR]=10.5) and creatinine concentrations were 1.18 (0.95) mg/dL. Overall, 21.2% of the patients had creatinine concentrations greater than 1.3 mg/dL (renal failure) on admission. Cardiac catheterization was done during admission in 44.8% of the patients (15.4% of all

patients underwent percutaneous revascularization and 6.3% had bypass surgery).

Association Between Renal failure and Other Risk Factors

Patients with creatinine greater than 1.3 mg/dL were older and tended to be men. In addition, a higher percentage of these patients had been smokers and had diabetes mellitus, whereas a lower percentage were active smokers and had a family history of early ischemic disease. Likewise, on admission, these patients showed higher maximum troponin I and myoglobin concentrations, and a higher percentage of these patients had heart failure (Table 1). This tendency can also be appreciated in the different subgroups according to estimated GFR (Table 2). That is, the lower the estimated GFR, the higher the percentage of men, hypertense patients, those with a history of ischemic heart disease, and heart failure at the time of admission. These patients were also older, smoked less, and had a more extensive family history of early heart disease.

Serum Creatinine Levels and Glomerular Filtration Rate as Prognostic Factors

Variables associated with mortality during follow-up according to the bivariate analysis are shown in Table 3. It should be pointed out that the patients who died were older and had a more extensive history of diabetes and ischemic heart disease, and that a higher percentage of these patients presented with heart failure at the time of admission. These patients also presented higher concentrations of troponin I, myoglobin, and creatinine, and a smaller percentage were dyslipidemic and smokers.

The Kaplan-Meier survival curve reflects the increased risk of all-cause death as a function of

creatinine concentrations greater than 1.3 mg/dL (Figure 1A) and as a function of the different subgroups of estimated GFR (Figure 1B). This difference is already apparent at the start of follow-up, as can be appreciated in both figures.

Age, diabetes, maximum concentration of troponin I, presence of heart failure on admission (Killip >1), and creatinine concentrations at the time of admission were identified as independent predictors of death in the multivariate Cox regression analysis (Table 4). The same predictors were identified with estimated GFR instead of creatinine concentrations, although in this case men were also at a significantly greater risk (Table 5). Both these multivariate analyses had very high predictive parameters (C statistic), suggesting that the information provided by the model with creatinine as a variable is very similar to the model that uses estimated GFR as a variable.

A separate analysis of patients with heart failure on admission was carried out to avoid the influence of pump failure in renal function (prerenal failure), but both creatinine concentrations and estimated GFR behaved as independent predictors of death in the follow-up of both groups (Tables 4 and 5, models 2 and 3).

Creatinine Concentrations/Glomerular Filtration Rate and Functional Risk of Death

In the analysis of functional form of creatinine and estimated GFR, as determined with the final multivariate model by fractional polynomials, it is worth highlighting that both variables showed a linear increase in risk of overall mortality (Figure 2A and 2B). This risk is greater after passing theoretically normal values—greater than 1.2 mg/dL for creatinine and below 45 mL/min/1.73 m^2 for estimated GFR, with the same increase in risk for each increment in these values.

TABLE 2. Characteristics of the Study Population, Stratified According to the Estimated Glomerular Filtration Rate Categories of the National Kidney Foundation (mL/min/1.73 m^2 of Body Surface): Univariate Analysis*

EGFR	<15 (n=25)	15-29 (n=59)	30-59 (n=313)	60-89 (n=489)	≥90 (n=153)	P
Men, %	69.6	43.5	56.0	70.3	78.9	<.001
Mean age±SD, years	69.1±12.7	74.9±10.4	74.3±9.5	67.8±11.5	59.1±10.7	<.001
Smokers, %	13	8.7	14.1	20.7	43.7	.001
Ex-smokers, %	39.1	30.4	32.0	35.6	25.4	NS
Hypertension, %	91.3	82.6	71.5	63.0	53.5	<.001
Dyslipidemia, %	60.9	45.7	39.9	44.1	52.8	NS
Diabetes mellitus, %	34.8	50.0	34.7	30.1	32.4	NS
Family history of IHD, %	0	6.5	4.1	10.5	14.1	<.001
History of IHD, %	60.9	47.8	52.9	48.4	36.6	.002
ST-segment depression, %	43.5	39.1	26.8	25.1	24.6	NS
Killip >1, %	43.5	43.5	34.4	11.4	4.9	<.001
Mean±SD troponin I, ng/mL	15.3±23.7	24.2±36.6	13.5±25.3	9.6±21.8	9.5±18.8	<.001
Death, %	52.2	37.0	24.4	8.4	1.4	<.001

*IHD indicates ischemic heart disease; EGFR, estimated glomerular filtration rate; NS, not significant.
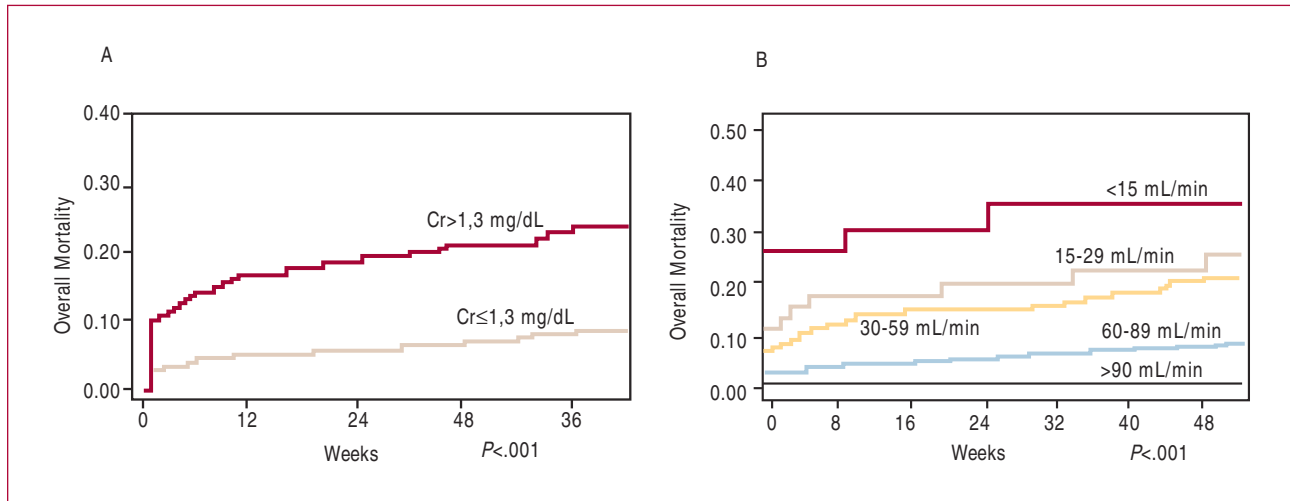
Figure 1. Kaplan-Meier curve for overall mortality in patients with non-ST-elevation acute coronary syndrome, stratified according to serum creatinine concentrations (Cr) on admission (A) or according to estimated glomerular filtration rate (B).

TABLE 3. Prognostic Predictors of Death at 1 Year: Univariate Analysis*

	Death (n=139)	No Death (n=890)	P
Men, %	66.6	61.2	NS
Years, mean age±SD	76.3±9.1	67.2±11.8	.000
Hypertension, %	69.1	65.2	NS
Smokers, %	10.1	24.0	.000
Ex-smokers, %	36.0	31.7	NS
Dyslipidemia, %	33.8	46.5	.003
Diabetes mellitus, %	48.2	29.0	.000
Family history of IHD, %	4.4	9.9	.037
History of IHD, %	56.1	44.7	.028
Killip >1, %	48.9	13.4	.000
ST-segment depression, %	34.6	26.3	.033
Mean±SD troponin I, ng/mL	21.0±31.7	9.21±20.6	.000
Mean±SD myoglobin, mg/mL	233.5±257	103.6±151	.000
Mean±SD creatinine (on admission), mg/dL	1.80±1.56	1.09±0.78	.000
Creatinine >1.3 mg/dL, %	47.9	16.8	.000
Mean±SD EGFR, mL/min/1.73 m²	48.5±23.7	70.5±28.6	.000

*IHD indicates ischemic heart disease; EGFR, estimated glomerular filtration rate; NS, not significant.

DISCUSSION

This single-center prospective observational study conducted according to a strict methodology, in which new definitions of acute coronary syndromes were used,[14] shows that determination of creatinine on admission is one of the important variables to be considered for initial stratification of patients with NSTE-ACS.

Assessment of renal function, however, is not used when drawing up the most widely used scores for risk in this type of patient,[23] although there is growing interest in the prognostic importance of renal failure in patients with ACS mainly because this condition is becoming increasingly prevalent. A number of reasons have been put forward to explain this increase such as increased incidence of the most common causes of renal failure (hypertension, diabetes mellitus, and generalized arteriosclerosis). Additionally, the most recent studies may provide a more accurate picture of renal function in such patients.[11,24] Finally, most previous studies that provided information on the prevalence of renal failure in patients with ACS were based on selected populations (coronary unit, clinical trials), which in some cases expressly excluded such patients.[1,2,4,7,12,13]

In agreement with the most recent studies,[15] a little over 20% of the patients in our study admitted to hospital had renal failure. These results can be extrapolated to the general population, as our study population was a consecutive unselected population.

For the analysis of prognosis, we used not only creatinine concentrations but also GFR estimated with the MDRD equation,[20] which, according to previous

TABLE 4. Independent Predictors of Mortality at 1 Year of Follow-Up: Multivariate Analysis (Cox Regression) With Variables Obtained on Admission, Including Creatinine*

	P	HR	95% CI
Age (per year)†	.000	1.08	1.06-1.10
Diabetes mellitus†	.001	1.70	1.26-2.49
Killip >1†	.000	2.74	1.92-3.92
Maximum troponin I concentration (for each ng/mL)†	.010	1.01	1.00-1.01
Creatinine (for each 0.1 ng/mL)†	.000	1.04	1.03-1.05
Creatinine (for each 0.1 ng/mL)‡	.000	1.46	1.27-1.69
Creatinine (for each 0.1 mg/dL)$			
C statistic for the model†=0.8103	.000	1.49	1.27-1.75

*HR indicates hazard ratio; CI, confidence interval.
†Analysis of all patients.
‡Analysis of patients without heart failure on admission (the model includes age, diabetes, maximum troponin I, and creatinine).
$Analysis of patients with heart failure on admission (the model includes age, diabetes, maximum troponin I, and creatinine).

TABLE 5. Independent Predictors of Mortality at 1 Year of Follow-Up: Multivariate Analysis (Cox Regression) With Variables Obtained on Admission, Including Glomerular Filtration Rate*

	P	HR	95% CI
Age (per year)†	.000	1.06	1.04-1.08
Men†	.012	1.59	1.10-2.27
Diabetes mellitus†	.002	1.71	1.26-2.49
Killip >1†	.000	2.30	1.60-3.31
Maximum troponin I concentration (for each ng/mL)†	.011	1.01	1.00-1.01
EGFR (per mL/min/1.73 m²)†	.000	0.97	0.97-0.98
EGFR (per mL/min/1.73 m²)‡	.000	0.98	0.96-0.99
EGFR (per mL/min/1.73 m²)$	.000	0.97	0.96-0.98

C statistic for the model† =0.8124
*HR indicates hazard ratio; CI, confidence interval; EGFR, estimated glomerular filtration rate.
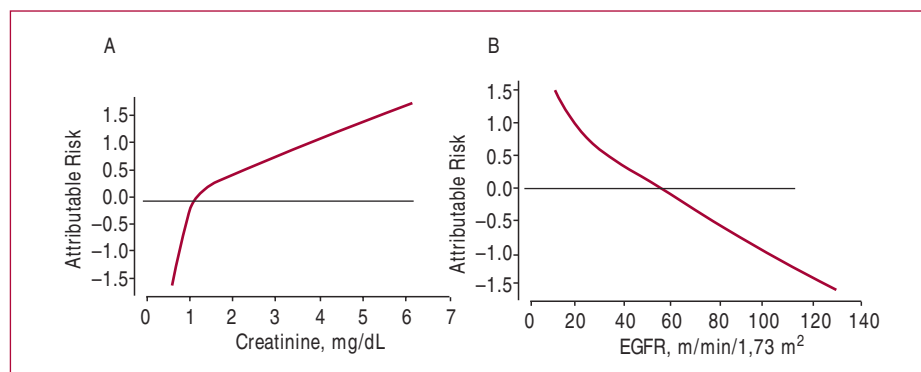†Analysis of all patients.
‡Analysis of patients without heart failure on admission (the model includes age, diabetes, maximum troponin I, and creatinine).
$Analysis of patients with heart failure on admission (the model includes age, diabetes, maximum troponin I, and creatinine).

studies,[15,25] is more accurate and provides a better assessment of renal function in elderly patients and women. Moreover, the equation is easier to apply than other formulae for estimating filtration because it does not require the weight of the subject (which may be hard to measure in critically ill patients and not available for those who die prematurely). Nevertheless, this variable did not have a higher predictive capacity than creatinine on its own in our multivariate models (Tables 4 and 5), and the estimated GFR is of relative value in the present study.

As we mentioned earlier, the increase in risk is proportional to the elevated levels of serum creatinine (or the decrease in estimated GFR) on admission. This increase in risk is linear (Figure 2) and there is no cutoff point beyond which the patients show a clear increase in risk—the higher the concentration of creatinine, the higher the risk (even within the normal range). This observation agrees with similar recent studies.[11,26,27]

This increased risk could be due to a variety of reasons. On the one hand, patients with renal failure have a higher prevalence of documented cardiovascular risk factors, such as diabetes mellitus, dyslipidemia, left ventricular hypertrophy, or generalized atherosclerosis.[28-30] Also, as shown in Tables 1 and 2, these patients present in the emergency room with a less favorable clinical outlook in terms of, for example, Killip class or maximum troponin concentrations. These patients, who according to the clinical guidelines of the leading international societies, should receive aggressive treatment, receive less effective therapeutic strategies, as reflected in previous publications.[9,31,32] Thus, for example, in the study by Berger et al,[31] patients with renal failure received aspirin, angiotensin converting enzyme (ACE) inhibitors, and beta-blockers (even though this is shown to be the most beneficial treatment) less often than those with normal renal function.[31,33] Furthermore, according to Freeman et al,[7] such patients are less likely to undergo

Figure 2. Risk profile attributable to serum creatinine concentrations on admission (A) and to estimated glomerular filtration rate (EGFR) (B).

revascularization procedures (angioplasty) and antiplatelet agents are used less.

It has also been shown that the drugs and treatments prescribed (contrasts, ACE inhibitors, IIb/IIIa receptor antagonists) are more toxic in such patients and this, along with the increased number of bleeding complications,[7,9] is responsible for a less favorable prognosis.

This study, like all observational studies, was limited by the lack of stratified randomization. A further limitation of the study was the failure to analyze treatments prescribed during admission, which might in part explain the results obtained. These data were not included because our aim was to determine the prognosis from the outset, and so we only used variables obtained on admission. Another limitation is that the measurement of creatinine, and therefore the estimated GFR on admission, was susceptible to the initial hemodynamic state of the patient and so would not accurately reflect baseline renal function.

CONCLUSIONS

Assessment of renal function by determining creatinine (or estimating GFR) provides independent and valuable prognostic information for immediate stratification of patients with NSTE-ACS (regardless of whether or not heart failure is present), although this variable is not included in current risk scales for this type of patient. Any increase in creatinine concentrations (or decrease in GFR) reflects an increased risk of all-cause death after 1 year of follow-up, an increase that is even larger than that associated with other traditional predictors. This marker is immediately and readily obtained, and available to all hospitals.

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