

In-Hospital Prognostic Value of Glomerular Filtration Rate in Patients With Acute Coronary Syndrome and a Normal Creatinine Level

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Introduction and objectives. Kidney failure is more prevalent in patients with ischemic heart disease than in the general population. A high serum creatinine level is known to be a predictor of an adverse outcome in acute coronary syndrome. The aim of this study was to investigate the clinical significance of the glomerular filtration rate in patients with acute coronary syndrome and a normal baseline creatinine level.

Methods. The study included 583 consecutive patients admitted to a coronary care unit with acute coronary syndrome (with or without ST-segment elevation) whose baseline serum creatinine level was less than 1.3 mg/dL. The creatinine clearance rate at admission was calculated using the Cockcroft-Gault equation, and the presence of cardiovascular risk factors, coronary anatomy (from angiography), type of revascularization, maximum cardiac enzyme levels, left ventricular ejection fraction and, ultimately, in-hospital mortality were recorded.

Results. Around 50.8% of patients presented with ST-segment elevation acute coronary syndrome. The median serum creatinine level on admission was 0.98 mg/dL (0.9-1.1 mg/dL) and the median creatinine clearance rate was 81.29 mL/min (61.2-98.4 mL/min). The in-hospital mortality rate was 2.7%. Glomerular filtration rate, previous coronary disease, Killip class on admission, and the need for intraaortic balloon counterpulsation were found to be independent predictors of mortality.

Conclusions. In patients with acute coronary syndrome and a normal creatinine level on admission, estimation of the glomerular filtration rate provided important information on short-term prognosis. This parameter should be included in the risk assessment of patients with normal serum creatinine levels.

Key words: Prognosis. Acute coronary syndrome. Creatinine. Creatinine clearance. Glomerular filtration rate.

Valor pronóstico intrahospitalario del filtrado glomerular en pacientes con síndrome coronario agudo y creatinina normal

Introducción y objetivos. La insuficiencia renal es más prevalente en los pacientes con cardiopatía isquémica que en la población general. La presencia de creatinina sérica elevada es un conocido factor de mal pronóstico en el síndrome coronario agudo. En este estudio se evalúa la relevancia clínica del filtrado glomerular renal en los pacientes con síndrome coronario agudo y un valor de creatinina basal normal.

Métodos. Se incluyó a 583 pacientes consecutivos que ingresaron en la unidad coronaria con síndrome coronario agudo (con y sin elevación del segmento ST) y creatinina basal < 1,3 mg/dl. Se estimó el filtrado glomerular renal en el momento del ingreso mediante la fórmula de Cockcroft-Gault y se revisó la presencia de factores de riesgo cardiovascular, la anatomía coronaria (coronariografía), el tipo de revascularización, los niveles máximos de las enzimas cardíacas, la fracción de eyección y, finalmente, la mortalidad hospitalaria.

Resultados. El 50,8% de los pacientes presentaba síndrome coronario agudo con elevación del segmento ST. La mediana de la creatinina sérica en el momento del ingreso fue de 0,98 mg/dl (0,9-1,1 mg/dl) y del aclaramiento de creatinina de 81,29 ml/min (61,2-98,4 mg/dl). La mortalidad intrahospitalaria fue del 2,7%. Se encontraron como factores predictores independientes de mortalidad el filtrado glomerular renal, los antecedentes de cardiopatía isquémica, la clase Killip en el momento del ingreso y la necesidad de balón de contrapulsación.

Conclusiones. En pacientes con un síndrome coronario agudo y creatinina normal en el momento del ingreso, el cálculo del filtrado glomerular renal aporta una información relevante para el pronóstico en la fase aguda. Este parámetro debería añadirse en la valoración del riesgo de los pacientes con cifras normales de creatinina basal.

Palabras clave: Pronóstico. Síndrome coronario agudo. Creatinina. Aclaramiento de creatinina. Filtrado glomerular renal.

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INTRODUCTION

Ischemic heart disease is more prevalent and more aggressive in patients with advanced renal disease. Cardiovascular disease is the most common cause of

ABBREVIATIONS

LVEF: left ventricular ejection fraction

GFR: glomerular filtration rate

OR: odds ratio

ACS: acute coronary syndrome

death among such patients, while impaired renal function is associated with a poor long term prognosis in patients with heart disease; the progress of the disease is quicker, complications more frequent, and restenosis more common among revascularized patients, etc.¹⁻⁴

Numerous authors have investigated the prognostic value of kidney failure in acute coronary syndrome (ACS), but the majority of these studies have involved the use of data from large, multicenter clinical trials, commonly with strict inclusion criteria and non-consecutive patients.^{3,5,6} In addition, they have generally used a serum creatinine level above the normal limit as an indicator of kidney failure, when the glomerular filtration rate (GFR) is the best index of renal function.⁷⁻⁹ There are numerous formulae and equations for estimating the GFR, among which the Cockcroft-Gault equation is one of the best known and validated. This equation was designed to determine creatinine clearance, the most commonly used method for measuring the GFR.^{7,8} The hypothesis of the present work was that, since GFR is the best indicator of renal function, mildly impaired renal function (measured as a function of the estimated GFR) should also be taken into account when determining an early prognosis for patients with ACS and normal creatinine levels.

The main aim of this work was to determine the relationship between the GFR at the time of admission and the in-hospital mortality of patients with ACS (with or without elevation of the ST segment) whose baseline creatinine levels were within normal limits. The relationships between in-hospital death and the presence of classic cardiovascular risk factors, a history of ischemic heart disease, Killip class at the moment of admission, maximum troponin I level, the left ventricular ejection fraction (LVEF), and length of hospital stay were also studied. In addition, in patients who underwent coronary angiography, the number of affected vessels was recorded and related to in-hospital mortality.

METHODS

This observational study included consecutive patients admitted to the coronary unit of our hospital (from the emergency room or other units) between January 1, 2005 and March 31, 2006 with a diagnosis of ACS and a baseline serum creatinine level of ≤ 1.3 mg/dL. The study involved the prospective inclusion of patients but the

retrospective collection of certain data. Patients who required invasive ventilatory support (with or without vasoactive agents) before their admission to the coronary unit were excluded. The diagnostic criteria used to determine ACS with ST-segment elevation were pain of an ischemic nature plus an electrocardiogram (ECG) with an ST segment elevation of at least 1 mm as determined by 2 or more contiguous bipolar leads, or of more than 2 mm as determined by 2 or more precordial leads, for more than 20 min. All patients received urgent reperfusion treatment (primary angioplasty or fibrinolysis). A diagnosis of high risk ACS without of the ST-segment elevation was made for all patients with chest pain of an ischemic nature plus ECG results suggestive of ischemia (ST segment depression or alterations in the T wave) and/or an increase in myocardial necrosis markers (troponin I >0.2 ng/mL). The majority of patients with ACS without ST-segment elevation were subject to invasive correction with coronary angiography within 24-48 h of admission.

This study did not include patients referred from other hospitals for coronary angiography. Our hospital is the referral hospital for several centers that lack catheterization facilities. Including these patients could have introduced a bias since not all their data were available (eg, anamneses and complementary tests); neither would the sample have been homogeneous in terms of inclusion criteria. In addition, many of these patients were later sent back to their original centers; it would therefore have been difficult to know how they progressed towards the end of their hospital stay.

The following information was collected from the medical history of each patient: the presence of cardiovascular risk factors such as use of tobacco in the 3 months prior to admission, high blood pressure, dyslipidemia and diabetes mellitus, and any background on ischemic heart disease, such as stable angina under treatment, a history of myocardial infarction, and/or prior revascularization treatment.

Hemoglobin and baseline creatinine levels were determined in blood tests performed at admission. Patients with a serum creatinine concentration of >1.3 mg/dL (the normal limit used at our laboratory) were excluded.

The GFR was calculated using the Cockcroft-Gault formula^{7,8,10}:

$$\text{GFR estimated [mL/min]} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{\text{serum creatinine [mg/dL]} \times 72}$$

The result is multiplied by 0.85 for women.

The Killip class and LVEF of all patients were recorded at admission. Also recorded were the maximum troponin I concentration, the duration of hospital stay (days), whether diagnostic coronary angiography was performed,

and if so the number of vessels affected. In hospital all-cause mortality was the main outcome recorded.

Continuous variables with a normal distribution were described in terms of mean (standard deviation [SD]) and compared using the Student *t* test after examining the homogeneity of the variance. The variables that did not follow a Gaussian distribution were expressed as a median plus interquartile range, and were compared using the Mann Whitney U test or the median test when the dispersion was wide. Categorical variables were recorded as absolute values and percentages and were compared using Fisher's Exact Test or the Pearson χ^2 test. Finally, a logistic regression analysis was performed to determine the relationships between the clinical and laboratory variables measured and GFR in order to predict the likelihood of in-hospital death. This analysis included the variables significantly related to mortality in univariate analysis. Adjusted odds ratios (OR) are provided, along with the 95% confidence limits (95% CI). For this analysis, some variables were recoded: GFR as three intervals (< 60, 60-80, and >80 mL/min),^{8,11} the Killip class at admission (classes I-II or III-IV), and the number of lesions seen in coronary angiography (1, 2, or 3 vessels affected, and left main coronary artery lesion [with or without other lesions]).

A *P* value less than .05 was considered significant. All statistical analyses were performed using SPSS v.12 software.

TABLE 1. Baseline Characteristics of the Study Population*

Variable	Result, n (%)
Diagnosis ACS with ST-segment elevation	296 (50.8%)
ACS without ST-segment elevation	287 (49.2%)
Male sex	417 (71.5%)
Age, mean (SD), y [†]	63.9 (13)
Cardiovascular risk factors	
Diabetes mellitus	153 (26.2%)
High blood pressure	318 (54.5%)
Smoking	254 (43.6%)
Dyslipidemia	271 (46.5%)
History of ischemic heart disease	139 (23.8%)
Baseline serum creatinine concentration, mg/dL [‡]	0.98 (0.9-1.1)
GFR, mL/min [‡]	81.29 (61.2-98.4)
Hemoglobin at admission, mg/dL [‡]	13.8 (12.9-15)
Killip class at admission \geq III	20 (3.4%)
Lesions revealed by coronary angiography	
No significant lesions	34 (6%)
One vessel with disease	265 (47%)
Two vessels with disease	158 (28%)
Three vessels with disease and/or left main coronary artery disease	107 (19%)
Maxim troponin I, ng/ml [‡]	18.9 (4.2-61.0)
LVEF [‡]	57 (45-60)

*LVEF indicates left ventricular ejection fraction; GFR, glomerular filtration rate; ACS, acute coronary syndrome.

[†]Mean (standard deviation).

[‡]Median (interquartile range).

RESULTS

Between January 1, 2005 and March 31, 2006, 681 patients with a diagnosis of ACS were attended to in our coronary unit. Of these, 98 had a baseline serum creatinine concentration of >1.3 mg/dL. The remaining 583 (86%) patients with normal serum creatinine concentrations made up the study population. Some 50.8% (n=296) of these presented with ACS with ST-segment elevation, 71.5% (n=417) were men, and the mean age was 63.9 (13) years. Table 1 records the presence of cardiovascular risk factors and other baseline characteristics. The median serum creatinine value at admission was 0.98 mg/dL (range, 0.9-1.1 mg/dL), while that for the GFR was 81.29 mL/min (range, 61.2-98.4 mL/min). The GFR was >80 mL/min in 263 patients (45.1%), between 60 and 80 mL/min in 189 (32.4%), and <60 mL/min in 131 (22.5%).

A Killip class of III was recorded for 3.4% of patients; intra-aortic balloon counterpulsation was provided for a total of 2.6%. The median hospital stay was 7.6 days (range, 4.1-8.4 days). Diagnostic coronary angiography was performed in 96.9% of cases. Revascularization by angioplasty was performed in 434 patients (74.4%) and by heart surgery in 47 patients (8.1%). Sixteen patients (2.7%) died while during their hospital stay. The median GFR of those who died was 62.4 mL/min (range, 43.3-75.9 mL/min), while for those who survived it was 81.8 mL/min (range, 61.8-98.6 mL/min).

Univariate analysis showed a significant association between in-hospital mortality and GFR (*P*=.007), a history of ischemic heart disease (*P*=.005), Killip class at the time of admission (*P*<.001), the need for intra-aortic balloon counterpulsation (*P*<.001), the number of lesions revealed by coronary angiography (*P*=.003), and the hemoglobin concentration at admission (*P*=.001). No significant relationship was seen between in-hospital mortality and the presence of the classic cardiovascular risk factors of smoking, diabetes mellitus, high blood pressure, and dyslipidemia, nor with patient age, LVEF nor the maximum troponin I concentration. Neither was any significant relationship found with the baseline serum creatinine concentration (*P*=.65). However, a diagnosis of ACS with ST-segment elevation at admission was significantly associated with in-hospital mortality (Table 2). Figure shows the relationship of in-hospital mortality with three categories of GFR (<60 mL/min, 60-80 mL/min, and >80 mL/min; *P*=.008).

Multivariate analysis revealed a history of ischemic heart disease, Killip class at admission, the need for balloon counterpulsation, and GFR to be independent predictors of in-hospital mortality (Table 3).

DISCUSSION

This single center observational study shows that calculating the at-admission GFR of patients with ST-

TABLE 2. Univariate analysis. Relationship of Clinical and Laboratory Variables With in-Hospital Mortality*

	No Death (n=567), n (%)	Death (n=16), n (%)	P
Age, mean (SD), y†	63.7 (13)	69.8 (10.5)	.063
Male sex	409 (72.1%)	8 (50%)	.087
Diabetes	149 (26.3%)	4 (25%)	1
Smoking	249 (43.9%)	5 (31.3%)	.314
High blood pressure	310 (54.7%)	8 (50%)	.711
Dyslipidemia	263 (46.4%)	8 (50%)	.775
Prior ischemic heart disease	130 (22.9%)	9 (56.3%)	.005
ACS with ST-segment elevation	290 (51.1%)	6 (37.5%)	.31
Hemoglobin at admission, mg/dL‡	13.8 (12.9-15)	12 (10-13.2)	.001
Serum creatinine conc. at admission, mg/dL‡	0.98 (0.9-1.1)	1 (0.9-1.1)	.65
GFR, mL/min‡	81.8 (61.8–98.6)	62.4 (43.3-75.9)	.007
Killip class at admission ≥III	14 (2.5%)	6 (37.5%)	<.001
Counterpulsation balloon required	10 (1.8%)	5 (31.3%)	<.001
LVEF‡†	57 (45-60)	45 (30-60)	.137
Maxim troponin I, ng/mL‡	19.3 (4.2-61.8)	10.2 (1.4-73.3)	.549
Three vessels with disease and/or left main coronary artery disease	97 (17.1%)	9 (56.3%)	<.001

*LVEF indicates left ventricular ejection fraction; GFR, glomerular filtration rate; ACS, acute coronary syndrome.

†Mean (standard deviation).

‡Median (interquartile range).

segment elevation or without ST-segment elevation of high risk who show a normal serum creatinine concentration provides important information with regard to prognostic stratification during the acute phase. Renal failure is known to be a sign of poor prognosis (both in the short and long term) for patients with ischemic heart disease.^{3,6,11-16} However, only the stratification provided by the GRACE study¹⁷ includes the creatinine concentration along with other variables (7) in the estimation of the risk of mortality associated with ACS with or without ST-segment elevation at admission. Other types of initial stratification systems, such as the well known TIMI Risk Score for un stable angina and non-Q-Wave myocardial infarction¹⁸ don't include kidney function data.

The index that best assesses renal function is GFR. However, the serum creatinine concentration is the factor most commonly used, even though its value is influenced by patient age, sex, muscular mass, and diet. In addition, its relationship with GFR is not linear, and its sensitivity is poor with respect to the detection of chronic kidney failure. For these reasons the National Kidney Foundation recommends in its clinical practice guidelines that the Cockcroft-Gault or MDRD equations be used to determine the GFR¹⁰ (which is easily calculated)^{7,10} as a measure of renal function. This provides better information on renal function than the serum creatinine concentration despite its limitations (the need for a stable serum creatinine concentration, and the fact that there is no standardized method for its determination [different laboratories use different methods]). This can cause problems when comparing the results of different populations. More precise methods for determining the GFR include measuring the clearance of creatinine in

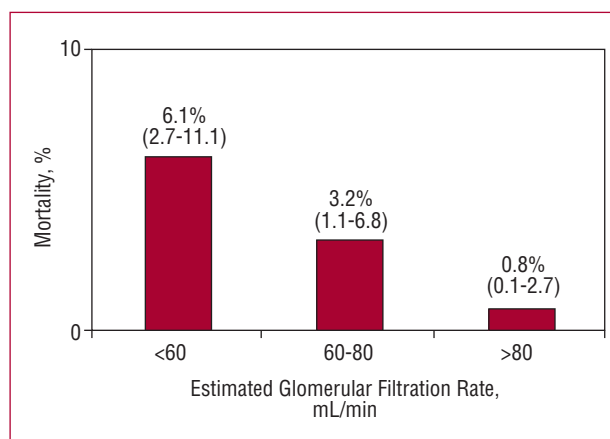


Figure 1. In-hospital mortality (%) with respect to glomerular filtration rate.

urine collected at 24 h or the plasma clearance of an exogenous marker, eg, inulin. However, these are of less clinical usefulness since results cannot be obtained rapidly; neither are they free of errors during urine sampling. Thus, their routine use with patients with ACS does not seem advisable; with such patients results that can help physicians arrive at a prognosis—which could help them make treatment decisions—are required rapidly.

The present study supports the idea that the presence or absence of renal failure be precisely determined since, when serum creatinine concentrations are normal, even mild renal failure (GFR around 60 mL/min) can have a negative impact on the prognosis of patients with ACS. It should be noted that, in the present work, the absolute value for serum creatinine was not found to be significantly

TABLE 3. Multivariate Analysis: Factors Predictive of in-Hospital Death in the Studied Population*

	OR (95% CI)	P
GFR (3 intervals)†	4.13 (1.29-13.21)	.017
Killip class at admission ≥III	42.57 (5.49-329.92)	<.001
History of ischemic heart disease	9.53 (1.64-55.52)	.012
Counterpulsation balloon required	20.05 (3.15-127.67)	.002

*CI indicates confidence interval; OR, odds ratio.

†Intervals: 1: >80; 2: 60-80; 3: <60 mL/min.

associated with mortality. Thus, the GFR—which provides a much more exact index of renal function in these patients—should always be calculated. In addition to the prognostic value of a more accurate appreciation of renal function in ACS, knowledge of the GFR is useful for optimizing treatment. It allows for the better dosing of agents that are eliminated via the kidney, permits more careful consideration of the use of nephrotoxic agents, and allows prophylactic measures to be taken against contrast medium-induced kidney damage when performing coronary angiography.

The mortality among the studied patients may seem too low. However, if the prognostic scale provided by the GRACE study¹⁷ is consulted, the expected mortality associated with a typical patient of the present study group, ie, in Killip class I, with a normal blood pressure, heart rate and serum creatinine concentration, a displaced ST segment and raised cardiac enzyme levels, would be just 2.9%. If this typical patient were in Killip class III at admission, the associated mortality rate would be 9.8%. The results suggest that including the GFR of patients with a normal baseline creatinine concentration would improve the prognostic stratification process.

A strong relationship exists between renal failure and coronary artery disease. Kidney failure, including even a relatively mild deterioration of the GFR, is associated with cardiovascular events. Weiner et al¹⁹ analyzed several observational studies and found that a reduction in GFR to below 60 mL/min significantly increases the incidence of death, infarction, or ictus in persons with no previously detected cardiovascular disease. In the VALIANT study, it was observed that a GFR of <81 mL/min was associated with an increase in the number of adverse events recorded in patients with myocardial infarction, even after adjustment for several variables.¹¹ In the present study this was seen in patients with ACS and normal baseline creatinine concentrations.

Renal failure seems to have an etiological role in the development of ischemic heart disease. Impairments in mineral metabolism relate renal failure with calcium deposits in the coronary arteries. In the CARE study,²⁰ serum phosphate concentrations were found to be inversely related to kidney function when the GFR was

<60 mL/min, and to be an independent predictor of myocardial infarction. The early stages of kidney failure are associated with an increase in the amplitude of the pulse and high renin concentrations, which can lead to hypertrophy of the left ventricle. In addition, reductions in hemoglobin levels have been reported even with mild renal failure.²¹ An association has also been found between a reduction in GFR and the levels of tumor necrosis factor α , reactive protein C, and fibrinogen, as well as with dyslipidemia and other biomarkers.^{22,23}

The limitations of this study include the fact that some of the data were collected retrospectively (via the patients' medical histories and release forms), although the patients were included in a prospective manner upon admission.

CONCLUSIONS

Impaired renal function is a sign of poor prognosis during the acute phase of ACS, even though it is commonly not assessed in patients admitted for this problem. The GFR, determined using the Cockcroft-Gault equation, is a more precise and accurate way of estimating kidney function than measuring the baseline serum creatinine concentration, and should probably substitute it for the short-term prognostic stratification of patients with ACS. At the very least it should be calculated and borne in mind when treating such patients with normal baseline creatinine levels.

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