ORIGINAL ARTICLE

Worsening renal function during an episode of acute heart failure and its relation to short- and long-term mortality: associated factors in the Epidemiology of Acute Heart Failure in Emergency Departments–Worsening Renal Function study

Lluís Llauger[1], Javier Jacob[2], Luis Arturo Moreno[3], Alfons Aguirre[4], Enrique Martín-Mojarro[5], Juan José Romero-Carrete[6], Gemma Martínez-Nadal[7], Josep Tost[8], Gerard Corominas-Lasalle[1], Àlex Roset[2], Carlos Cardozo[3], Guillem Suñén-Cuquerella[4], Brigitte Alarcón[5], Sergio Herrera-Mateo[6], José Carlos Ruibal[2], Aitor Alquézar-Arbé[6], Víctor Gil[7], Ruxandra Donea[8], Marta Berenguer[8], Pere Llorens[9], Bernat Villanueva-Cutillas[2], Francisco Javier Martín-Sánchez[10], Pablo Herrero[11], Òscar Miró[7] (en representación del grupo ICA-SEMES*)

Objective. To identify factors associated with worsening renal function (WRF) and explore associations with higher mortality in patients with acute heart failure (AHF).

Methods. Seven emergency departments (EDs) in the EAHFE–EFRICA study (Spanish acronym for Epidemiology of AHF in EDs — WRF in AHF) consecutively included patients with AHF and creatinine levels determined in the ED and between 24 and 48 hours later. Patients with WRF were identified by an increase in creatinine level of 0.3 mg/dL or more. Forty-seven clinical characteristics were explored to identify those associated with WRF. To analyze for 30-day all-cause mortality we calculated odds ratios (ORs). To analyze mortality at the end of follow-up and by trimester, adjusted for between-group differences, we calculated hazard ratios (HRs). The data were analyzed by subgroups according to age, sex, baseline creatinine levels, AHF type, and risk group.

Results. A total of 1627 patients were included. The subgroup of 220 (13.5%) with WRF were older, had higher systolic blood pressure, were more often treated with morphine, and had chronic renal failure; there was also a higher rate of hypertensive crisis as the trigger for AHF in patients with WRF. However, only chronic renal failure was independently associated with WRF (adjusted OR, 1.695; 95% CI, 1.264–2.273). The rate of 30-day mortality was 13.1% overall but higher in patients with WRF (20.9% vs 11.8% in patients without WRF; adjusted OR, 1.793; 95% CI, 1.207–2.664). Accumulated mortality at 18 months (average follow-up time, 14 mo/patient) was 40.0% overall but higher in patients with WRF (adjusted HR, 1.275; 95% CI, 1.018–1.598). Increased risk was greater in the first trimester. Subgroup analyses revealed no differences.

Conclusion. AHF with WRF in the first 48 hours after ED care is associated with higher mortality, especially in the first trimester after the emergency.

Keywords: Acute heart failure. Kidney failure. Mortality. Creatinine.

Factores asociados con el empeoramiento de la función renal durante un episodio de insuficiencia cardiaca aguda y su relación con la mortalidad a corto y largo plazo: estudio EAHFE - EFRICA

Objetivo. Identificar los factores asociados con el empeoramiento de la función renal (EFR) y si este se asocia a mayor mortalidad en pacientes que presentan un episodio de insuficiencia cardiaca aguda (ICA).

Método. Participaron 7 servicios de urgencias (SU) que incluyeron consecutivamente pacientes con ICA con determinación de creatinina en urgencias y a las 24-48 horas, y se identificaron aquellos con EFR (incremento de creatinina ≥ 0,3 mg/dL). Entre 47 características clínicas, se identificó las asociadas a EFR. Se investigó la mortalidad por cualquier causa a 30 días (OR) y al final del seguimiento (HR), esta última global y por periodos trimestrales, que se ajustó por las diferencias entre grupos. Se analizaron subgrupos según edad, sexo, creatinina basal, tipo de ICA y grupo de riesgo.

Resultados. Se incluyeron 1.627 pacientes, 220 (13,5%) con EFR, los cuales presentaban mayor edad, presión arterial sistólica, crisis hipertensiva como precipitante, tratamiento con morfina e insuficiencia renal crónica, aunque solo esta

Author affiliation:
[1]Emergency Department, Hospital Universitari de Vic, Barcelona, Spain.
[2]Emergency Department, Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat, Barcelona, Spain.
[3]Emergency Department, Hospital Universitario Austral, Buenos Aires, Argentina.
[4]Emergency Department, Hospital del Mar, Barcelona, Spain.
[5]Emergency Department, Hospital Santa Tecla, Tarragona, Spain.
[6]Emergency Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.
[7]Emergency Department, Hospital Clínic, University of Barcelona, Spain.
[8]Emergency Department, Hospital de Terrassa, Barcelona, Spain.
(Continues at foot of page)

Contribution of the authors:
All authors have confirmed their authorship of the document of responsibilities of the author, publication agreement and transfer of rights to EMERGENCIAS.

Corresponding author:
Lluís Llauger
C/ Francesc Pla "El Vigatà", 1
08500 Vic, Barcelona, Spain.

E-mail:
llauger.doc@gmail.com

Article information:
Received: 9-3-2020
Accepted: 2-4-2020
Online: 31-8-2020

Editor in charge:
Agustín Julián-Jiménez

[9]Emergency Department, Short Stay and Home Hospitalization, General Hospital of Alicante, Miguel Hernández University, Alicante, Spain. [10]Emergency Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain. [11]Emergency Department, Central University Hospital of Asturias, Oviedo, Spain.

última se asoció independientemente a EFR ($OR_{ajustada}$ = 1,695, IC 95% = 1,264-2,273). La mortalidad a 30 días fue de 13,1% (mayor en pacientes con EFR: 20,9% *vs* 11,8%, $OR_{ajustada}$ = 1,793, IC 95% = 1,207-2,664) y la mortalidad acumulada a 18 meses (tiempo medio de seguimiento 14 meses/paciente) fue del 40,0% (mayor en pacientes con EFR: $HR_{ajustada}$ = 1,275, IC 95% = 1,018-1,598). Este incremento de riesgo fue durante el primer trimestre. El análisis de subgrupos no mostró diferencias.

Conclusión. La ICA con EFR en las primeras 48 horas posteriores a la atención en el SU se asocia a mayor mortalidad, que se concentra durante el primer trimestre.

Palabras clave: Insuficiencia cardiaca aguda. Insuficiencia renal. Mortalidad. Creatinina.

Introduction

Acute heart failure (AHF) is a heterogeneous syndrome with an increasingly high impact on the healthcare system[1]. Prevalence of patients with AHF and preserved or intermediate ventricular function in relation to population aging is associated with increased co-existence with other comorbidities[2-4]. Renal dysfunction (RD), in its interaction with AHF, is included in the definition of type 1 cardiorenal syndrome CRS-1, and has been identified as one of the most important prognostic variables. However, it should be noted that this evidence comes from very heterogeneous cohorts, in which the definition of RD was also made using non-standardized criteria[5-7].

The term worsening of renal function (WRF), defined as the absolute variation in serum creatinine values of ≥ 0.3 mg/dL compared to values recorded at admission, is commonly used because of its association with poorer results, especially if it is a non-transitory phenomenon or with the presence of persistent congestion[8-13]. However, transitory elevations of creatinine have also been reported, which usually coincide with correct decongestion or the start of neurohormonal blocking drugs, whose most plausible physiopathological mechanism seems to be hemodynamic changes in glomerular function and not structural alterations of the renal tubules, so their presence does not suggest a worse prognosis[14]. The use of other variables of glomerular function, such as estimated glomerular filtration rate (eGFR) or cystatin-C has led to similar results[15-17]. Likewise, validation has been sought for the criteria of acute renal injury RIFLE, AKIN or KDIGO, for risk stratification in CRS-1, which also use urinary volume as a variable of tubular function[18]. However, coming from cohorts of hospitalized patients with chronic kidney disease or critical patients has not allowed them to reach general acceptance. Nor are there extensive studies of WRF in patients treated in hospital emergency departments (EDs) for AHF, of which up to 25% do not require hospitalization.

Consequently, the aim of this study was to explore the relationship between the WRF identified in the ED and the occurrence of adverse events during an AHF episode, as well as to investigate factors that may help predict their occurrence.

Method

The EAHFE-EFRICA study ("Worsening of Kidney Function During an AHF Episode") is a secondary analysis of the Epidemiology of Acute Heart Failure in Emergency Departments (EAHFE) registry. This is a multi-center, multi-purpose, non-interventional analytical registry with a prospective follow-up that includes all patients who visit an ED for an episode of AHF consecutively. Six different recruitment phases have been carried out (in 2007, 2009, 2011, 2014, 2016 and 2018) in a total of 45 Spanish EDs, with a final recruitment of 18,370 patients with AHF. The details and characteristics of these patients have already been published[19,20]. For the inclusion of patients, any case with suspected AHF based on the Framingham criteria was confirmed by the head researcher of each center with the determination of plasma natriuretic peptides or with the performance of an echocardiogram during admission for AHF or in the previous six months, following the recommendations of the current guidelines of the European Society of Cardiology[21]. The head researcher of each center was responsible for awarding the final diagnosis of each case. The only exclusion criterion was the concomitant presence of an acute coronary syndrome with ST segment elevation and AHF.

The ethical principles of the Declaration of Helsinki on human research were followed, and informed consent was requested from all patients to participate in the study. The protocol was approved by the Ethics and Clinical Research Committee of the Hospital Universitario Central de Asturias as the main committee, in addition to those of the other participating centers.

For this study, patients from the EAHFE registry collected in 7 EDs (Hospital Universitari de Vic, Hospital Universitari de Bellvitge, Hospital Clínic, Hospital del Mar, Hospital de la Santa Creu i Sant Pau and Hospital de Terrassa, in Barcelona, and Hospital de Sant Pau i Santa Tecla, in Tarragona) during phases 3, 4, 5 and 6 (2011, 2014, 2016 and 2018) were included. The creatinine was determined in the ED and in the first 48 hours of this baseline determination. Patients were divided into two groups, a group with WRF defined by an increase of creatinine ≥ 0.3 mg/dl (26.5 µmol/l), and a control group. A total of 47 variables were collected, 2 demographic (age and sex), 13 comorbidities (high blood pressure, diabetes mellitus, dyslipemia, ischemic

heart disease, chronic kidney disease, cerebrovascular disease, atrial fibrillation, valvular disease, peripheral artery disease, chronic obstructive pulmonary disease, dementia, neoplasm and previous heart failure), 3 baseline (Barthel index, New York Heart Association [NYHA] functional class IIIIV, left ventricular ejection fraction), 6 chronic treatment (loop diuretics, thiazide diuretics, angiotensin converting enzyme inhibitors [ACEI] or angiotensin II receptor antagonists [ARA-II], beta-blockers, aldosterone and digoxin receptor antagonists), 6 of precipitating factors (infection, tachyarrhythmia, hypertensive crisis, anemia, pharmacological or dietary transgression, acute non-ST segment elevation coronary syndrome), 3 regarding vital signs on arrival at the emergency department (systolic blood pressure, heart rate and oxygen saturation by pulse-oximetry), 6 of analytical data (hemoglobin, creatinine, sodium, potassium, troponin and NT-proBNP), 7 of treatment in the emergency department (intravenous diuretic, intravenous nitroglycerin, morphine, digoxin, amiodarone, inotropes or vasopressors, non-invasive ventilation), and 1 of severity of the episode (risk category in the MEESSI scale).

The primary outcome variable was all-cause mortality at 30 days and the end of follow-up. This was done through telephone contact or access to hospital and primary care records.

The qualitative variables were described by means of frequencies and percentages. The quantitative ones with the mean and the standard deviation (SD), if they followed a normal distribution, which was checked with the Kolmogorov-Smirnov test, or alternatively with the median and the interquartile range (IQR). The analysis of the distribution of the qualitative variables was carried out with the Chi-square test or Fisher's exact test, as appropriate, and the analysis of the quantitative variables was carried out with the Student's t-test or Mann-Whitney's U-test on the variables that did not follow a normal distribution.

To determine the factors associated with the presence or absence of WRF, a logistic regression model was used and odds ratios (OR) were calculated with their 95% confidence intervals (95% CI), raw and adjusted for the significant differences between both groups found in the univariate study.

The prognostic value of the WRF was evaluated from two different angles. First, mortality was analyzed at 30 days (primary objective) by logistic regression and the risk of patients presenting WRF compared to controls was expressed as OR (95% CI). Second, mortality was also analyzed at the end of the follow-up period (secondary objective) by Cox regression, and the risk of patients with WRF was expressed as a hazard ratio (HR, with 95% CI). In both cases, the results were expressed in a crude form and adjusted for the differences found between both groups (WRF and control) in the univariate study. In addition, the HR analysis was performed globally for all the follow-up and by quarterly periods in the first year of follow-up in the adjusted model. To this end, the time series of each quarter began on day zero of each quarter with the cases that remained in the global series at that time and those cases in which the monitoring continued beyond day 90 of that quarter were censored at 90 days. Finally, the study was completed with a subgroup analysis for the primary objective and the calculation of the interaction p. The segmentation variables were age, sex, basal creatinine, type of AHF and risk group (according to the MEESSI scale).

In all comparisons, it was accepted that differences were statistically significant if the P value was less than 0.05, or if the 95% CI of the HR or OR excluded the value 1. The statistical analysis was performed with the SPSS program version 24.0 for Windows (SPSS Inc, Chicago, USA).

Results

The 7 EDs participating in the EAHFE-EFRICA study recruited a total of 4,286 patients during phases 3, 4, 5 and 6 of the EAHFE registry. In 1,627, a basal serum creatinine concentration and another one in the first 48 hours were available, as well as clinical follow-up (Figure 1). Two hundred and twenty of these 1,627 patients formed the group with WRF (13.5%) and 1,407 the control group (86.5%).

Table 1 shows the results of the total population studied and the differences between the two groups. The EFR group presented increased age, systolic blood pressure, chronic renal failure, hypertensive crisis as a precipitant of AHF and treatment with morphine, but only chronic renal failure was independently associated with the presence of WRF, with an adjusted OR = 1.695 (95% CI: 1.264-2.273) (Table 2).

Mortality from all causes at 30 days was 13.1%. In the WRF group, it was higher than in the control group (20.9% vs. 11.8%) with an OR = 1,967 (95% CI: 1,368-2,828). Mortality adjusted for differences between groups obtained an adjusted OR = 1.793 (95% CI: 1.207-2.664).

The cumulative mortality at 18 months was 40.0% (mean follow-up time 14 months/patient) and, as shown in Figure 2, was higher in the WRF group [adjusted HR = 1.275 (95% CI 1.018-1.598)]. In Figure 3 we can see how this increase in risk was greater and reached statistical significance only in the first quarter after decompensation [adjusted HR = 1.494, (95% CI: 1.125-1.958)].

Table 3 shows the results of the subgroup analysis, where no differences were found in 30-day adjusted mortality based on age, sex, type of ventricular dysfunction, initial ED creatinine or MEESSI scale risk category

Discussion

The results of the EAHFE-EFRICA study show that the presence of WRF in patients with an episode of

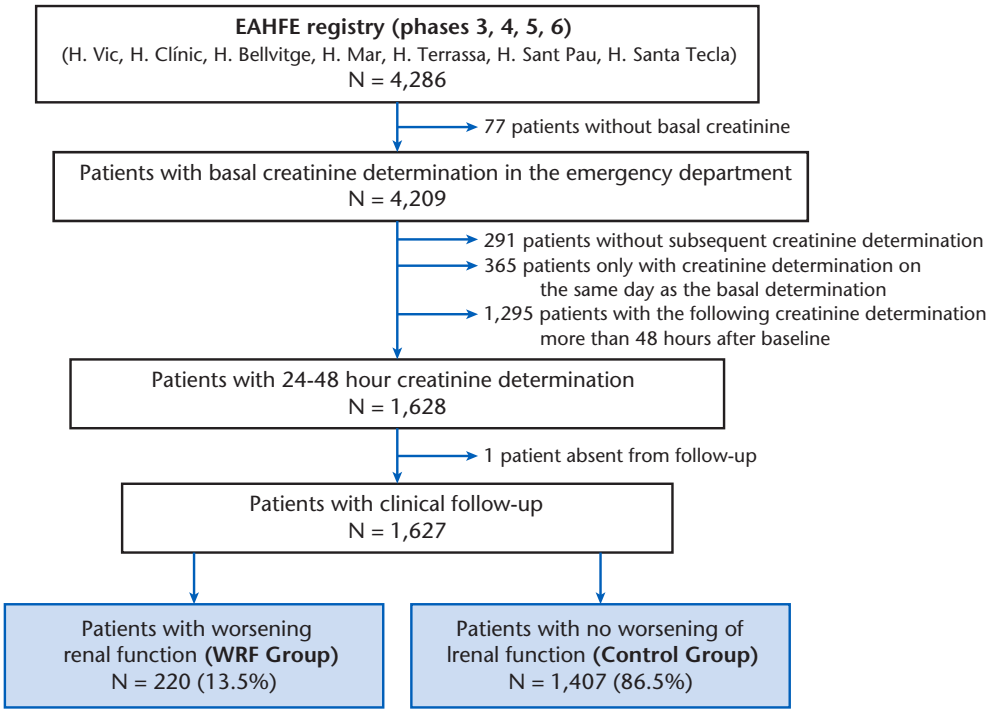

Figure 1. Patient inclusion flowchart.

AHF is low (13.5%) and lower than that published in other studies, which place it at around 23%[8,9]. Half of the patients who suffered from AHF already had an established CKD (chronic kidney disease) and, in fact, this was the only comorbidity that was independently associated with AHF. This result is consistent with most published studies[8]. On the other hand, the prognostic role of WRF was related to shorter survival both in the short term (30 days) and in the long term, highlighting that the increased risk was concentrated in the first quarter after decompensation.

Different mechanisms have been postulated in the physiopathology of WRF during an AHF episode, although it is not clearly established what they are and what role they play in the onset of WRF. The existing evidence comes mostly from works involving hospitalized patients, in which the most plausible mechanism would be renal hypoperfusion, either due to the presence of hypotension or reduced cardiac output, which would lead to neurohormonal activation of the renin-angiotensin-aldosterone system and the sympathetic system, with the consequent reabsorption of sodium and water to try to compensate for the deterioration of cardiac output and renal perfusion[22]. In our cohort, no data have been found that confirm this as the predominant mechanism, suggesting the presence of different or additional factors in the ED. The mean left ventricular ejection fraction (LVEF) of the groups was similar and mainly involved patients with preserved LVEF. Mean systolic blood pressure was in the normal range, even patients with WRF had higher figures, a situation that has already been described[8,23], and the use of vasopressors or inotropes was not greater in patients with WRF. Likewise, we did not find differences between both groups in the mean value of natriuretic peptides, which could lead to a higher volume load and myocardial stress. Consequently, it is very likely that this mechanism of renal hypoperfusion is more important in patients with signs of low cardiac output, especially in situations of cardiogenic shock, and that in the WRF of patients attending the ED there is the concurrence of other mechanisms, such as the use of drugs, both for the treatment of decompensation and chronic use, or the presence of renal venous congestion.

The use of drugs such as ACEi, AIIRA or diuretics can affect kidney function, but the results of different studies in patients with AHF are mixed[8]. These drugs can produce a WRF when treatment is initiated in patients with chronic heart failure, and their appearance is associated with poorer outcomes. But even so, the benefit is proven, since in this group it also reduces mortality from all causes[24]. This situation is different in patients with AHF who are receiving these drugs. In the EAHFE-EFRICA study, none of the chronic treatments of the patients studied, including the use of ACE or AIIRA and base diuretics, nor diuretic treatment in the ED, was associated with the appearance of WRF, although the widespread use of diuretics in both groups, over 95% of the cases, could have prevented the detection of significant differences. We believe that our work supports that the clinician should be cautious and avoid as much as possible to suspend these treatments based on the belief that they are the cause of WRF, which may have repercussions on the prognosis.

Table 1. Characteristics of the patients included in the EAHFE-EFRICA study and comparison between patients with worsening renal function and those without it (control)

	Total N = 1,627 n (%)	Lost values n (%)	WRF N = 220 n (%)	Control N = 1,407 n (%)	p
Demographic data					
Age (years) [mean (SD)]	79.6 (11.1)	0 (0.0)	81.2 (10.1)	79.4 (11.2)	**0.023**
Female	844 (52.0)	4 (0.2)	111 (50.7)	733 (52.2)	0.675
Comorbilities					
Arterial hypertension	1,333 (82.5)	11 (0.7)	188 (85.5)	1.145 (82.0)	0.213
Diabetes mellitus	737 (45.6)	12 (0.7)	107 (48.9)	630 (45.1)	0.303
Dyslipemia	833 (51.5)	11 (0.7)	112 (50.9)	721 (51.6)	0.839
Ischemic cardiopathy	481 (29.8)	12 (0.7)	59 (26.8)	422 (30.3)	0.301
Chronic kidney disease	642 (39.7)	11 (0.7)	113 (51.4)	529 (37.9)	< **0.001**
Cerebrovascular disease	232 (14.4)	11 (0.7)	36 (16.4)	196 (14.0)	0.361
Atrial fibrillation	745 (46.1)	11 (0.7)	91 (41.4)	654 (46.8)	0.129
Valvulopathy	405 (25.1)	13 (0.8)	55 (25.1)	350 (25.1)	0.994
Peripheral artery disease	213 (13.2)	12 (0.7)	27 (12.3)	186 (13.3)	0.666
Chronic obstructive pulmonary disease	387 (24.0)	13 (0.8)	53 (24.2)	334 (23.9)	0.934
Dementia	187 (11.6)	12 (0.7)	24 (10.9)	163 (11.7)	0.738
Neoplasia	278 (17.2)	13 (0.8)	33 (15.1)	245 (17.6)	0.363
Previous heart failure	961 (60.6)	41 (2.5)	128 (60.4)	833 (60.6)	0.945
Basal situation					
Barthel Index (points) [mean (SD)]	82.1 (22.6)	76 (4.7)	81.2 (21.8)	82.1 (22.7)	0.557
NYHA Class III-IV	361 (23.1)	64 (3.9)	41 (19.2)	320 (23.7)	0.152
LVEF (%) [mean (SD)]	52.2 (15.0)	471 (28.9)	52.9 (14.6)	52.1 (15.1)	0.548
Chronic treatment					
Loop diuretics	1,046 (65.3)	25 (1.5)	137 (63.1)	909 (65.6)	0.472
Thiazide diuretics	263 (16.5)	32 (2.0)	38 (17.8)	225 (16.3)	0.591
ACEIs or ARA-II	842 (52.8)	32 (2.0)	121 (56.5)	721 (52.)	0.237
Beta-blockers	736 (46.3)	37 (2.3)	104 (48.6)	632 (45.9)	0.467
Aldosterone receptor antagonists	217 (13.6)	32 (2.0)	25 (11.7)	192 (13.9)	0.378
Digoxin	168 (10.6)	43 (2.6)	19 (8.9)	149 (10.9)	0.390
Precipitating factor					
Infection	561 (35.2)	35 (2.2)	84 (38.5)	477 (34.7)	0.237
Tachyarrhythmia	249 (15.6)	35 (2.2)	30 (13.8)	219 (15.9)	0.411
Hypertensive crisis	111 (7.0)	35 (2.2)	24 (11.0)	87 (6.3)	**0.012**
Anemia	120 (7.5)	35 (2.2)	13 (6.0)	107 (7.8)	0.343
Pharmacological or dietary transgression	91 (5.7)	35 (2.2)	12 (5.5)	79 (5.7)	0.885
NSTSEACS	83 (5.1)	6 (0.4)	12 (5.5)	71 (5.1)	0.809
Vital signs on arrival at the ED					
SBP (mmHg) [mean (SD)]	139.6 (28.2)	12 (0.7)	143.8 (30.3)	138.9 (27.8)	**0.017**
Heart rate (bpm) [mean (SD)]	90.4 (25.5)	25 (1.5)	90.6 (24.9)	90.3 (25.6)	0.887
Oxygen saturation (%) [mean (SD)]	93 (6.2)	20 (1.2)	92.9 (6.9)	93.1 (6.0)	0.656
Analitics					
Hemoglobin (g/L) [mean (SD)]	11.7 (2.2)	8 (0.5)	11.6 (2.0)	11.7 (2.2)	0.310
Creatinine (mg/dL) [mean (SD)]	1.5 (1.0)	0 (0.0)	1.5 (1.1)	1.5 (0.9)	0.316
Hyponatremia (< 135 mmol/L)	270 (16.8)	22 (1.4)	36 (16.7)	234 (16.8)	0.974
Hyperkalaemia (> 5.5 mmol/L)	110 (7.1)	68 (4.2)	19 (9.3)	91 (6.7)	0.177
Elevated Troponin	502 (69.5)	905 (55.6)	65 (71.4)	437 (69.3)	0.674
NT-proBNP (pg/mL) [median (IQR)]	5,001 (2,394-10.482)	984 (60.5)	4,838 (1,825-10,794)	5,055 (2,491-10,465)	0.500
Treatment at ED					
Intravenous diuretic	1,555 (96.4)	14 (0.9)	216 (98.2)	1.339 (96.1)	0.128
Intravenous nitroglycerin	412 (25.5)	14 (0.9)	54 (24.5)	358 (25.7)	0.715
Morphine	139 (8.6)	14 (0.9)	27 (12.3)	112 (8.0)	**0.038**
Digoxin	260 (16.1)	14 (0.9)	35 (15.9)	225 (16.2)	0.927
Amiodarone	132 (8.2)	14 (0.9)	23 (10.5)	109 (7.8)	0.186
Inotropic/Vasopressor	57 (3.5)	15 (0.9)	10 (4.5)	47 (3.4)	0.383
Non-Invasive ventilation	166 (10.3)	13 (0.8)	23 (10.5)	143 (10.3)	0.929
Severity of the episode					
Risk category on the MEESSI scale		391 (24.0)			0.273
- Low	373 (30.2)		45 (23.3)	328 (31.0)	
- Intermediate	541 (43.8)		81 (45.5)	460 (43.1)	
- High/Very high	322 (26.1)		58 (29.2)	270 (25.5)	

WRF: worsening renal function; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitors; ARA-II: angiotensin-II receptor antagonists. NSTSEACS: non-ST-segment elevation acute coronary syndrome ; SBP: systolic blood pressure.
P values in bold highlight those differences that were considered statistically significant ($p < 0.05$).

Table 2. Factors associated with worsening renal function during the first 24-48 hours of treatment in the emergency department for acute heart failure

	Crude *Odds ratio* (IC 95%)	p	Adjusted *Odds ratio* (IC 95%)	p
Age (in years)	1.016 (1.002-1.030)	**0.023**	1.014 (0.999-1.028)	0.065
Chronic kidney disease (creatinine > 2 mg/dL)	1.731 (1.301-2.303)	< **0.001**	1.695 (1.264-2.273)	< **0.001**
Hypertensive crisis as a precipitating factor	1.830 (1.136-2.947)	**0.013**	1.473 (0.849-2.553)	0.168
Systolic blood pressure (in mmHg)	1.006 (1.001-1.011)	**0.017**	1.004 (0.998-1.009)	0.214
Morphine treatment in the ED	1.600 (1.024-2.501)	**0.039**	1.543 (0.976-2.441)	0.064

P values in bold highlight those differences that were considered statistically significant ($p < 0.05$).

Creatinine on arrival at the emergency department might be expected to be higher in patients who develop WRF, but this has not been the case. In previous studies, this circumstance has also not been present and the WRF percentages have been similar, regardless of the basal creatinine concentration[8,9,25]. In our study, as in most of those published, what is present, as a predictive variable of WRF, is the presence of CKD. In fact, it has been the only variable associated with WRF. In a meta-analysis that analyzed the data from 30 studies, in 28 of them CKD was associated with the appearance of WRF, and in 15 of them this association persisted after adjustment for confounding factors[8]. It is important to mention that we have based the definition of WRF on an absolute increase in creatinine (≥ 0.3 mg/dl or 26.5 µmol/l). This implies, indirectly, that absolute increases of similar serum creatinine values have a greater impact on eGFR in patients with lower eGFR than in those with higher eGFR. However, as mentioned above, baseline creatinine figures have not been predictive of WRF, even when results in the subgroup of patients with initial creatinine > 1.3 mg/dl have been analyzed.

The result of higher short and long-term mortality in patients with WRF in the EAHFE-EFRICA study has been consistent with the rest of the published studies, regardless of the cut-off point used to define WRF. We would like to emphasize that in our study this direct relationship with a worse prognosis was significant for both 30-day mortality and first-trimester follow-up. It is controversial whether a creatinine increase of 0.3 mg/dl (26.5 µmol/l) is adequate to assess WRF. However, this figure has been collected in most published studies, and when other values higher than this have been used, this association has also been found[8].

The clinical implications of our study's findings are clear to emergency physicians. A high percentage of patients are discharged directly, without requiring hospitalization. Knowing the fact that CKD is associated with the appearance of WRF, in these patients an analytical control should be done before discharge, within the first 48 hours, since if they present a WRF (≥ 0.3 mg/dl) their prognosis is worse. In this sense, it is clear that risk stratification with predictive scales and the availability of observation areas in the ED and alternative healthcare resources to conventional hospitalization such as short-stay units play an important role in decision-making in these patients[26-31].

This study presents several limitations to be considered. There is no data available related to the doses of drugs of the basic treatment, nor those administered in the emergency department, so that an effect on the appearance of WRF derived from aggressive therapies could not be assessed. Nor have we analyzed the evolution of renal function after WRF. That is to say, we do not know if a return to baseline creatinine or the persistence of WRF has an impact on long-term evolutionary data. However, the message for patient assessment in the ED is clear, since the mere presence of WRF in the first 48 hours is already associated with

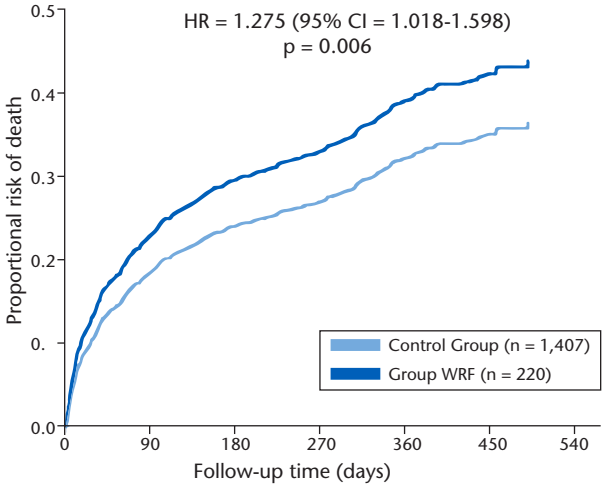

Figure 2. Adjusted proportional risk curves of death from any cause for patients with and without worsening renal function (WRF).

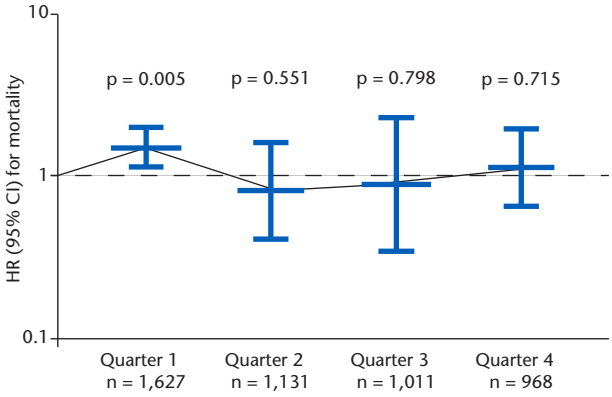

Figure 3. Detailed quarterly analysis of risk of death for the patient group with worsening renal function compared to the control group during the first year after the episode of acute heart failure.

Table 3. Stratified analysis of 30-day adjusted mortality in patients with worsening renal function during the first 24-48 hours of treatment in the ED for acute heart failure

	Adjusted *Odds ratio* (95% CI)	p	p (int.)
Age			0.880
< 80 years	1,264 (0.807-1,980)	0.306	
≥ 80 years	1,268 (0.976-1,648)	0.076	
Sex			0.172
Male	1,455 (1.065-1,987)	**0.018**	
Female	1,024 (0.731-1,432)	0.892	
Systolic dysfunction (LVEF < 40%)			0.614
No	1,369 (1.019-1,839)	**0.037**	
Yes	1,011 (0.501-2,040)	0.976	
Initial creatinine			0.871
≤ 1.3 mg/dL	1,310 (0.926-1,854)	0.128	
1.3 mg/dL	1,282 (0.948-1,735)	0.107	
Risk category (MEESSI score)			0.437
Low	1,488 (0.782-2,832)	0.226	
Increased (intermediate/high/ very high)	1,303 (0.990-1,709)	0.059	

P values in bold highlight those differences that were considered statistically significant (p < 0.05). The p value of the interaction is expressed as p (int.).
LVEF: left ventricular ejection fraction.

worse outcomes. The delta (increase) of creatinine should be considered more important than the basal creatinine itself, since the deleterious influence of WRF is observed independently of the basal creatinine at the outset. With regard to time, a WRF assessment was carried out in the first 48 hours, and therefore the WRF was not considered beyond this time, although we know from previous studies that in most cases the WRF occurs within this time interval[8]. Finally, another limitation is related to the heterogeneity in the resources available at discharge from the participating EDs, which may have an impact derived from greater short-term follow-up in certain patients, and which probably includes those with an WRF.

In conclusion, the presence of WRF during the first 48 hours in patients with AHF who visit the ED is associated with higher mortality, and this increased risk is concentrated during the first quarter. CKD is the only predictive variable associated with the appearance of WRF. Therefore, we recommend that emergency physicians should carry out a creatinine control during the first 48 hours to assess the appearance of WRF, especially in those suffering from CKD, and that they should be cautious when discharging patients in whom this increase in creatinine has been reported.

Conflicting interests: The authors declare no conflict of interest in relation to this article.

Financing: The authors declare the non-existence of funding in relation to this article.

Ethical responsibilities: All authors have confirmed the maintenance of confidentiality and respect for the rights of patients in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.
The protocol was approved by the Ethics and Clinical Research Committee of the Hospital Universitario Central de Asturias as the main committee, in addition to those of the other participating centers.

Article not commissioned by the Editorial Committee and with external peer review.

Acknowledgements: This study was made possible in part by grants from the Instituto de Salud Carlos III with funds from the Ministry of Health and the ERDF (PI15/01019, PI18/00773), La Marató de TV3 (2015/2510) and the Generalitat de Catalunya for consolidated research groups (GRC 2009/1385, 2014/0313, 2017/1424).

Addendum

Researchers of the ICA-SEMES Group: Marta Fuentes, Cristina Gil (Hospital Universitario de Salamanca), Héctor Alonso, Enrique Pérez-Llantada (Hospital Marqués de Valdecilla de Santander), Francisco Javier Martín-Sánchez, Guillermo Llopis García, Mar Suárez Cadenas (Hospital Clínico San Carlos de Madrid), Òscar Miró, Víctor Gil, Rosa Escoda, Sira Aguiló, Carolina Sánchez (Hospital Clínic de Barcelona), María José PérezDurá, Eva Salvo (Hospital Politénic La Fe de Valencia), José Pavón (Hospital Dr. Negrín de Las Palmas de Gran Canaria), Antonio Noval (Hospital Insular de Las Palmas de Gran Canaria), José Manuel Torres (Hospital Reina Sofía de Córdoba), María Luisa López-Grima, Amparo Valero, María Ángeles Juan (Hospital Dr. Peset de Valencia), Alfons Aguirre, Maria Angels Pedragosa, Silvia Mínguez Masó (Hospital del Mar de Barcelona), María Isabel Alonso, Francisco Ruiz (Hospital de Valme de Sevilla), José Miguel Franco (Hospital Miguel Servet de Zaragoza), Ana Belén Mecina (Hospital de Alcorcón de Madrid), Josep Tost, Marta Berenguer, Ruxandra Donea (Consorci Sanitari de Terrassa), Susana Sánchez Ramón, Virginia Carbajosa Rodríguez (Hospital Universitario Rio Hortega de Valladolid), Pascual Piñera, José Andrés Sánchez Nicolás (Hospital Reina Sofía de Murcia) Raquel Torres Garate (Hospital Severo Ochoa de Madrid), Aitor Alquézar-Arbé, Miguel Alberto Rizzi, Sergio Herrera (Hospital de la Santa Creu y Sant Pau de Barcelona), Javier Jacob, Alex Roset, Irene Cabello, Antonio Haro (Hospital Universitari de Bellvitge de Barcelona) Fernando Richard, José María Álvarez Pérez, María Pilar López Diez (Hospital Universitario de Burgos), Pablo Herrero Puente, Joaquín Vázquez Álvarez, Belén Prieto García, María García García, Marta Sánchez González (Hospital Universitario Central de Asturias de Oviedo) Pere Llorens, Patricia Javaloyes, Víctor Marquina, Inmaculada Jiménez, Néstor Hernández, Benjamín Brouzet, Begoña Espinosa, Adriana Gil (Hospital General de Alicante), Juan Antonio Andueza (Hospital General Universitario Gregorio Marañón de Madrid) Rodolfo Romero (Hospital Universitario de Getafe de Madrid), Martín Ruíz, Roberto Calvache (Hospital de Henares de Madrid), María Teresa Lorca Serralta, Luis Ernesto Calderón Jave (Hospital del Tajo de Madrid), Beatriz Amores Arriaga Beatriz Sierra Bergua (Hospital Clínico Lozano Blesa de Zaragoza), Enrique Martín Mojarro, Brigitte Silvana Alarcón Jiménez (Hospital Sant Pau i Santa Tecla de Tarragona), Lisette Travería Bécquer, Guillermo Burillo (Hospital Universitario de Canarias de Tenerife) Lluís Llauger García, Gerard Corominas LaSalle (Hospital Universitari de Vic de Barcelona), Carmen Agüera Urbano, Ana Belén García Soto, Elisa Delgado Padial (Hospital Costa del Sol de Marbella de Málaga), Ester Soy Ferrer, María Adroher Múñoz (Hospital Josep Trueta de Girona) José Manuel Garrido (Hospital Virgen Macarena de Sevilla), Francisco Javier LucasImbernón (Hospital General Universitario de Albacete), Rut Gaya (Hospital Juan XXIII de Tarragona), Carlos Bibiano, María Mir, Beatriz Rodríguez (Hospital Infanta Leonor de Madrid), José Luis Carballo (Complejo Hospitalario Universitario de Ourense), Esther Rodríguez-Adrada, Belén Rodríguez Miranda, Monika Vicente Martín (Hospital Rey Juan Carlos de Móstoles de Madrid). Pere Coma Casanova, Joan Espinach Alvarós (Hospital San Joan de Deu de Martorell, Barcelona).

References

1 Farmakis D, Parissis J, Lekakis J, Filippatos G. Acute heart failure: Epidemiology, risk factors, and prevention. Rev Esp Cardiol. 2015;68:245-8.
2 Miró Ò, Javaloyes P, Gil V, Martín-Sánchez FJ, Jacob J, Herrero P, et al. Comparative Analysis of Short-Term Outcomes of Patients With Heart Failure With a Mid-Range Ejection Fraction After Acute Decompensation. Am J Cardiol. 2019;123:84-92.
3 Formiga F, Chivite D. Insuficiencia cardiaca aguda: básico conocer al paciente. Emergencias. 2018;30:145-6.
4 Martín-Sánchez FJ, Rodríguez-Adrada E, Vidan MT, Díez Villanueva P, Llopis García G, González Del Castillo J, et al. Impacto de las variables geriátricas en la mortalidad a 30 días de los ancianos atendidos por insuficiencia cardiaca aguda. Emergencias. 2018;30:149-55.
5 Ronco C, Bellasi A, Di Lullo L. Cardiorenal Syndrome: An Overview. Adv Chronic Kidney Dis. 2018;25:382-90.
6 Llauger L, Jacob J, Miró Ò. Renal function and acute heart failure

outcome. Función renal y pronóstico de los episodios de insuficiencia cardiaca aguda. Med Clin (Barc). 2018;151:281-90.
7 Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies. Eur Heart J. 2013;34:1404-13.
8 Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455-69.
9 Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61-7.
10 Berra G, Garin N, Stirnemann J, Jannot A-S, Martin P-Y, Perrier A, et al. Outcome in acute heart failure: Prognostic value of acute kidney injury and worsening renal function. J Card Fail. 2015;21:382-90.
11 Ueda T, Kawakami R, Sugawara Y, Okada S, Nishida T, Onoue K, et al. Worsening of renal function during 1 year after hospital discharge is a strong and independent predictor of all-cause mortality in acute decompensated heart failure. J Am Heart Assoc. 2014;3:e001174.
12 Wattad M, Darawsha W, Solomonica A, Hijazi M, Kaplan M, Makhoul BF, et al. Interaction between worsening renal function and persistent congestion in acute decompensated heart failure. Am J Cardiol. 2015;115:932-7.
13 Núñez J, Llàcer P, Núñez E, Ventura S, Bonanad C, Bodí V, et al. Antigen carbohydrate 125 and creatinine on admission for prediction of renal function response following loop diuretic administration in acute heart failure. Int J Cardiol. 2014;174:516-23.
14 Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020;10.1002/ejhf.1697.
15 Lassus J, Harjola VP, Sund R, Siirilä-Waris K, Melin J, Peuhkurinen K, et al. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function NT-proBNP. Eur Heart J. 2007;28:1841-7.
16 Cerrada JC, Carrasco Sanchez FJ, Perez-Calvo JI, Manzano L, Formiga F, Aramburu Bodas O, et al. Prognostic value of glomerular filtration rate estimation equations in acute heart failure with preserved versus reduced ejection fraction. Int J Clin Pract. 2015;69:829-39.
17 Vanmassenhove J, Kielstein J, Jörres A, Biesen WV. Management of patients at risk of acute kidney injury. Lancet. 2017;389:2139-51.
18 Roy AK, Mc Gorrian C, Treacy C, Kavanaugh E, Brennan A, Mahon NG, et al. A Comparison of Traditional and Novel Definitions (RIFLE, AKIN, and KDIGO) of Acute Kidney Injury for the Prediction of Outcomes in Acute Decompensated Heart Failure. Cardiorenal Med. 2013;3:26-37.
19 Llorens P, Javaloyes P, Martín-Sánchez FJ, Jacob J, Herrero-Puente P, Gil V et al. Time trends in characteristics, clinical course, and outcomes of 13,791 patients with acute heart failure. Clin Res Cardiol. 2018;107:897-913.
20 Miró Ò, Gil V, Rosselló X, Martín-Sánchez FJ, Llorens P, Jacob J, et al. Patients with acute heart failure discharged from the emergency department and classified as low risk by the MEESSI score (multiple risk estimate based on the Spanish emergency department scale): prevalence of adverse events and predictability. Emergencias. 2019;31:5-14.
21 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
22 Tang WH, Mullens W. Cardiorenal syndrome in decompensated heart failure. Heart. 2010;96:255-60.
23 Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422e30.
24 Clark H, Krum H, Hopper I. Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail. 2014;16:41-8.
25 Breidthardt T, Socrates T, Noveanu M, Klima T, Heinisch C, Reichlin T, et al. Effect and clinical prediction of worsening renal function in acute decompensated heart failure. Am J Cardiol. 2011;107:730-5.
26 Comín-Colet J, Enjuanes C, Lupón J, Cainzos-Achirica M, Badosa N, Verdú JM. Transitions of Care Between Acute and Chronic Heart Failure: Critical Steps in the Design of a Multidisciplinary Care Model for the Prevention of Rehospitalization. Rev Esp Cardiol. 2016;69:951-61.
27 Miró Ò, Levy PD, Möckel M, Pang PS, Lambrinou E, Bueno H, et al. Disposition of emergency department patients diagnosed with acute heart failure: an international emergency medicine perspective. Eur J Emerg Med. 2017;24:2-12.
28 Llorens P. Necesidad de evaluar el riesgo de los pacientes con insuficiencia cardiaca aguda en los servicios de urgencias más allá del juicio clínico. Emergencias. 2018;30:75-6.
29 Masip J. ¿Es efectivo MEESSI para dar el alta desde urgencias a los pacientes con insuficiencia cardiaca aguda? Emergencias. 2019;31:3-4.
30 Llorens P. Necesidad de evaluar el riesgo de los pacientes con insuficiencia cardiaca aguda en los servicios de urgencias más allá del juicio clínico. Emergencias. 2018;30:75-6.
31 Miró O, Gil V, Rosselló X, Martín-Sánchez FJ, Llorens P, Jacob J, et al. Eventos adversos en pacientes con insuficiencia cardiaca aguda clasificados de bajo riesgo por la escala MEESSI y dados de alta desde urgencias: cuantificación y predictibilidad. Emergencias. 2019;31:5-14.