Usefulness of the Hepatocyte Growth Factor as a Predictor of Mortality in Patients Hospitalized With Acute Heart Failure Regardless of Ejection Fraction

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Hepatocyte growth factor (HGF) plays a role in the improvement of cardiac function and remodeling. Their serum levels are strongly related with mortality in chronic systolic heart failure (HF). The aim of this study was to study prognostic value of HGF in acute HF, interaction with ejection fraction, renal function, and natriuretic peptides. We included 373 patients (age 76 ± 10 years, left ventricular ejection fraction [LVEF] 46 ± 14%, 48% men) consecutively admitted for acute HF. Blood samples were obtained at admission. All patients were followed up until death or close of study (>1 year, median 371 days). HGF concentrations were determined using a commercial enzyme-linked immunosorbent assay (human HGF immunoassay). The predictive power of HGF was estimated by Cox regression with calculation of Harrell C-statistic. HGF had a median of 1,942 pg/ml (interquartile rank 1,354). According to HGF quartiles, mortality rates (per 1,000 patients/year) were 98, 183, 375, and 393, respectively (p <0.001). In Cox regression analysis, HGF (hazard ratio$_{1SD}$ = 1.5, 95% confidence interval 1.1 to 2.1, p = 0.002) and N-terminal pro b-type natriuretic peptide (NT-proBNP; hazard ratio$_{1SD}$ = 1.8, 95% confidence interval 1.2 to 2.6, p = 0.002) were independent predictors of mortality. Interaction between HGF and LVEF, origin, and renal function was nonsignificant. The addition of HGF improved the predictive ability of the models (C-statistic 0.768 vs 0.741, p = 0.016). HGF showed a complementary value over NT-proBNP (p = 0.001): mortality rate was 490 with both above the median versus 72 with both below. In conclusion, in patients with acute HF, serum HGF concentrations are elevated and identify patients at higher risk of mortality, regardless of LVEF, ischemic origin, or renal function. HGF had independent and additive information over NT-proBNP. **(Am J Cardiol 2016;118:543−549)**

Hepatocyte growth factor (HGF) is a disulfide-linked heterodimeric molecule comprising a 69-kDa kringle-containing α chain and a 34-kDa β chain.[1] The HGF system (HGF and its receptor c-*Met*) has been found in various tissues and integrates complex biologic processes.[2] HGF has been described as a potent mitogenic growth factor for hepatocytes thought to be liver specific but also reported to possess mitogenic, motogenic, morphogenic, and anti-apoptotic activities in different cell types.[3−5] Binding of HGF to its receptor c-Met leads to the activation of a signal cascade whose ultimate in vivo effects include organ development, angiogenesis, and tissue regeneration.[6−8] Plasma concentrations of HGF are increased in response to the damage of the liver and kidney.[9−11]

In the setting of cardiovascular diseases, an increase of HGF has been observed in hypertension, atherosclerosis, acute myocardial infarction, and chronic heart failure (HF).[12−15] In patients with advanced HF and depressed left ventricular ejection fraction (LVEF), HGF has been reported to be predictive of cardiovascular and all-cause mortality, especially in patients with ischemic HF.[16−18] This is possibly because of that ischemia is a strong inducer of HGF synthesis.[19] However, the value of HGF concentrations in the setting of acutely decompensated HF has not been evaluated, and data in HF patients with preserved LVEF are scarce.[18]

Therefore, this study was aimed to analyze the prognostic information yielded by serum HGF concentrations in patients admitted for acute HF and to evaluate the interaction

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Table 1
Baseline clinical characteristics according to vital status at the end of follow-up

Variable	Total population (N=373)	Alive (N=279) (74.8%)	Deaths (N=94) (25.2%)	p
Age (years)	76.32 (10.02)	75.25 (10.37)	79.50 (8.17)	<0.001
Male/Female	48.2%/51.8%	47.5%/52.5%	50.5%/49.5%	0.61
LVEF	46.43 (14.15)	47.05 (13.97)	44.51 (14.57)	0.14
LVEF >50%	**51.1%**	**52.6%**	**46.6%**	**0.32**
LA (mm)	47.31 (7.84)	46.62 (7.69)	49.77 (7.94)	0.007
LVMI (g/m^2)	129.37 (46.39)	130.70 (45.97)	124.75 (48.12)	0.49
BMI (Kg/m^2)	29.51 (5.55)	29.73 (5.76)	28.86 (4.84)	0.19
Atrial Fibrillation	51.5%	51.6%	51.1%	0.93
Hypertension	76.9%	76.7%	77.7%	0.85
IHD	36.7%	37.6%	34%	0.53
Valvular disease	39.2%	37.3%	45.5%	0.23
Diabetes mellitus	47.2%	45.2%	53.2%	0.17
Hyperlipidemia	43.3%	49.3%	26.1%	0.001
Stroke	16.3%	14.1%	23.2%	0.075
Peripheral vascular disease	10.9%	10.6%	12.2%	0.77
Hemoglobin (g/dL)	12.32 (2.16)	12.41 (2.15)	12.02 (2.15)	0.13
Uric acid (mg/dL)	7.71 (3.22)	7.53 (3.41)	8.31 (2.39)	0.32
Blood urea (mg/dL)	58.16 (47.42)	52.40 (42.99)	75.20 (55.42)	<0.001
Creatinine (mg/dL)	1.45 (0.96)	1.39 (0.98)	1.61 (0.86)	0.06
Sodium (mEq/l)	138.88 (4.72)	139.15 (4.50)	138.08 (5.26)	0.057
Potassium (mEq/l)	4.25 (0.646)	4.21 (0.64)	4.36 (0.65)	0.044
Albumin < 3.5 g/dl	34.2%	30.3%	47.5%	0.015
Hyperlipidemia	36.7%	49.3%	26.1%	0.001
NT-proBNP* (pg/mL)	4233 (7133)	3556 (5461)	7489 (15077)	<0.001
HGF* (pg/mL)	1942 (1354)	1759 (1262)	2299 (1439)	<0.001
Cystatin* (mg/L)	1.45 (0.86)	1.37 (0.85)	1.67 (0.81)	<0.001
eGFR MDRD (mL/min/1.72m^2)	54.97 (24.54)	56.94 (24.79)	49.07 (22.89)	0.007
eGFR CKD-EPI (mL/min/1.72m^2)	50.98 (21.70)	53.02 (21.70)	44.86 (20.59)	0.002
eGFR Hoek13 (mL/min/1.72m^2)	52.22 (21.48)	54.99 (22.30)	43.85 (16.23)	0.000

BMI = body mass index; eGFR = estimated glomerular filtration rate; eGFR CKD-EPI crea = eGFR (CKD-EPI equation) based on Creatinine; eGFR CKD-EPI cys = eGFR (CKD-EPI equation) based on Cystatin C; eGFR Hoek13 = eGFR (Hoek 13 equation) based on Cystatin C; HGF = hepatocyte growth factor; IHD = ischemic heart disease; LA = left atria; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MDRD = eGFR by modified diet renal disease formula; NT-proBNP = amino terminal fragment of B type natriuretic peptide.

* Data are expressed as mean (SD) or median (IQR).

with EF, HF origin, renal function, and natriuretic peptides (NP).

Methods

From September 2009 to February 2013, we prospectively recruited a total of 373 patients consecutively admitted with acute HF. Local ethics committees approved the study, and informed consent was obtained from each patient. Blood samples were collected at admission and stored at −80°C until processed. Echocardiography was performed on all patients. A final diagnosis of acute HF was established following the criteria of contemporary guidelines.[20] In addition to these criteria, a concentration of N-terminal pro b-type natriuretic peptide (NT-proBNP) >900 pg/ml at admission was an inclusion criteria. Reference values from the N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study were followed.[21] Patients with acute coronary syndrome, significant valvular heart disease, chronic obstructive pulmonary disease as source of dyspnea, pulmonary embolism, ventricular arrhythmias, stage 5 chronic kidney disease, liver cirrhosis, hyperthyroidism, Cushing's syndrome, and life expectancy <1 year were not included. Clinical, echocardiographic, and biochemical characteristics were prospectively recorded. Laboratory workup was performed according to manufacturer instructions.

Blood samples for HGF measurement were centralized at the immunology laboratory of one center. HGF concentrations in human serum were determined by enzyme-linked immunosorbent assay, according to manufacturer instructions (human HGF immunoassay, Quantikine ELISA; R&D Systems Europe, Ltd, Abingdon, UK). The intra-assay coefficient of variation for HGF was 7.1% for 339 pg/ml and 4.1% for 3,759 pg/ml. The interassay coefficient of variation for HGF was 7.1% for 363 pg/ml and 5.4% for 3,790 pg/ml. Glomerular filtration rate (GFR) was estimated through several formulae: Modification of Diet in Renal Disease Study equation, Chronic Kidney Disease Epidemiology Collaboration equations based on creatinine, and Hoek formula based on cystatin C.

During hospitalization, the physician responsible for patients was unaware of HGF levels. Study end point was

Table 2
Characteristics of patients according to Hepatocyte Growth Factor quartiles

	Q1 ≤ 1350 Mean ± SD	Q2 1350-1900 Mean ± SD	Q3 1901-2700 Mean ± SD	Q4 ≥ 2700 Mean ± SD	P
HGF (pg/mL)	1127 (226)	1642 (254)	2299 (313)	3466 (1699)	<0.001
LVEF	45.72 (14.92)	45.81 (13.52)	48.26 (13.51)	45.55 (14.44)	0.56
LVEF >50%	**49.4%**	**53%**	**58%**	**43.9%**	**0.32**
LA (mm)	45.86 (9.42)	47.71 (8.96)	48.92 (6.71)	46.15 (6.45)	0.12
LVMI (g/m2)	151.17 (71.16)	129.18 (37.09)	124.15 (39.58)	125.79 (45.91)	0.17
Age (years)	74.19 (11.42)	76.38 (9.73)	77.32 (9.31)	77.06 (10.08)	0.18
Male/Female	60.7%/39.3%	50.6%/49.4%	43.5%/56.5%	42.4%/57.6%	0.06
BMI (Kg/m^2)	29.02 (5.47)	28.70 (4.74)	29.81 (6.26)	30.52 (5.64)	0.14
Albumin < 3.5 mg/dL	25.6%	32.1%	43.5%	38.2%	0.11
Hemoglobin (g/dL)	12.43 (2)	12.43 (2.23)	12.14 (2.06)	12.15 (2.31)	0.69
Uric acid (mg/dL)	7.49 (4.70)	6.78 (1.59)	8.17 (2.48)	7.78 (2.48)	0.66
Sodium (mEq/L)	137.84 (4.63)	139.35 (4.55)	139.58 (4.45)	138.84 (5.19)	0.08
Potasium (mEq/L)	4.22 (0.58)	4.24 (0.70)	4.28 (0.55)	4.27 (0.70)	0.93
Blood urea (mg/dL)	48.58 (31.87)	56.18 (60.61)	56.17 (46.47)	69.29 (48.15)	0.04
Creatinine (mg/dL)	1.21 (0.38)	1.52 (1.51)	1.46 (0.81)	1.63 (0.87)	0.04
Atrial fibrillation	48.8%	58.8%	58.8%	38.8%	0.21
Hypertension	75%	72.9%	76.5%	82.4%	0.21
IHD	38.1%	35.3%	41.2%	37.6%	0.84
Valvular disease	34%	54.7%	40.6%	29.2%	0.16
Diabetes mellitus	41.7%	44.7%	49.4%	49.4%	0.25
Hyperlipidemia	47.9%	38.2%	51.8%	41.4%	0.78
Stroke	16.7%	17.9%	15.5%	17.2%	0.98
Peripheral vascular disease	5.9%	5.7%	22.5%	13.3%	0.12
eGFR MDRD ($mL/min/1.72m^2$)	62.13 (21.82)	57.75 (29.04)	52.5 (22.96)	47.46 (22.36)	0.001
eGFR CKD-EPI ($mL/min/1.72m^2$)	58.01 (19.80)	53.09 (23.26)	48.61 (20.84)	44.12 (20.97)	<0.001
eGFR Hoek 13 ($mL/min/1.72m^2$)	58.49 (23.45)	51.90 (19.39)	50.48 (21.48)	46.82 (18.94)	0.004
NT-proBNP* (pg/mL)	3195 (5041)	4513 (7079)	4661 (6715)	5408 (12346)	0.004
Cystatin C* (mg/L)	1.32 (0.59)	1.44 (0.82)	1.52 (1.07)	1.67 (0.90)	0.008
Loop diuretics	75.6%	83.1%	88.7%	90.5%	0.007
ACE inhibitors	62.7%	55.3%	46.9%	50.6%	0.016
ARB	24.1%	28.2%	30.9%	22.6%	0.8
MRA	45.5%	33.3%	50%	43.3%	0.9
BB	60.2%	57.6%	66.7%	57.1%	0.9

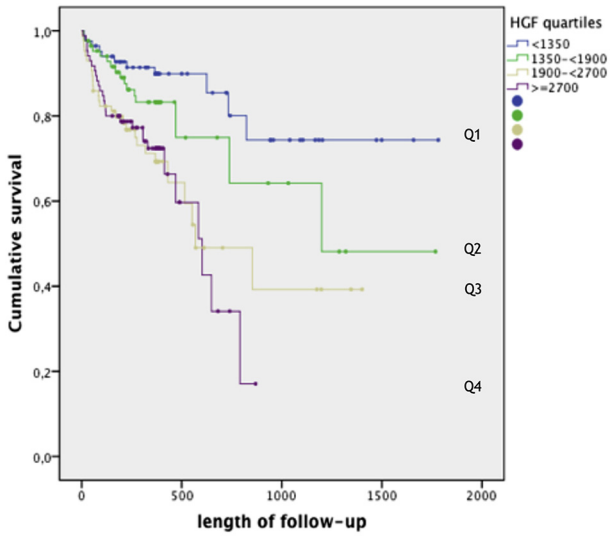
HGF concentration in pg/mL.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; BB = beta-blockers; BMI = body mass index; eGFR = estimated glomerular filtration rate; eGFR CKD-EPI crea = eGFR (CKD-EPI equation) based on Creatinine; eGFR CKD-EPI cys = eGFR (CKD-EPI equation) based on Cystatin C; eGFR Hoek13 = eGFR (Hoek 13 equation) based on Cystatin C; HGF = hepatocyte growth factor; IHD = ischemic heart disease; LA = left atria; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MDRD = eGFR by modified diet renal disease formula; MRA = mineral receptor antagonists; NT-proBNP = amino terminal fragment of B type natriuretic peptide.

* Data are expressed as mean (SD) or median (IQR).

all-cause mortality. All patients were followed up until death or close of study in August 2014 (371 days, range 2 to 1,782). Quantitative variables are described as mean values (±SD) or median values (interquartile rank). Qualitative variables are shown as frequency distribution. For comparisons between quantitative variables, either Student's *t* test, ANOVA, or nonparametric Mann-Whitney or Kruskal-Wallis tests were performed. For comparison of qualitative variables, chi-square tests were used with evaluation of linear trend in variables with ordered categories. Primary variable of results was all-cause mortality. Mortality rates are expressed as events per 1,000 patients-year. For comparison between mortality rates among HGF quartiles, Kaplan-Meier and log-rank test were used. Additionally Cox regression analysis was performed to estimate hazard ratio (HR) and 95% confidence intervals (CIs) of mortality. The main predictive variable was HGF levels. It was stratified in 4 categories using quartiles as cut-off points and then merged into 2 categories according to median value. By orthogonal polynomials, it was found that the linear trend of risk produced by HGF was significant; hence, it was also examined as a quantitative variable. For this purpose, HGF was standardized to a mean of 0 and SD of 1 to enable the comparison of the size effect with NT-proBNP, which was also standardized.

The independent predictive power of mortality associated with HGF was performed with adjustment for potential confounders. Model 1 included HFG concentration and age. Model 2 included model 1 plus estimated GFR, hemoglobin, albumin, diabetes, atrial fibrillation, and ischemic HF. Model 3 included model 2 plus LVEF and NT-proBNP concentrations. Model 4 included model 3 plus diuretic doses and therapies for HF. In model 4, a sequential exclusion was performed to evaluate independent predictors



HGF Quartiles (pg/mL)	Mortality rate (1000 patients/year)
Q1 ≤ 1350	98
Q2 1350-1900	183
Q3 1900-2700	375
Q4 ≥ 2700	393

Figure 1. Kaplan-Meier survival curves and mortality rates (1,000 patients/year) according to HGF quartiles.

Table 3
Mortality risk associated with HGF concentrations (as per each SD increase or above median) progressively adjusted for variables indicated in the successive models

	1 SD HGF			HGF ≥ 1900		
	HR	95% CI	p	HR	95% CI	p
Model 1	1.45	1.19-1.76	<0.001	2.46	1.54-3.92	<0.001
Model 2	1.46	1.08-1.99	0.015	2.83	1.42-5.68	0.003
Model 3	1.39	1.01-1.92	0.042	3.29	1.57-6.87	0.002
Model 4	1.55	1.10-2.18	0.013	3.36	1.49-7.55	0.003

Model 1: HFG concentration and age; Model 2: model 1 plus GFR, hemoglobin, albumin, diabetes, atrial fibrillation and IHD; Model 3: model 2 plus LVEF and NT-proBNP concentrations; Model 4: model 3 plus diuretic doses and evidence based therapies for HF.

of mortality. The predictive ability of HGF was tested by comparing the C Harrell statistical applied to variables included in model 4 both with and without introduction of HGF and by calculating the Integrated Discrimination Improvement.

Finally, patients were classified into 4 categories according to a combination of HGF and NT-proBNP values above or below median: category 1: both below median; category 2: only NT-proBNP above median; category 3: only HGF above median; category 4: both above median. A Kaplan-Meier analysis and a multivariate Cox regression analysis were also conducted using this combined variable to assess prognosis. Statistical results were considered

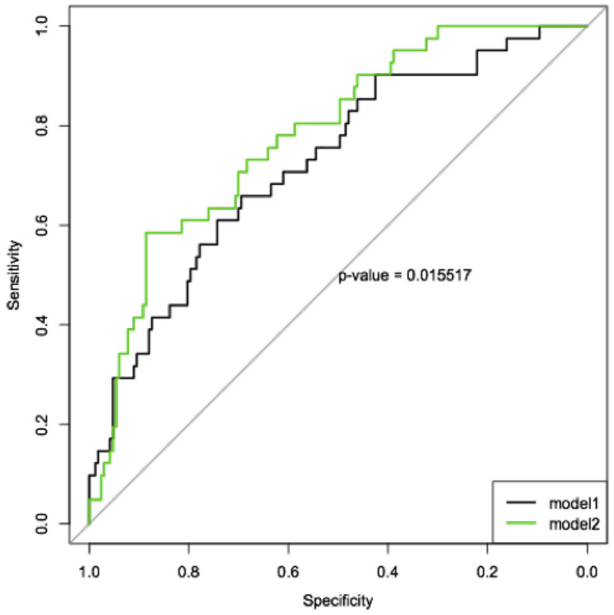


Figure 2. Area under the curve for the discrimination of death: effect of adding HGF to the best clinical model. Model 1 *(black line)*: age, GFR, hemoglobin, EF, treatment with loop diuretics and β blockers, diabetes, atrial fibrillation, ischemic heart disease, and NT-proBNP. Model 2 *(green line)*: model 1 plus HGF concentrations.

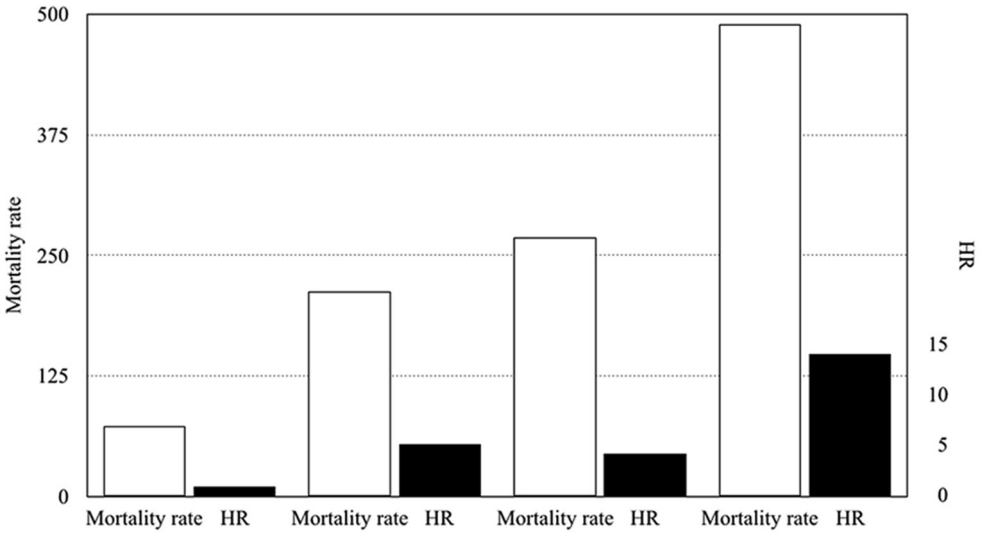
significant when the value of p was <0.05. Statistical procedures were performed with IBM Statistical Package for the Social Sciences, version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0., IBM Corp, Armonk, New York).

Results

Three hundred seventy-three patients admitted to the hospital with acute HF were recruited. Characteristics for the population are presented in Table 1. Preserved ejection fraction (LVEF ≥50%) represented 51% of patients. HGF values were available for 338 of patients (90.6%). Patients with missing values did not differ in any of the variables analyzed (data not shown). Characteristics of patients according to HGF quartiles are listed in Table 2. Concentrations of HGF were associated with higher NT-proBNP and cystatin C values and less satisfactory renal function values.

Mortality rates showed a significant and linear relation with serum HGF quartiles (Figure 1). In univariate Cox regression analysis and using Q1 as reference value, the increase of risk between Q1 and Q2 was nonsignificant (HR 1.8, 95% CI 0.9 to 4, p = 0.12), whereas the increase of risk between Q1 and Q3 (HR 3.6, 95% CI 1.8 to 7.3, p <0.0001) and between Q1 and Q4 (HR 3.8, 95% CI 1.8 to 7.7, p <0.0001) were significant. Hence, HGF levels were regrouped into 2 categories with a cut-off point in the median value of distribution. In univariate analysis, HGF concentrations above median increased mortality risk almost threefold (HR 2.7, 95% CI 1.7 to 4.3, p <0.0001). Furthermore, in quantitative analysis, each elevation in 1 SD of HGF increased risk of death by 47% (HR 1.47, 95% CI 1.2 to 1.78, p <0.0001).

The independent contribution of HGF to mortality risk in the successive models considered is reflected in Table 3. In



	Mortality rate*	Multivariate HR	95% CI
Both below	73	Reference	-
NT-proBNP above	212	5.4	1.05-27.4
HGF above	269	4.4	1-21.5
Both above	490	14.7	3.2-67.9

Figure 3. Mortality rates and HR according to HGF and NT-proBNP serum concentrations above or below the median. "*," Mortality rate is expressed per 1,000 patients/year). Data are expressed as HR and 95% CI.

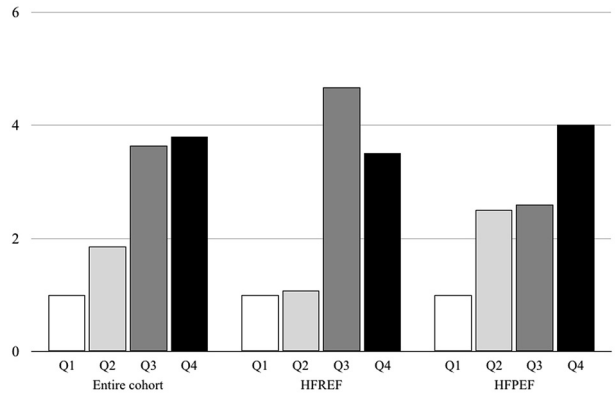
Cox regression analysis, using a sequential exclusion procedure, only HGF (HR_{1SD} = 1.5, 95% CI 1.1 to 2.1, p = 0.002) and NT-proBNP (HR_{1SD} = 1.8, 95% CI 1.2 to 2.6, p = 0.002) were independent predictors for mortality. The addition of HGF to the best predictive model significantly improved predictive ability (Figure 2) and power of discrimination (integrated discrimination improvement = 0.034, p = 0.018).

Importantly, classification of patients into categories according to NT-proBNP and HGF concentrations showed a gradual increase in mortality rates (Figure 3). There were no significant interactions between serum HGF and LVEF, ischemic HF, estimated GFR, or NT-proBNP concentrations, except for a nonsignificant trend observed for a better predictive value of HGF in the presence of low NT-proBNP concentrations (below median: HR_{1SD} = 1.76, 95% CI 1.2 to 2.5, p = 0.002, vs above median: HR_{1SD} = 1.3, 95% CI 1.04 to 1.6, p = 0.02) and preserved LVEF (preserved LVEF: HR_{1SD} = 1.7, 95% CI 1.2 to 2.4, p = 0.001 vs reduced LVEF: HR_{1SD} 1.36, 95% CI 1.1 to 1.7, p = 0.008). As shown in Figure 4, the risk of death increased across quartiles of HGF regardless of the presence of preserved or reduced LVEF.

Discussion

Our results show that after an acute HF episode, serum HGF concentrations are elevated and identify patients at higher risk of all-cause mortality, regardless of LVEF status. The information yielded by HGF serum concentration is independent of clinical variables, including ischemic origin and renal function. Interestingly, HGF showed an additive effect with NT-proBNP, and the presence of high concentrations of both biomarkers significantly increased the risk of death.

Several studies have found that serum HGF is elevated in patients with HF and systolic dysfunction.[15–17] A small study in patients with acute HF showed that HGF is higher at admission and gradually decreases during hospitalization.[15] Further studies have suggested that levels of HGF correlate with severity and prognosis; Lamblin et al[16] found median HGF serum levels of 818 pg/ml in stable ambulatory



	Q1	Q2	Q3	Q4	p
Entire cohort	1	1.85 (0.85-4.01)	3.64 (1.80 – 7.35)	3.79 (1,86 – 7.71)	<0.0001
HFREF	1	2.50 (0.90-6.94)	2.60 (0,92 -7.34)	4.01 (1.56 -10.30)	0.038
HFPEF	1	1.07 (0,31– 3.71)	4.67 (1.71-12.70)	3.51 (1.19 – 10.34)	0.002

Figure 4. Mortality risk according to quartiles of serum concentration of hepatocyte growth factor and the presence of preserved or reduced LVEF. Q1 reference risk. Data are expressed as HR and 95% CI; p Value for global interaction between HGF and EF, p = 0.34. HFREF = heart failure with reduced ejection fraction.

patients, whereas Rychli et al[17] reported 2,460 pg/ml in patients with advanced HF. Our study focused on patients with acute HF at the time of admission and also found elevated levels of HGF with a median of 1,942 pg/ml, which is more than twice the concentration in ambulatory patients and close to the values observed in patients with advanced HF.[16,17] As in the other studies, we also found a correlation with NP concentrations and renal function measures but not with LVEF, although the other studies did not include patients with preserved LVEF.[15–17] This question is of interest because our findings suggest that role of HGF is not limited to systolic HF and HGF increased in a similar magnitude irrespective of LVEF. The present study is the first to provide data supporting a prognostic value of HGF in 2 relevant settings: acutely decompensated HF and patients with HF with preserved LVEF. As in the other published studies,[16–18] HGF emerged as a powerful and independent prognosticator and identified patients at higher risk of death. HGF concentrations and prognostic value were not influenced by LVEF, and ischemic origin suggests that the source of HGF is not influenced by systolic function or origin. Although an increased RNA myocardial expression of HGF and its receptor c-Met has been observed in animal models of ischemia/reperfusion injury, an increased expression has also been found in other organs such as kidney, liver, and lung and also endothelial cells.[22,23] Zhu et al[24] observed that levels of HGF in monocytes were elevated and correlated with infarct size, suggesting that inflammation is a determinant of enhanced production as a response to organ injury. In acute HF, this defensive response is present and correlates with severity, regardless of LVEF. As a defensive response to organ damage, HGF has anti-apoptotic, anti-fibrotic, and anti-inflammatory properties and mediates regenerative and angiogenic effects actions recognized as beneficial in HF.[3,5] Moreover, in experimental models, the antagonism of HGF determines organ dysfunction, whereas stimulation or exogenous administration improves survival and exerts organ protection.[23,25]

We found a significantly linear correlation between serum concentrations of cystatin C, NT-proBNP, HGF, and mortality, as in previous studies.[17,18] In the present study, we found that both HGF and NT-proBNP provide complementary information, namely that patients with both biomarkers above the median had the highest risk of death, suggesting the usefulness of this combination for refining risk stratification in acute HF. Survival time shortened as both HGF and NT-proBNP concentrations increased. This complementary information may reflect what happens at a cellular and organ level, not only in the myocardium but also in other target organs given that HGF has a multiorgan source. Nowadays, the pathophysiology of acute HF is understood as multiorgan damage in which congestion and inflammation participate and determine a higher risk phenotype.[26]

Although speculative, it is plausible to think that during the acute phase of decompensation, both biomarkers reflect complementary responses. The degree of HGF expression and its association with prognosis reflects the degree of disease. It would be similar to natriuretic peptides, which represent a defensive response with biologic beneficial effects. It is in this context that increased levels of both biomarkers should be interpreted—HGF and natriuretic peptides reflect beneficial responses but, simultaneously, are markers of severity. The potentiation of a hypothetical beneficial physiological response may be of interest as a therapeutic approach. Therefore, the additive value of HGF and NP could be of additional interest, not only because they are complementary in prognosis evaluation but also because both responses could be synergistic from a therapeutic point of view.

The main limitations of this study are the observational nature and the lack of serial measurements reflecting the dynamics of an acute event. Nevertheless, the study provides meaningful information because it is the first to evaluate the prognostic value of HGF at admission for acute HF and also it provides information irrespective of LVEF. The value of its combination with NP is novel and could also serve as a basis for further research.

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Disclosures

The authors have no conflicts of interest to disclose.

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