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

Juan-Ignacio Pérez-Calvo, MD, PhD[a,*], José-Luis Morales-Rull, MD, PhD[b], José-Antonio Gimeno-Orna, MD, PhD[c], Pilar Lasierra-Díaz, MD, PhD[d], Claudia Josa-Laorden, MD[a], Juan-José Puente-Lanzarote, MD, PhD[e], Paulo Bettencourt, MD, PhD[f], and Domingo A. Pascual-Figal, MD, PhD[g]

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

[a]Servicio de Medicina Interna, Facultad de Medicina, Instituto de Investigación Sanitaria de Aragón, [c]Servicio de Endocrinología y Metabolismo, [d]Laboratorio de Inmunología, and [e]Laboratorio de Bioquímica Clínica, Hospital Clínico Universitario "Lozano Blesa", Zaragoza, Spain; [b]Servicio de Medicina Interna, Hospital Universitario "Arnau de Villanova", Lleida, Spain; [f]Serviço de Medicina Interna, Hospital CUF—Porto, Faculdade Medicina Porto, Portugal; and [g]Servicio de Cardiología, Hospital Universitario "Virgen de la Arrixaca", Facultad de Medicina, Murcia, Spain. Manuscript received November 22, 2015; revised manuscript received and accepted May 9, 2016.

See page 548 for disclosure information.

*Corresponding author: Tel: (+0034) 976768864; fax: (+00 34) 976 351 661.

E-mail address: jiperez@unizar.es (J.-I. Pérez-Calvo).

0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.05.048

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