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Clinica Chimica Acta 381 (2007) 145–150
www.elsevier.com/locate/clinchim

Hemoglobin and N-terminal pro-brain natriuretic peptide: Independent and synergistic predictors of mortality in patients with acute heart failure Results from the International Collaborative of NT-proBNP (ICON) Study

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Received 5 January 2007; received in revised form 1 March 2007; accepted 1 March 2007
Available online 19 March 2007

Abstract

Background: Hemoglobin and amino-terminal pro-brain natriuretic peptide (NT-proBNP) are both independent predictors of mortality in patients with chronic HF. Their combined predictive power for mortality in the setting of acute HF is uncertain.
Methods: In an international prospective cohort design, we evaluated the relationships between hemoglobin, NT-proBNP, and 60-day mortality in 690 patients with acute HF.
Results: The median hemoglobin for the entire cohort was 13.0 g/dL (interquartile range 11.6–14.3). The WHO criterion for anemia was met by 44% ($n=305$). The 60-day mortality rate for anemic patients was 16.4% vs. 8.8% in non-anemic patients ($p<0.001$). Anemia was an independent predictor of short-term mortality (OR = 1.72, 95% CI = 1.05–2.80, $p=0.03$), as was a NT-proBNP concentration > 5180 pg/mL (OR = 2.32, 95% CI = 1.36–3.94 $p=0.002$). Consideration of four risk groups: not anemic/low NT-proBNP (reference group, $n=220$), anemic/low NT-proBNP ($n=152$), not anemic/high NT-proBNP ($n=165$), and anemic/high NT-proBNP ($n=153$) revealed respective 60-day mortality rates of 5.0% (referent), 9.2% (OR = 1.93, 95% CI = 0.85–4.36; $p=0.12$), 13.9% (OR = 3.07, 95% CI = 1.45–6.50, $p=0.003$), and 23.5% (OR = 5.84, 95% CI = 2.87–11.89, $p<0.001$).
Conclusions: Anemia was common in this cohort of subjects with acute HF and was related to adverse short-term outcome. Integrated use of hemoglobin and NT-proBNP measurements provides powerful additive information and is superior to the use of either in isolation.

Keywords: Anemia; Heart failure; Natriuretic peptides; Prognosis

1. Introduction

Brain natriuretic peptide (BNP) and its N-terminal congener NT-proBNP, are cardiac peptides secreted from ventricular myocardium in response to elevations in transmural pressure and are useful adjuncts for the diagnosis of acute heart failure (HF) [1–3]. Natriuretic peptide testing provides not only important diagnostic information, but also prognostic information in the setting of acute HF [4,5].

Other biomarkers may be additively useful for prediction of adverse outcomes in HF. Hemoglobin may be such a marker. Low hemoglobin may be a consequence of the neurohumoral and hemodynamic abnormalities that underlie HF and simultaneously may be a trigger for decompensation and a contributor to progressive myocardial remodeling, symptom severity, and reduced survival [6,7]. Recent reports have shown anemia to be a prevalent and important comorbidity in patients with chronic HF; however, its prognostic impact in the setting of acutely decompensated disease has not been well characterized [8,9].

Concentrations of natriuretic peptides and hemoglobin may reflect different pathophysiologic components of HF and, as such, might have additive prognostic value. Using data from the

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doi:10.1016/j.cca.2007.03.010

International Collaborative of NT-proBNP (ICON) study, we proposed to define the relationship between anemia at presentation and short-term mortality in patients with acute HF. We then examined the integrative roles of natriuretic peptide and hemoglobin measurements in improving prognostic accuracy over either strategy used alone.

2. Methods

2.1. Study subjects

We used baseline and follow-up information from the ICON Study, a multicenter registry comprised of trial data assessing the role of NT-proBNP for the diagnosis of acute HF [10]. The ICON Study population consists of patients from three previously reported prospective clinical trials of NT-proBNP testing from Christchurch, New Zealand, Barcelona, Spain and Boston, MA [11,1,2]. In addition, previously unpublished data from patients in an HF registry at the University Hospital of Maastricht, The Netherlands were also included. All data sources had compatible inclusion/exclusion criteria, and all studies collected similar clinical information, including standard demographics, medical history, drug therapy, presenting symptoms and signs (including severity of breathlessness by the New York Heart Association [NYHA] classification), physical examination, radiographic studies (typically plain chest radiographs), electrocardiography results and results of hematology, blood chemistry and NT-proBNP testing.

Of the 1256 patients in ICON, 720 (57%) were diagnosed with acute HF. Of those with acute HF, 690 (96%) had available hemoglobin data and were therefore considered eligible for this analysis. The diagnosis of acute HF was determined as described in each study [11,1,2].

2.2. Baseline data

Plasma samples for the measurements of hemoglobin and NT-proBNP concentrations were obtained at the time of enrollment. Hemoglobin concentrations were measured in an unblinded fashion at each institution, using conventional lab methods. NT-proBNP was measured using a validated, commercially available immunoassay (Elecsys® proBNP, Roche Diagnostics, Indianapolis, IN), using established methodology. This assay has been reported to have <0.001% cross-reactivity with bioactive BNP, and in the constituent studies in this report, this assay had inter-run coefficients of variation ranging from 0.9% to 5.5%. For the purposes of this report, NT-proBNP levels are expressed in pg/mL (to convert pg/mL to pmol/L, multiply × 0.118). Historical information, physical findings, and the results of routine diagnostic testing obtained during the initial presentation were considered. Creatinine clearance values were calculated by the Modified Diet in Renal Disease (MDRD) equation [12].

2.3. Endpoints

The primary endpoint of this analysis was 60-day mortality. Death information was ascertained from hospital medical records, death certificates and telephone follow-up with referring physicians.

2.4. Statistical analysis

Data are presented as medians with intra-quartile ranges (IQR) for non-normally distributed variables and means ± standard deviations (SD) for all other continuous variables. The World Health Organization definition of anemia (hemoglobin <13.0 g/dL [male] and <12.0 g/dL [female]) was used [13]. To perform multi-marker stratification, we categorized patients into 2 groups based on presentation NT-proBNP level (>5180 pg/mL vs. ≤5180 pg/mL), as previous receiver–operator curve analysis had determined this to be the optimal cut-point for predicting 60-day and 76-day mortality in acute HF [10].

Differences in baseline variables between survivors and non-survivors were analyzed using analysis of variance and Pearson's chi-square testing as appropriate. Survival curves were calculated using the Kaplan–Meier method and differences between the curves were evaluated using the log-rank statistic. Univariate screening of baseline variables was used to identify candidate independent predictors of 60-day mortality. Multivariable analysis with forward step-wise logistic regression, including all candidate variables with *p*-values ≤0.10, was performed to identify independent predictors of 60-day mortality.

Table 1
Comparisons of patients with acute heart failure as a function of 60-day survival

Characteristic	Alive at day 60 (*n*=606)	Deceased by day 60 (*n*=84)	*p*-value
Age (mean±SD)	74.4±11.7	78.5±10.6	0.002
Male gender	51.2%	52.4%	0.833
Black race	2.5%	0%	0.237
Past medical history			
Hypertension	62.0%	51.2%	0.056
Coronary artery disease	50.7%	65.5%	0.011
Prior acute myocardial infarction	33.3%	42.2%	0.112
Prior congestive heart failure	51.7%	54.8%	0.593
Prior obstructive airways disease	29.3%	26.2%	0.561
Smoking (past or present)	51.9%	52.4%	0.985
Loop diuretic use prior to presentation	58.9%	69.9%	0.056
Symptoms/signs			
Paroxysmal nocturnal dyspnea	33.2%	19.0%	0.009
Orthopnea	51.6%	48.4%	0.635
Lower extremity edema	46.5%	45.2%	0.823
Chest pain	33.5%	32.5%	0.861
Cough	32.8%	27.4%	0.361
Fever	4.1%	10.7%	0.009
Increased sputum	18.3%	16.7%	0.713
NYHA Class IV	44.2%	50.0%	0.319
Physical examination			
Pulse rate (mean±SD)	92.8±25.8	95.5±26.0	0.381
Jugular venous distension	48.8%	56.0%	0.222
S3 gallop	6.9%	8.3%	0.639
Lower extremity edema	56.3%	52.4%	0.501
Rales	68.7%	67.9%	0.882
Wheezing	16.9%	10.7%	0.151
ECG findings			
Sinus rhythm	59.6%	64.3%	0.408
Atrial fib/flutter	34.5%	32.1%	0.671
Left ventricular hypertrophy	10.7%	8.3%	0.499
Left bundle branch block	15.0%	25.0%	0.020
Chest X-ray findings			
Interstitial edema	37.6%	29.8%	0.161
Infiltrate	11.7%	16.7%	0.196
Pleural effusion	26.6%	22.6%	0.440
Cephalization of vessels	29.4%	35.7%	0.235
Cardiomegaly	37.0%	39.3%	0.680
Laboratory findings			
Hemoglobin, g/dL (mean±SD)	12.7±2.1	12.0±2.0	0.003
World Health Organization Anemic	42.1%	59.6%	0.003
Creatinine, mg/dL (median, IQR)	1.12 (0.87–1.50)	1.41 (1.02–2.10)	<0.001
Creatinine clearance (median, IQR)	60.70 (42.90–79.22)	43.90 (30.92–64.03)	<0.001
Troponin T >0.00 ng/mL	78.4%	93.3%	<0.001
Troponin T >0.10 ng/mL	47.5%	77.3%	<0.001
NT-proBNP, pg/mL (median, IQR)	4077 (1740–9989)	9448 (3805–22179)	<0.001

Abbreviations: SD=Standard Deviation; IQR=Interquartile Range.