American Journal of Emergency Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Predictors of 30-day mortality in patients admitted to emergency departments for acute heart failure

Marchetti Matthieu, MD [a,*], Benedetti Antoine, MD [a], Mimoz Olivier, PhD [a,b], Lardeur Jean-Yves, MD [a], Guenezan Jérémy, MD [a,b], Marjanovic Nicolas, MD [a,b]

[a] Emergency Department, University Hospital of Poitiers, 86000 Poitiers, France
[b] University of Poitiers, Medical School, 86000 Poitiers, France

ARTICLE INFO

Article history:
Received 16 July 2016
Received in revised form 16 November 2016
Accepted 21 November 2016
Available online xxxx

Keywords:
Acute heart failure
Mortality
Emergency
Natriuretic brain peptide

ABSTRACT

Objectives: Acute heart failure (AHF) is a leading cause of admission in emergency departments (ED). It is associated with significant in-hospital mortality, suggesting that there is room for improvement of care. Our aims were to investigate clinical patterns, biological characteristics and determinants of 30-day mortality.
Methods: We conducted a single site, retrospective review of adult patients (≥18 years) admitted to ED for AHF over a 12-month period. Data collected included demographics, clinical, biological and outcomes data. Epidemiologic data were collected at baseline, and patients were followed up during a 30-day period.
Results: There were a total of 322 patients. Mean age was 83.9 ± 9.1 years, and 47% of the patients were men. Among them, 59 patients (18.3%) died within 30 days of admission to the ED. The following three characteristics were associated with increased mortality: age > 85 years (OR = 1.5[95%CI:0.8–2.7], $p = 0.01$), creatinine clearance <30 mL/min (OR = 2.6[95%CI:1.4–5], $p < 0.001$) and Nt-proBNP >5000 pg/mL (OR = 2.2[95%CI:1.2–4], $p < 0.001$). The best Nt-proBNP cut-off value to predict first-day mortality was 9000 pg/mL (area under the curve (AUC) [95%CI] of 0.790 [0.634–0.935], $p < 0.001$). For 7-day mortality, it was 7900 pg/mL (0.698 [0.578–0.819], $p < 0.001$) and for 30-day mortality, 5000 pg/mL (0.667 [0.576–0.758], $p < 0.001$).
Conclusions: Nt-proBNP level on admission, age and creatinine clearance, are predictive of 30-day mortality in adult patients admitted to ED for AHF.

1. Introduction

Acute heart failure (AHF) is a leading cause of admission in emergency departments (ED) in Western countries. Its prevalence is estimated at between 1 and 2% of the adult population and is higher than 10% in patients older than 70 years [1–3]. Recommendations for diagnosis and management of AHF were issued by the European Society of Cardiology (ESC) in 2016 [4] and by the American Heart Association (AHA) in 2013 [5] with an update in 2016 [6]. Initial diagnosis is based on clinical history, physical examination and electrocardiogram (ECG). Some abnormalities on ECG provide information on aetiology and may give indication for therapy. The plasma concentration of natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-BNP [Nt-proBNP]) can be used as a complementary diagnostic test. Echocardiography provides crucial information on chamber volumes, ventricular systolic and diastolic function, valve function and pulmonary hypertension [5–7]. The information provided by the above-mentioned tests and clinical evaluation allow for initial treatment plan in most patients.

AHF is associated with significant in-hospital mortality and high rates of rehospitalization after discharge [8]. Early identification of patients at high risk of death might help emergency physicians to optimize their prompt management and thus expect an improvement in prognosis. The aim of this study was to determine the clinical and biological patterns that could successfully predict the short-term prognosis (30-day mortality) of patients with AHF at the time of admission to the ED.

2. Methods

2.1. Study design and population

We conducted a single site, retrospective study to assess risk factors associated with 30-day mortality in patients with AHF. We reviewed the clinical course of 322 patients, 18 years or older, admitted to ED with the primary diagnosis of AHF, in a large academic center, between January 1 and December 31, 2014. The outcome in this study was defined as 30-day mortality. Patients surviving and not surviving the 30-day period after discharge were matched with their clinical and biological data.

* Corresponding author at: Emergency Department, University Hospital of Poitiers, 2 Rue de la Milétrie, 86000 Poitiers, France.
E-mail address: matthieu.marchetti@gmail.com (M. Marchetti).

http://dx.doi.org/10.1016/j.ajem.2016.11.050
0735-6757/

Data were anonymized and stored electronically. The study was conducted in accordance with the principles of the Declaration of Helsinki. According to French law, institutional review board approval was not requested due to the retrospective design of the study and the use of anonymous data only.

2.2. Study protocol

Data collection was performed using patients' computerized medical records. Final diagnosis at ED discharge was used for inclusion and medical records were retrospectively reviewed to ensure that the 2012 ESC Guidelines [1] criteria were met for the diagnosis of AHF. Medical history, demographics, clinical and biological data were collected with the following software: ResUrgences® (Intuitive, Paris, France), Hopital Manager® (Softway Medical, Meyreuil, France) and CyberLab® (Clinical Biology Institute, Brussels, Belgium). All data were recorded at baseline, and patients' vital status at 30 days was ascertained by consulting hospital registries. In case of death within 30 days from ED admission, the interval (days) between admission and death was also recorded. When patients returned home before the thirtieth day, vital status was ascertained by telephone contact with the patient's general practitioner. No patient was lost during the 30-day follow up. For patients who presented to the ED more than once, only data from their first visit were included in the study. According to ESC Guidelines, patients were classified into six clinical presentations of AHF: acute pulmonary edema, cardiogenic shock, acutely decompensated chronic heart failure (CHF), hypertensive heart failure (HF), isolated right HF and acute coronary syndrome (ACS) with HF. Severe renal insufficiency was defined as a creatinine clearance according to Modification of Diet in Renal Disease (MDRD) formula lower than 30 mL/min/1.73m^2.

2.3. Statistical analysis

Data were recorded using Excel® software (Microsoft Corporation, Richmond, USA). Statistical analyses were performed using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA). Comparative univariate analyses were performed using the Chi-square test and Fisher's test for percentage comparisons. Differences in continuous variables were evaluated by the Student *t*-test. The log-rank test, odd-ratios (OR) with 95% confidence intervals (CI) and receiver operating characteristic (ROC) analyses were used to determine the prognostic value of clinical and biological patterns on 30-day mortality. All tests were two-tailed and statistical significance was considered for $p \leq 0.05$.

3. Results

Overall, 322 patients with a primary diagnosis of AHF and complete data were analyzed. Their mean age was 83.9 ± 9.1 years and 47% of them were men (Table 1). Sixty percent of the patients were older than 85 years. Evidence of chronic heart failure was reported in 88.8% of cases. The most common co-morbidities were hypertension (74.5%) and atrial fibrillation (54.3%). Acutely decompensated CHF was the most frequent clinical presentation (58.1%). Acute pulmonary edema was present in 14.3%, while hypertensive HF, ACS with HF, isolated right HF and cardiogenic shock was reported respectively in 11.5, 6.2, 5.6 and 4.3% (Table 1).

A total of 59 (18.3%) patients died within 30 days of admission to the ED. Their clinical presentations were acutely decompensated CHF in 44.1% of cases, and acute pulmonary edema, cardiogenic shock and ACS with HF in 16.9, 15.2 and 11.8% of cases, respectively (Table 1). On univariate analysis, clinical pictures associated with 30-day

Table 1
SD : Standard Deviation, COPD : Chronic Obstructive Pulmonary Disease, HF : Heart Failure, MDRD : Modification of diet in renal disease.

Variables	Overall population (n = 322)	Survival patients (n = 263)	Not survival patients (n = 59)	OR	95%CI	p-Value
Demographic data						
Age (y), mean ± SD	83.9 ± 9.1					
Age > 85 y	192 (59.6%)	150 (57%)	42 (71%)	1.5	0.84–2.68	0.01
Gender (male)	150 (47%)	122 (46%)	28 (47%)	1.04	0.59–1.84	0.9
Previous medical history						
Hypertension	240 (74.5%)	200 (76%)	40 (67.6%)	0.54	0.24–1.18	0.16
Diabetes	97 (30.1%)	81 (30.8%)	16 (27%)	0.84	0.44–1.57	0.57
COPD	44 (13.6%)	38 (14.4%)	6 (10.1%)	0.67	0.27–1.67	0.38
Chronic renal failure	67 (20.8%)	51 (19.4%)	16 (27%)	1.54	0.8–2.96	0.18
Coronary heart disease	106 (32.9%)	93 (35.3%)	13 (22%)	0.51	0.26–1.005	0.05
Valvular heart disease	66 (20.4%)	50 (19%)	16 (27%)	1.57	0.82–3.04	0.13
Dyslipidemia	102 (31.7%)	89 (33.8%)	13 (22%)	0.55	0.28–1.076	0.07
Chronic heart failure (CHF)	286 (88.8%)	237 (90.1%)	49 (82.8%)	1.29	0.6–2.76	0.02
Atrial fibrillation	175 (54.3%)	151 (57.4%)	24 (40.6%)	0.51	0.29–0.90	0.02
Clinical presentation						
Acute pulmonary oedema	46 (14.3%)	36 (13.7%)	10 (16.9%)	1.29	0.6–2.76	0.21
Cardiogenic shock	14 (4.3%)	5 (1.9%)	9 (15.2%)	9.29	2.99–28.88	<0.001
Isolated right heart failure (HF)	18 (5.6%)	15 (5.7%)	3 (5.1%)	0.89	0.25–3.06	0.81
Acutely decompensated CHF	199 (61.8%)	170 (64.6%)	29 (49%)	0.53	0.3–0.93	0.02
Hypertensive HF	37 (11.5%)	33 (12.5%)	4 (6.8%)	0.51	0.17–1.5	0.21
ACS with HF	20 (6.2%)	13 (4.9%)	7 (11.8%)	2.6	0.98–6.8	0.02
Clinical patterns						
Heart rate (beats per minute)						
40–120	297 (92.2%)	244 (92.8%)	53 (89.8%)	0.69	0.26–1.80	0.52
>120	25 (7.8%)	19 (7.2%)	6 (10.2%)	1.37	0.53–3.59	0.52
Systolic blood pressure < 90 mm Hg	16 (5%)	6 (2.3%)	10 (16.9%)	13.6	3.49–53	<0.001
Biological patterns						
Nt-proBNP (pg/mL)						
5000–9999	59 (18.3%)	51 (19.4%)	8 (13.5%)	2.16	1.16–4.02	<0.001
10,000–14,999	35 (10.9%)	32 (12.2%)	3 (5.1%)	2.85	1.55–5.23	<0.001
15,000–29,999	30 (9.3%)	21 (8%)	9 (15.2%)	5.1	2.48–10.4	<0.001
>30,000	28 (8.7%)	13 (4.9%)	15 (25.3%)	10.3	3.5–30.5	<0.001
MDRD <30 mL/min/1.73m^2	61 (18.9%)	42 (16%)	19 (32.1%)	2.6	1.38–5	<0.001

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mortality were cardiogenic shock (OR = 9.3 [95%CI: 3–28.9], $p < 0.001$) and ACS with HF (OR = 2.6 [95%CI: 1–6.8], $p = 0.02$) (Table 1). Systolic blood pressure under 90 mm Hg at presentation was associated with higher mortality (OR = 13.6 [95%CI: 3.5–53.0], $p < 0.001$). By contrast, medical history of coronary heart disease (OR = 0.5 [95%CI: 0.26–1], $p = 0.05$) and atrial fibrillation (OR = 0.5 [95%CI: 0.3–0.9], $p = 0.02$) were associated with lower mortality (Table 1).

Predictors for 30-day mortality were age > 85 years (OR = 1.5[95%CI:0.8–2.7], $p = 0.01$), severe renal insufficiency (OR = 2.6[95%CI:1.4–5], $p = 0.001$) and Nt-proBNP >5000 pg/mL (OR = 2.2[95%CI:1.2–4], $p < 0.001$). The optimal Nt-proBNP cut-off value for predicting 30-day mortality was 5000 pg/mL (Area under the curve (AUC) [95%CI]: 0.667 [0.576–0.758], $p < 0.001$) (Fig. 1). The cut-off for predicting first-day and seven-day mortality were 8991 pg/mL (0.790 [0.634–0.935], $p < 0.001$) and 7900 pg/mL (0.698 [0.578–0.819], $p < 0.001$), respectively. Kaplan-Meier survival curves confirm that patients with Nt-proBNP levels above 5000 pg/mL had significantly ($p = 0.02$) higher 30-day mortality than patients with Nt-proBNP levels below this cut-off (Fig. 2).

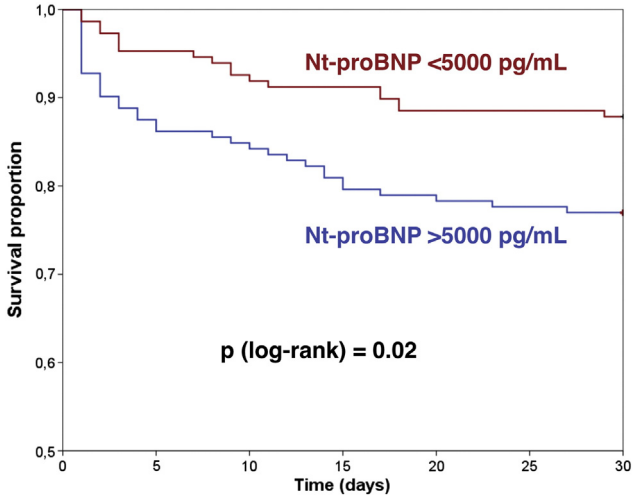

Fig. 2. Kaplan-Meier survival curves according to initial Nt-proBNP level above or below 5000 pg/mL.

4. Discussion

Our study showed that age > 85 years, creatinine clearance (MDRD formula) <30 mL/min and Nt-proBNP level > 5000 pg/mL are three early predictors of 30-day mortality in elderly patients admitted to ED for AHF.

The mean age of our patients was 84 years. This is comparable than in most other recent studies [8–11]. Co-morbidities and clinical presentations were similar to those reported in most other studies or registries [5–7,12,13]. These findings are comparable to those observed in large registries of AHF such as the OPTIMIZED-HF registry [14] including >48,000 patients in the USA and the OFICA study [15], a single-day snapshot among 1868 patients in French hospitals. In these studies, mean age was closed to 80 years, and the majority of patients were over 85 years. Similarly, as in our results, patients with cardiogenic shock represented 4 to 6% of cases, and the EHFS-II study [9] show a 16% acute pulmonary edema rate. Many of our patients had a history of atrial fibrillation (AF), which may be explained by the increase in the prevalence of AF with age [16]. The majority of our patients had a medical history of chronic heart failure, as in most similar studies [9–15].

In our study, 30-day mortality was 18.3%. It was higher than in similar studies on short-term mortality (1-day or 7-day) [11–13,15]. In a prospective study, Golcuk et al. [17] examined 100 patients with AHF at ED admission, with a 30-day mortality of 21%. In two other studies, Aaronson et al. [18] and Krumholz et al. [19] found a lower 30-day mortality of 11%. Fabbri et al. [20] found a 30-day and one-year mortality of 10 and 50%, respectively. In our study, clinical presentation of cardiogenic shock and ACS with HF were associated with higher mortality, and systolic blood pressure below 90 mm Hg is an acknowledged criterion for intensive care unit (ICU) admission [4]. But surprisingly, medical history of AF and coronary heart diseases were associated with a lower rate of death. This may be explained by more extensive follow-up of these patients, with optimal treatment [14,15].

Several studies reported admission Nt-proBNP cut-off value as a risk stratification tool and prognostic indicator in patients with AHF [21–25]. The 30-day mortality period seemed to be more pertinent from a pathophysiological point of view, than shorter duration (first day) or longer (1 to 4 years) duration. However, from an emergency physician perspective, 1-day and 7-day mortality could be considered even more important, as these early endpoints may help driving ED therapy and ICU admission. Cardiologists and intensivists interventions may also impact late mortality, but overall survival is mainly determined by the quality of the initial management [4–6]. With our study design, we could assess the association with mortality of the variables classically described as prognostic predictors. Analysis of the area under the ROC curve suggests that a Nt-proBNP cut-off value of 5000 pg/mL provides prognostic information regarding 30-day survival in our ED population admitted for AHF. Gegenhuber et al. [26] found an optimal Nt-proBNP cut-off point of 2060 pg/mL for predicting 1-year mortality. In another study, Velibey et al. [27] showed that Nt-proBNP value of 2300 pg/mL is a predictive factor of 4-year mortality. Our study reinforces Nt-proBNP as the standard for AHF prognostic prediction and helps to better define subgroups

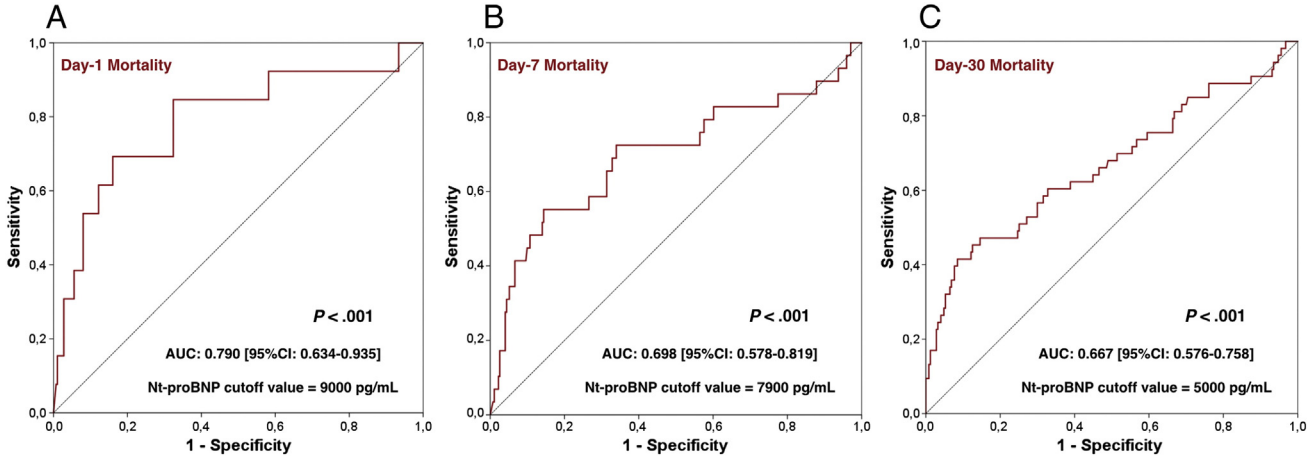

Fig. 1. Receiver operating characteristic curves of Nt-proBNP cut-off values as predictors of 1-day (A), 7-day (B) and 30-day mortality (C).

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in need of more intensive care [16–27]. Older age (>85 years) and severe renal insufficiency were also associated with 30-day mortality. This correlation has been found in several similar studies [28–32].

These findings suggest that in elderly patients presenting to the ED with AHF, assessment of Nt-proBNP concentrations could also be useful to stratify patients according to their prognosis. We suggest that prompt aggressive treatment should be applied to patients with Nt-proBNP levels above 5000 pg/mL, to reduce in-hospital and short-term mortality. This includes identification of causes leading to AHF and requiring urgent management (acute coronary syndrome, hypertensive emergency, acute pulmonary embolism, arrhythmias), search of criteria for hospitalization in ICU, and management of the early phase with oxygen therapy, diuretics, vasodilators (in the absence of symptomatic hypotension) or other drugs (digoxin, amiodarone, thrombo-embolism prophylaxis) as per ESC and AHA guidelines [4,6].

Some study limitations should be acknowledged. It was a single-center study, with patients potentially not representative of the whole population of patients with AHF. However, the characteristics of our population were similar to those observed in large registries. Despite systematic recruitment with computerized medical records, the analysis was retrospective with all its inherent setbacks. Our population was not homogenous with regard to clinical presentation: acutely decompensated CHF was the most common presentation (58%), while cardiogenic shock, with higher mortality, was reported in only 4%. Biological data were collected at the time of ED admission, and our analyses were based on a single baseline determination, thereby precluding any comparison between admission and pre-mortem data values or variations. Moreover, the effects of unmeasured variables such as duration of AHF, socioeconomic factors and obesity cannot be excluded.

5. Conclusion

Nt-proBNP level ≥ 5000 pg/mL on admission, age and severe renal failure are predictors of all-causes 30-day mortality in elderly patients admitted to ED for AHF. Additional large, prospective and multicenter studies are needed to confirm our findings.

Acknowledgement

The authors would like to thank Mr. Jeffrey Arsham for copy editing the manuscript.

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