The impact of admission cystatin C levels on in-hospital and three-year mortality rates in acute decompensated heart failure

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Abstract

Background: Although tremendous advances have been made in preventative and therapeutic approaches in heart failure (HF), the hospitalisation and mortality rates for patients with HF is high. The aim of this study was to investigate the association between cystatin C and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and in- and out-of-hospital mortality rates in acute decompensated HF (ADHF).

Methods: Between February 2008 and November 2011, 57 consecutive patients who were admitted with ADHF were included in this prospective study. These patients were clinically followed up every three months by means of visits or telephone interviews. The primary clinical endpoint of this study was any death from heart failure rehospitalisation and/or other causes.

Results: The subjects who died during the in-hospital follow up were younger than the survivors (47.4 ± 17.5 vs 60.8 ± 15.8, $p = 0.043$). There was a notable correlation between plasma cystatin C and NT-proBNP levels ($r = 0.324$, $p = 0.014$) and glomerular filtration rate (GFR) ($r = –0.638$, $p < 0.001$). Multivariate logistic regression analysis revealed that only cystatin C level [odds ratio (OR): 12.311, 95% confidence interval (CI): 1.616–93.764, $p = 0.015$] and age [OR: 0.925, 95% CI: 0.866–0.990, $p = 0.023$] were linked to in-hospital mortality rate. In the multivariate Cox proportional hazard model, only admission sodium level appeared as a significant independent predictor of death during the 36-month follow up [hazard ratio: 0.937, 95% CI: 0.880–0.996, $p = 0.037$].

Conclusion: Evaluation of admission cystatin C levels may provide a reliable prediction of in-hospital mortality, compared to estimated GFR or NT-proBNP levels among patients with ADHF. However, in this trial, during long-term follow up, only admission sodium level significantly predicted death.

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Worldwide, chronic heart failure (HF) syndrome is increasing in prevalence. Despite advances in preventative and therapeutic approaches, mortality and hospitalisation rates in this population remain high. Impaired renal function often accompanies HF, and co-existence of these diseases is correlated with an increased rate of cardiovascular risk and death.[1]

The exact mechanism underlying the complex interaction between HF and renal disease remains unclear. Recently, cystatin C, an inhibitor of cysteine proteases of the cathepsin family has gained valuable recognition, being a more reliable measure of renal function than serum creatinine-based calculations.

Cystatin C is created by all nucleated cells and is simply drained at the glomerulus and not secreted from the tubules. Unlike creatinine, it does not seem to be affected by gender, race or muscle volume, which makes it a more definite marker of glomerular capacity.[2,3] Increased levels of cystatin C are related to impaired renal function and correlated with a decline in estimated glomerular filtration rate (eGFR).[4] In both acute and chronic stages of HF, cystatin C level is a better predictor of mortality and unfavourable cardiovascular outcome, compared to serum creatinine-based assessments.[5-7]

HF causes volume overload, which results in myocardial stretch and excretion of cardiac peptides such as N-terminal pro-B-type natriuretic peptide (NT-proBNP).[8] NT-proBNP is not only useful for diagnostic purposes, but also provides relevant information about clinical responses to HF regimens and prognosis of the HF.[9,10] In a previous report, a combination of cystatin C and NT-proBNP level was used as a predictor of unfavourable results in subjects with acute decompensated HF (ADHF).[11]

The authors reported that combination of the two parameters was useful in predicting patients who had the highest risk for worse outcomes. However, in the literature, there are no data about the relationship between hospital admission cystatin C levels and mortality on an annual basis. We intended to assess the association between in-hospital mortality rate among patients with ADHF and both cystatin C and NT-proBNP levels. Another aim was to evaluate whether out-of-hospital mortality rate was associated with in-hospital levels of cystatin C during regular follow up (36 months).

Methods

Between February 2008 and November 2011, 57 consecutive patients (mean age 54.1 ± 16.3 years, male 68.4%) with typical symptoms and signs of ADHF and with low left ventricular ejection fraction (LVEF < 40%) were enrolled in this study.[12] During the hospital stay, all of the patients received appropriate HF treatment measures in accordance with contemporary guideline recommendations.[13]

Patients with concomitant unstable ischaemic diseases, those presenting with shock, severe renal failure [GFR estimated by Modification of Diet in Renal Disease (MDRD) equation < 30 ml/min/1.73 m^2] or hepatobiliary dysfunction, anaemia or haematological disease, acute or chronic infection and inflammation, malignant neoplasms and patients with echocardiographic LVEF values ≥ 40% were excluded. A gender- and age-matched control group (n = 31) with normal LVEF and renal function was included to compare plasma NT-proBNP and cystatin C levels with the patient group.

Surviving participants were clinically followed up every three months for three years by means of visits or telephone interviews. In the case of death during the follow-up period, follow-up duration was calculated in months (time interval from admission to death) for that subject. Mean follow-up duration for the entire group was 17.2 months.

The primary clinical endpoint of this study was determined as all-cause mortality. From each patient, oral informed permission for the study was obtained by one of the investigators, and the study protocol was approved by the local ethics committee of our hospital.

Blood samples for biochemical parameters, including haemoglobin, blood urea nitrogen (BUN), creatinine, electrolytes, cystatin C and NT-proBNP were drawn at admission for ADHF. GFR was determined using two different contemporary formulae: the MDRD and the Cockroft–Gault formulae.[14,15] For cystatin C assessment, an immediate centrifugate of the collected sample was obtained. Aliquot serum samples were stored in microcentrifuge tubes at −80°C until assayed.

Measurements of cystatin C levels were performed using a particle-enhanced immune nephelometric method (Dade Behring GmbH, Liederbach, Germany). Intra-assay and inter-assay coefficients were 2.5 and 2.0%, respectively. NT-proBNP was measured by ARCHITECT i2000 platform (Abbott Laboratories, Abbott Park, Illinois).

All patients underwent standard echocardiographic imaging in the left lateral decubitus position with a commercially available device (Vivid 7 Ultrasound System; GE, Horten, Norway) on admission. The echocardiographic assessments were based on the criteria proposed by the American Society of Echocardiography. A modified Simpson's method was used for LVEF calculation.[16]

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version IBM 11.5 (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation (SD) or median (min–max), where applicable. Categorical variables are presented as percentages. The Student's t-test was used to analyse mean differences between two independent groups. The Mann–Whitney U-test was employed for identification of medians between two independent groups. As both plasma cystatin C and NT-proBNP levels were normally distributed. Correlation coefficients and their significance were calculated with Pearson's correlation test.

To define the predictors that changed in-hospital mortality, multiple logistic regression analyses were used. Odds ratios (OR) and 95% confidence intervals (CI) for the different independent variables were also determined. Univariate and multivariate Cox regression analyses were performed to delineate independent predictors of mortality during 36 months of follow up. A p-value < 0.05 was considered statistically significant.

Results

In this study, 57 subjects who met the inclusion criteria constituted the final research group. Plasma NT-proBNP and cystatin C levels were determined among patients with ADHF and the control subjects (n = 31). Plasma NT-proBNP concentrations of the patients were greater than in the control group (641.6 ± 31.7 vs 23.2 ± 31.7 pg/ml, $p < 0.001$). However, there were no notable differences in plasma cystatin C levels between the patient and control groups (1.27 ± 0.48 mg/l in the patients vs 1.11 ± 0.43 mg/l in the controls, $p = 0.095$).

Baseline demographic characteristics of the patients are reviewed in Table 1. During the in-hospital period, seven (12.3%) patients died. Comparisons of variables were made between survivors and those who died during the hospital stay.

There were no notable differences regarding gender, hypertension, diabetes mellitus, smoking and myocardial infarction between the groups ($p > 0.05$). However, the subjects who died during the in-hospital period were younger than the survivors (47.4 ± 17.5 vs 60.8 ± 15.8 years, $p = 0.043$). Also, the rate of prior cerebrovascular accident was significantly higher in patients who died (28.6 vs 6.0%, $p = 0.048$). Moreover, among patients who died during the hospital stay, lower sodium concentrations, and higher cystatin C and NT-proBNP levels were observed ($p = 0.003$, $p = 0.023$, $p = 0.001$, respectively) (Table 2).

Baseline echocardiographic characteristics of the patients are reviewed in Table 3. There were no differences between the two groups regarding echocardiographic parameters ($p > 0.05$).

Table 1. Baseline demographic characteristics of the study population

Variables	*In-hospital survivors (n = 50)*	*In-hospital deaths (n = 7)*	p-*value*
Age (years)	60.8 ± 15.8	47.4 ± 17.5	0.043
Male gender, *n* (%)	34 (68.0)	5 (71.4)	0.855
Diabetes mellitus, *n* (%)	15 (30.0)	4 (57.1)	0.154
Hypertension, *n* (%)	24 (48.0)	5 (71.4)	0.246
Hyperlipidaemia, *n* (%)	12 (24.0)	1 (14.3)	0.566
Cigarette smoking, *n* (%)	6 (12.0)	1 (14.3)	0.863
History of MI, *n* (%)	9 (18.0)	2 (28.6)	0.507
History of CVA, *n* (%)	3 (6.0)	2 (28.6)	0.048
History of PCI, *n* (%)	5 (10)	1 (14.3)	0.729
History of CABG, *n* (%)	6 (12.0)	1 (14.3)	0.863
New diagnosis of HF, *n* (%)	7 (14)	0 (0.0)	0.291
BMI (kg/m^2)	26.1 ± 4.9	22.4 ± 3.8	0.062
Hospitalisation length (days)	15.2 ± 22.2	23.6 ± 27.2	0.345
NYHA functional class	3.2 ± 4.9	3.4 ± 5.6	0.237

BMI: body mass index, CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, HF: heart failure, MI: myocardial infarction, NYHA: New York Heart Association, PCI: percutaneous coronary intervention.

Table 2. Baseline laboratory characteristics of the study population

Variables	*In-hospital survivors (n = 50)*	*In-hospital deaths (n = 7)*	p-*value*
Fasting glucose (mg/dl)	113.6 ± 48.7	124.7 ± 49.1	0.559
(mmol/l)	6.30 ± 2.70	6.92 ± 2.73	
Urea (mg/dl)	69.5 ± 33.7	93.9 ± 51.7	0.100
Creatinine (mg/dl)	1.15 ± 0.43	1.27 ± 0.61	0.784
Total cholesterol (mg/dl)	136.5 ± 35.8	127.0 ± 38.9	0.518
(mmol/l)	3.54 ± 0.93	3.29 ± 1.01	
Triglycerides (mg/dl)	85.6 ± 34.5	106.6 ± 35.2	0.138
(mmol/l)	0.97 ± 0.39	1.20 ± 0.40	
Sodium (mmol/l)	135.5 ± 5.1	128.9 ± 7.6	0.003
Potassium (mmol/l)	4.3 ± 0.6	4.2 ± 0.7	0.794
Haemoglobin (g/dl)	12.4 ± 1.9	11.5 ± 1.2	0.218
Cystatin C (mg/l)	1.22 ± 0.39	1.62 ± 0.62	0.023
NT-proBNP (pg/ml)	577.2 ± 585.5	1101.6 ± 228.7	0.001
GFR (ml/min/1.73 m^2)	72.8 ± 30.0	74.3 ± 44.8	0.907
Cockcroft (ml/dk)	74.5 ± 33.2	78.2 ± 54.1	0.803

GFR: glomerular filtration rate, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Multivariate logistic regression analysis confirmed that only cystatin C level (OR: 12.311, 95% CI: 1.616–93.76, $p = 0.015$) and age (OR: 0.925, 95% CI: 0.866–0.990, $p = 0.023$) were linked to in-hospital deaths. Also there was a notable correlation between plasma cystatin C and NT-proBNP levels ($r = 0.324$, 95% CI: 0.069–0.539, $p = 0.014$) and GFR ($r = –0.638$, 95% CI: –0.770 to –0.453, $p < 0.001$) (Table 4).

During the 36-month follow-up period, the primary endpoint (death) occurred in 38 subjects. When we compared the admission cystatin C levels among survivors and those who died, we did not observe any significant difference between the two groups ($p > 0.05$) (Table 5).

Univariate and multivariate analyses were performed to examine independent predictors of mortality for the entire 36-month follow-up period. When univariate Cox proportional regression analysis was applied to baseline parameters, cystatin C level was found to have no effect on mortality rate during the 36-month follow-up period [hazard ratio (HR): 1.531, 95% CI: 0.696–3.371, $p = 0.290$], but age (HR: 0.978, 95% CI: 0.960–0.997, $p = 0.023$) and sodium level (HR: 0.927, 95% CI: 0.874–0.982, $p = 0.010$) were found to be related to mortality rate. In the multivariate Cox proportional hazard model including age, cystatin C, NT-proBNP and sodium levels, LVEF and GFR variables, only admission sodium level was a significant independent predictor of death during the 36-month follow up (HR: 0.937, 95% CI: 0.880–0.996, $p = 0.037$) (Table 6, Fig. 1).

Table 3. Baseline echocardiographic characteristics of the study population

Variables	*In-hospital survivors (n = 50)*	*In-hospital deaths (n = 7)*	p-*value*
LVEDD (cm)	6.3 ± 1.0	6.1 ± 0.4	0.607
EF (%)	25.6 ± 7.0	20.7 ± 8.9	0.101
sPAP (mmHg)	43.0 ± 11.5	40.9 ± 10.2	0.638

EF: ejection fraction, LVEDD: left ventricular end-diastolic diameter, sPAP: systolic pulmonary artery pressure.

Table 4. Correlation analysis of the variable

		Cystatin C (95% CI)		
Variables	r-*value*	*Lower*	*Upper*	p-*value*
NT-proBNP	0.324	0.069	0.539	0.014
MDRD	–0.638	–0.770	–0.453	< 0.001
Cockcroft	–0.486	–0.663	–0.258	< 0.001
Age	0.179	–0.086	0.420	0.183
Hospitalisation time	–0.007	–0.267	–0.331	0.957

CI: confidence interval, MDRD: Modification of Diet in Renal Disease, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Discussion

This study showed that higher admission cystatin C levels among patients with ADHF were related to in-hospital mortality rates, and in multivariate analysis, both cystatin C level and age were regarded as independent predictors of in-hospital death. However, during long-term follow up, when the two groups were compared in terms of mortality assessed on an annual basis, sodium level was the only independent predictor of death.

The combination of acute cardiac and renal dysfunction, termed cardiorenal syndrome,[17] is associated with unfavourable consequences in patients with acute HF.[18] Possible mechanisms for renal dysfunction in HF are low cardiac output, higher central blood pressure, renin–aldosterone–angiotensin axis dysfunction, activation of sympathetic tone, oxidative damage, and impaired renal perfusion.[19] Therefore, assessing renal function may simply show haemodynamic and neurohormonal perturbations in the setting of heart failure hospitalisations but may predict unfavourable consequences.[20] Although markers such as eGFR, BUN and creatinine level are easily available in routine blood tests, they may not always represent renal function properly.[21] In this context, using cystatin C levels may provide a more reliable assessment of renal function.[22]

In some subsets of patients with chronically impaired renal function, volume overload and haemodilution at the time of ADHF hospitalisation may mask underlying dysfunction, while patients with previously preserved renal function may present with worsening renal function due to accompanying low cardiac output and resultant low renal perfusion.[23] Therefore, since small changes in GFR can be detected by cystatin C level,[22] it may be preferred over standard renal function tests and may also be

Table 5. Comparison of admission cystatin C levels according to survival, assessed on an annual basis

	Cystatin C (mg/l)		
Follow up	*Survivor (n)*	*Deceased (n)*	p-*value*
In hospital	1.22 ± 0.39 (50)	1.62 ± 0.62 (7)	0.023
12 months	1.24 ± 0.35 (30)	1.31 ± 0.52 (27)	0.373
24 months	1.21 ± 0.39 (22)	1.31 ± 0.47 (35)	0.393
36 months	1.21 ± 0.40 (19)	1.30 ± 0.46 (38)	0.491

Table 6. Multivariate analysis of predictors of mortality during 36-month follow up

				95% CI	
Independent variables	*HR*	*Wald*	p-*value*	*Lower*	*Upper*
Age	0.975	2.599	0.107	0.944	1.006
Cystatin C	0.959	0.005	0.946	0.287	3.201
NT-proBNP	1.000	0.512	0.474	1.000	1.001
Sodium	0.937	4.336	0.037	0.880	0.996
LVEF	0.952	2.697	0.101	0.897	1.010
GFR	0.984	3.509	0.061	0.967	1.001

CI: confidence interval, LVEF: left ventricular ejection fraction, GFR: glomerular filtration rate, HR: hazard ratio, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

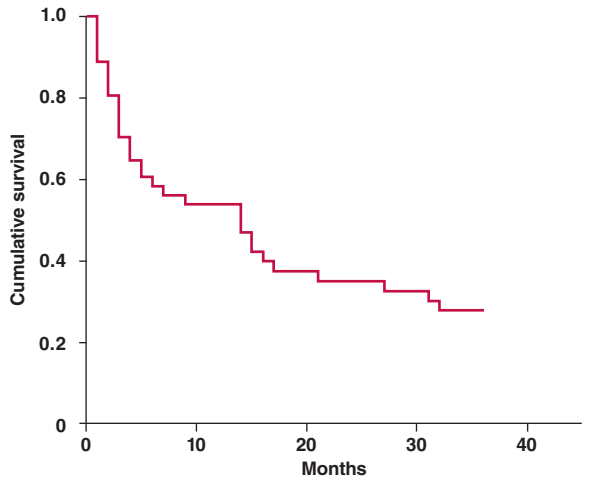

Fig. 1. Plot of the survival curve for patients with acutely decompensated heart failure.

useful in outcome measures.

Inazumi *et al*. found that cystatin C levels were more accurate for mortality prediction than eGFR in patients with ADHF.[23] They showed that even without a decrease in eGFR, increases in cystatin C level were associated lower long-term, event-free survival (180 days). Also, Rafouli-Stergiou *et al*. reported that in-hospital rise in cystatin C and NT-proBNP levels was useful in predicting 60-day cardiac death and rehospitalisation.[24] Similarly, we found that, rather than estimated GFR calculations, in-hospital mortality rate was related to higher cystatin C and NT-proBNP levels. However, during long-term follow up, only sodium level was an independent predictor of death, which affirms that hyponatraemia is a surrogate marker for mortality.[25]

Interestingly, we found that younger patients were more prone to suffer a cardiac death than older subjects. The possible reason for this finding may be that our hospital is a tertiary referral centre for heart transplant candidates, and younger patients with a worse clinical condition are mostly referred to our centre for advanced therapies. When we looked at similar studies evaluating mortality differences in ADHF patients, they principally included older subjects (60 years or more),[11,23,24] with an absence of younger patients, which might have limited data on differences in mortality rates in such patients.

Compared to the above studies, including younger patients may add further information about the association between cystatin C levels and mortality rates in such populations. Furthermore, among patients who died during their hospital stay, the rate of prior cerebrovascular accident was significantly higher than among survivors. The presence of cerebrovascular accident is a risk factor for HF,[26] but the co-existence of these conditions may be related to increased mortality rate.

In the ASCEND trial, 180-day follow up of patients with ADHF showed that baseline cystatin C level was a strong predictor of adverse events.[27] However, increase in cystatin C levels did not predict adverse outcomes. In contrast to the ASCEND trial, we did not observe differences in mortality rate with regard to baseline cystatin C levels during the 36-month follow-up time. Despite the fact that the sample size of our study was small, our results provide complementary data for long-term follow up of subjects with ADHF and raised cystatin C levels.

Although our study had a prospective design and followed patients for a considerable period, the number of recruited patients was relatively small, which probably lowered the statistical power of the study. Also, the recruited patients represent a relatively young population compared to previous studies. Because our centre is a tertiary referral hospital, the patient characteristics may not represent the whole HF population. Finally, we did not analyse GFR, cystatin C and plasma NT-proBNP levels according to heart failure aetiology, and only admission levels were evaluated rather than follow-up values. The cost-effectiveness of serial measurements of cystatin C levels in the prognostication of HF patients should be confirmed in large prospective studies.

Conclusion

In subjects with ADHF, evaluation of admission cystatin C levels may provide a reliable prediction of death compared to eGFR or NT-proBNP levels. Higher cystatin C levels provided important prognostic data about unfavourable in-hospital outcomes. For the post-discharge follow-up period, sodium level was the marker that had prognostic significance.

The preliminary results of this study (in-hospital mortality) were accepted as an oral presentation at the American College of Cardiology congress in 2013 (http://dx.doi.org/10.1016/j.cardfail.2013.06.088). The three-year follow-up results were accepted as an abstract presentation at the European Society of Cardiology Heart Failure congress (21–24 May 2016) in Florence, Italy.

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