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Predictors of clinical outcome in heart failure patients treated with vasopressin type 2 receptor antagonist

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Abstract

Objectives: There are well-established risk prediction models of in-hospital mortality due to heart failure (HF). However, the predictors of mortality during acute hospitalization in individuals with HF receiving tolvaptan, a vasopressin type 2 receptor antagonist, are poorly understood.

Methods: Sixty-one hospitalized patients prescribed tolvaptan to treat worsening HF were consecutively enrolled in this study. The study endpoint was death during hospitalization.

Results: Compared with survivors, patients who died in hospital had higher Get With The Guidelines-Heart Failure (GWTG-HF) risk scores, decreased albumin levels, increased serum creatinine levels, smaller inferior vena cava (IVC) diameters on echocardiography, and were more likely to have received catecholamine infusion. A multivariate logistic regression analysis revealed that in addition to GWTG-HF risk score >47, albumin level ≤2.4 g/dL, creatinine level >1.5 mg/dL, IVC diameter ≤15 mm, and catecholamine infusion were all novel and significant predictors of in-hospital death. Moreover, combining these novel predictors to the GWTG-HF risk score significantly improved prediction of in-hospital death, as shown by the greater area under the receiver operating characteristic (ROC) curve.

Conclusions: In patients with worsening HF receiving oral tolvaptan, we identified novel predictors of in-hospital death. Our findings may be helpful in developing novel treatment strategies for patients receiving tolvaptan for HF in clinical settings.

Keywords: Prognostic factor, Heart failure, Diuretics, Vasopressin type 2 receptor antagonist

Introduction

Heart failure (HF) is a major international public health concern and imposes a significant burden of morbidity and mortality.[1] There has been substantial progress in pharmacologic treatment of HF, with clinical options now including angiotensin-converting enzyme inhibitors (ACEs), angiotensin II-receptor blockers (ARBs) and β-receptor blockers that inhibit neurohumoral systems. Many patients with HF, however, are unavoidably hospitalized, and mortality rates remain high.[2–5]

Loop diuretics remain a standard treatment for patients with worsening HF, although several studies have demonstrated an association between higher doses of loop diuretics and poor clinical outcomes.[6–9] Hyponatremia induced by loop diuretics stimulates the non-osmotic release of arginine vasopressin, which subsequently contributes to fluid preservation and hyponatremia, both of which are associated with poor clinical outcomes in patients with HF.[10] Tolvaptan, a vasopressin type 2 receptor antagonist, suppresses free water reabsorption in the collecting tubules in the kidneys,[11] and oral tolvaptan is often combined with standard treatments for HF.[11–13] The efficacy and safety of oral tolvaptan in patients with acute HF are well established.[14–16] Although there are well-established risk prediction models of in-hospital HF mortality based on large registry datasets,[17,18] the predictors of in-hospital mortality in HF patients receiving tolvaptan during acute hospitalization have not yet been fully elucidated.

Materials and Methods

We prospectively observed 61 consecutive patients who were admitted to Fujita Health University Banbuntane Hotokukai Hospital with worsening HF and treated with tolvaptan between September 2011 and October 2013. Worsening of HF was defined as either new-onset HF or decompensation of chronic HF.[19] HF was diagnosed according to the Framingham criteria for clinical diagnosis of HF.[20] Signs of volume overload (rales, jugular venous distention and/or ankle edema) were confirmed by the attending physician, and all patients underwent laboratory measurements and echocardiography prior to starting tolvaptan therapy. The Get With The Guidelines-Heart Failure (GWTG-HF) risk score for each patient was calculated as set out previously.[18] In accordance with the recommendations outlined in the Declaration of Helsinki, all participants provided written informed consent, and our institutional ethics committee approved the protocol for the

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study and the chart review.

All statistical analyses were performed using SPSS version18 (SPSS, Chicago, IL, USA). Normally-distributed continuous variables were presented as means±standard deviations, and differences between means were evaluated using the Student's unpaired t-test. Continuous variables distributed non-normally were presented as medians and interquartile ranges, and differences between medians were evaluated using the Mann–Whitney U-test. Categorical variables were presented as numbers and percentages, and comparisons across groups were made using the chi-squared test or Fisher's exact test. For each clinical parameter, cut-off values for prediction of in-hospital death were determined using a receiver operating characteristic (ROC) curve analysis. Univariate and multivariate analyses were conducted to identify independent predictors of in-hospital death among potential explanatory variables. To assess whether predictions of in-hospital death improved after adding novel predictors, the area under the ROC curve was calculated for a baseline model including GWTG-HF risk scores, and for enriched models including GWTG-HF risk scores and novel predictors using the Delong method. A two-tailed p-value of <0.05 was considered to be statistically significant.

Results

In total, 61 patients were enrolled in the study. The mean age of the patients was 79±14 years, and 32 patients (52%) were male. The patients were divided into two groups: those who died in hospital (n=21) and survivors (n=40). The characteristics of each group are described in Table 1.

The etiology of HF was dilated cardiomyopathy, ischemic cardiomyopathy and other in 2 (10%), 10 (48%) and 9 (43%) of the patients who died in hospital and 9 (23%), 18 (45%) and 11 (28%) survivors, respectively (p=0.349). Etiologies classified as other included valvular heart disease, hypertensive heart disease, and other types of cardiomyopathy. The New York Heart Association (NYHA) class was I, II, III and IV in 0, 0, 10 (48%) and 11 (52%) patients who died in hospital and 0, 2 (5%), 31 (78%) and 7 (18%) survivors, respectively (p=0.011). Patients who died in hospital had significantly higher GWTG-HF risk scores than did survivors (52±8 vs. 44±7, p=0.001). On blood examination, significantly decreased albumin levels (2.5±0.73 g/dL vs. 3.0±0.55 g/dL, p=0.001) and significantly increased serum creatinine levels (2.0±1.2 mg/dL vs. 1.3±0.69 mg/dL, p=0.046) were observed in patients who died in

Table 1 Patient characteristics

	Died in hospital n=21	Survivors n=40	p
Age (years)	82±14	77±13	0.204
Male [n (%)]	11 (52)	21 (53)	1.00
Body mass index (kg/m^2)	22±5	23±4	0.402
Clinical history			
Hypertension [n (%)]	10 (48)	16 (40)	0.596
Diabetes mellitus [n (%)]	7 (33)	17 (43)	0.586
Dilated cardiomyopathy/ischemic cardiomyopathy/others [n (%)]	2/10/9 (10/48/43)	9/18/11 (23/45/28)	0.349
Systolic blood pressure (mmHg)	117±25	119±23	0.731
Diastolic blood pressure (mmHg)	63±13	68±17	0.301
Heart rate (beats per minute)	87±15	81±17	0.209
NYHA class (I/II/III/IV) [n (%)]	0/0/10/11 (0/0/48/52)	0/2/31/7 (0/5/78/18)	0.011
GWTG-HF risk score	52±8	44±7	0.001
Blood tests			
Hemoglobin (g/dL)	9.9±1.6	11.0±2.2	0.056
Albumin (g/dL)	2.5±0.73	3.0±0.55	0.001
Creatinine (mg/dL)	2.0±1.2	1.3±0.69	0.046
Sodium (mEq/L)	133±9	137±7	0.075
Potassium (mEq/L)	4.3±1.0	4.2±0.75	0.851
NT-proBNP (pg/mL)	9115 (2692–27337)	4960 (2494–18015)	0.405
Echocardiography			
LV diastolic diameter (mm)	50±11	53±10	0.355
LV ejection fraction (%)	51±18	46±17	0.385
LV ejection fraction <50% [n (%)]	10 (48)	27 (68)	0.277
E/A	1.2±0.83	1.5±0.97	0.313
IVC diameter (mm)	15±3	17±4	0.015
Medications			
ACE-I/ARB [n (%)]	10 (48)	20 (50)	1.000
β-blockers [n (%)]	7 (33)	24 (60)	0.062
Aldosterone antagonists [n (%)]	4 (19)	4 (10)	0.270
Loop diuretics [n (%)]	19 (90)	36 (90)	1.000
Carperitide infusion [n (%)]	11 (52)	14 (35)	0.274
Catecholamine infusion [n (%)]	14 (67)	10 (25)	0.002

Values reported are mean±SD, median (interquartile ranges), or numbers (%).
Abbreviations: NYHA=New York Heart Association, GWTG-HF=Get With The Guidelines-Heart Failure, BNP=brain natriuretic peptide, LV=left ventricular, IVC=inferior vena cava, ACE-I=Angiotensin converting enzyme inhibitors, ARB=Angiotensin II receptor blockers

Table 2 Multivariate logistic regression analyses for in-hospital death

Variable	Univariate		Multivariate	
	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p
NYHA class IV	5.2 (1.6–16.9)	0.006	3.9 (0.56–27.2)	0.168
GWTG-HF risk score >47	11.0 (3.1–40.8)	<0.001	6.7 (1.1–41.5)	0.041
Albumin ≤2.4 g/dL	11.2 (2.6–48.0)	0.001	10.6 (1.1–103.1)	0.041
Creatinine >1.5 mg/dL	5.6 (1.8–17.7)	0.004	8.0 (1.1–58.0)	0.039
IVC diameter ≤15 mm	4.2 (1.4–12.8)	0.015	80.1 (2.2–2864.7)	0.016
Catecholamine infusion	6.0 (1.9–19.1)	0.002	43.9 (1.4–1426.2)	0.033

Abbreviations: NYHA=New York Heart Association, GWTG-HF=Get With The Guidelines-Heart Failure, IVC=inferior vena cava

hospital compared with those of survivors. In addition, hemoglobin levels and sodium levels tended to be lower in patients who died in hospital than in survivors, although the difference was not statistically significant (9.9±1.6 g/dL vs. 11.0±2.2 g/dL, p=0.056 and 133±9 mEq/L vs. 137±7 mEq/L, p=0.075). Furthermore, when patients received their first dose of tolvaptan, a significantly lower inferior vena cava (IVC) diameter on echocardiography was noted in patients who died in hospital than in survivors (15±3 mm vs. 17±4 mm, p=0.015), and more patients who died in hospital were treated with catecholamine infusions than were survivors [14 (67%) vs. 10 (25%), p=0.002].

Based on the ROC curve analysis, GWTG-HF risk score >47 [sensitivity: 81%, specificity: 73%, area under the curve (AUC): 0.77 [95% confidence interval (CI) 0.64–0.87], p<0.001], albumin level ≤2.4 g/dL [sensitivity: 48%, specificity: 93%, AUC: 0.74 (95%CI 0.61–0.84), p<0.001], creatinine level >1.5 mg/dL [sensitivity: 62%, specificity: 78%, AUC: 0.67 (95%CI 0.54–0.79), p=0.039], and IVC diameter ≤15 mm [sensitivity: 67%, specificity: 68%, AUC 0.69 (95%CI 0.55–0.80), p=0.010] were adopted as cut-off scores for predicting death in hospital for HF patients treated with tolvaptan.

The proportion of patients who died in hospital and odds ratios (ORs) associated with each parameter were as follows: NYHA class IV positive vs. negative, 11 (61%) vs. 10 (23%), OR: 5.2 (95%CI 1.6–16.9,=0.006); GWTG-HF risk score >47 vs. ≤47, 17 (61%) vs. 4 (12%), OR: 11.0 (95%CI 3.1–40.8, p<0.001); albumin level ≤2.4 g/dL vs. >2.4 g/dL, 10 (77%) vs. 11 (23%), OR: 11.2 (95%CI 2.6–48.0, p=0.001); creatinine level >1.5 mg/dL vs. ≤1.5 mg/dL, 13 (59%) vs. 8 (21%), OR: 5.6 (95%CI 1.8–17.7, p=0.004); IVC diameter ≤15 mm vs. >15 mm, 14 (52%) vs. 7 (21%), OR: 4.2 (95%CI 1.4–12.8, p=0.015); and catecholamine infusion positive vs. negative, 14 (58%) vs. 7 (19%), OR: 6.0 (95%CI 1.9–19.1, p=0.002) (Table 2). A multivariate logistic regression analysis revealed that GWTG-HF risk score >47 [OR: 6.7 (95%CI 1.1–41.5), p=0.041], albumin level ≤2.4 g/dL [OR: 10.6 (95%CI 1.1–103.1), p=0.041], creatinine level >1.5 mg/dL [OR: 8.0 (95%CI 1.1–58.0), p=0.039], IVC diameter ≤15 mm [OR: 80.1 (95%CI 2.2–2864.7), p=0.016] and catecholamine infusion [OR: 43.9 (95%CI 1.4–1426.2), p=0.033] independently and significantly predicted in-hospital death (Table 2). Thus, albumin level ≤2.4 g/dL, creatinine level >1.5 mg/dL, IVC diameter ≤15 mm and catecholamine infusion were defined as novel predictors of in-hospital death for patients with acute HF. Moreover, combining these novel predictors with the GWTG-HF risk score significantly improved prediction of in-hospital death, as shown by the greater area under the ROC curve [0.78 (95%CI 0.64–0.87) vs. 0.94 (95%CI 0.84–0.98), p<0.001] (Table 3).

Table 3 Discriminatory ability of risk prediction models for in-hospital death

Model	Area under ROC curve (95%CI)	p-value for difference
GWTG-HF risk score >47	0.78 (0.64–0.87)	reference
+*Novel predictors	0.94 (0.84–0.98)	<0.001

*Novel predictors included albumin ≤2.4 g/dL, creatinine >1.5 mg/dL, IVC diameter ≤15 mm, and catecholamine infusion.
Abbreviations: ROC=receiver-operating characteristic, GWTG-HF=Get With The Guidelines-Heart Failure

Discussion

The major findings of this study were as follows: (i) in addition to GWTG-HF risk score, low albumin level (≤2.4 g/dL), elevated creatinine level (>1.5 mg/dL), small IVC diameter (≤15 mm) and previous catecholamine infusion were identified as independent and significant predictors of in-hospital death for patients prescribed tolvaptan for worsening HF; and (ii) combining these novel predictors to the GWTG-HF risk score significantly improved predictions of in-hospital death for these patients.

The vasopressin type 2 receptor antagonist tolvaptan has been clinically available for the treatment of HF in Japan since December 2010. Because of its favorable clinical effects, such as increasing the excretion of free water in the urine, stabilizing the patient's hemodynamics, and correcting hyponatremia,[21–23] tolvaptan is now commonly prescribed to treat HF in Japan.[11] Previous studies have developed predictive models for in-hospital outcomes in HF,[17,18] but did not include HF patients treated with tolvaptan. Therefore, we sought to clarify the predictors of acute clinical outcome for HF patients treated with tolvaptan. Clinical management of HF patients treated with tolvaptan may require careful attention.

In this study, much poorer clinical outcomes were observed for patients who received tolvaptan compared with the expected outcomes based on the EVEREST study.[13] However, there were differences in the baseline characteristics of patients in our study vs. those in the EVEREST study. For example, the EVEREST study included only HF patients with a decreased LV ejection fraction, while our study included HF patients with both preserved and decreased LV ejection fractions. In our study, patients who died in hospital were more likely to have exhibited a preserved LV ejection fraction compared with survivors. The patients included in our study were also characterized by extremely high ages. Notably, fewer patients in our study received treatments for HF on admission, such as renin-angiotensin system inhibitors and β-blockers, compared with those in the EVEREST study. In addition, the patients who died

in hospital in our study tended to have decreased hemoglobin and sodium levels compared with survivors. Moreover, the frequency of catecholamine infusion may be related to disease severity in patients with acute HF who die in hospital.[24,25] All of these reasons may account for the discrepancies the clinical outcomes noted between our study and the EVEREST study.

Our study had some limitations. The study population comprised a relatively small number of patients recruited from a single center. It is therefore possible that the relatively low statistical power of the study resulted in failure to detect additional predictors of in-hospital mortality. As well, selection bias in the patient population cannot be ruled out.

In conclusion, we identified novel predictors of in-hospital clinical outcome in HF patients receiving tolvaptan during acute hospitalization. Our findings could contribute to development of treatment strategies for patients with HF receiving tolvaptan in clinical settings.

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Conflict of Interest

H.I. has received grant support through his institution from Takeda, Shionogi, Dainippon-Sumitomo, Otsuka, Pfizer, and Daiichi-Sankyo; and honoraria for lectures from Otsuka and Daiichi-Sankyo.

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