Journal of Geriatric Cardiology (2018) 15: 476–478

Perspective · Open Access ·

Prognostic utility of NT-proBNP greater than 70,000 pg/mL in patients with end stage renal disease

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J Geriatr Cardiol 2018; 15: 476–478. doi:10.11909/j.issn.1671-5411.2018.07.002

Keywords: End stage renal disease; Heart failure; Heart failure reduced ejection fraction; Mortality; NT-proBNP

Natriuretic peptides are synthesized in ventricular myocytes and released into the circulation in response to increased myocardial wall stress.[1] Causes of myocardial wall stress include pulmonary hypertension, ventricular dilatation, as well as heart failure with reduced or preserved left ventricular function.[1] The 108 amino acid pro-brain natriuretic peptide (pro-BNP) is the cleavage product of the 134-amino acid hormone Pre-Pro-BNP,[2] which once released into circulation it further cleaves into C-terminal pro-BNP (32 amino acids, BNP) and N-terminal pro-BNP (76 amino acids, NT-proBNP).[3,4] Physiological effects of pro-BNP include reduction of sympathetic tone and activity of the renin-angiotensin system, promotion of vasodilation, natriuresis and diuresis.[5]

Multiple studies have determined the diagnostic and prognostic value of BNP and NT-proBNP in patients with heart failure with reduced as well as preserved ejection fraction.[6–10] Although defined NT-proBNP cutoffs support the diagnosis of heart failure among patients with normal as well as impaired renal function,[11] there is no consensus regarding specific NT-proBNP levels and their prognostic utility in patients with end stage renal disease (ESRD).[12–19] In addition, no study to date has evaluated the significance of severely elevated NT-proBNP values in mortality rates.

To evaluate the prognostic value of NT-proBNP values > 70,000 pg/mL, a total of 157 patients were identified at the University of Florida Health-Jacksonville (UF) in the time period of January 1st, 2012 through January 30th, 2016. Characteristics including age, gender, race, body mass index (BMI), medical therapy, ejection fraction (EF), renal function and presence of diastolic dysfunction were all gathered via systematic chart review. Patients without a transthoracic echocardiogram (TTE) or those missing E/e' on tissue doppler imaging were excluded. One hundred and forty-one patients were included in the final analysis and mortality was determined by review of electronic medical records and the social security death index.

All-cause mortality was 45.39% over four years with a mean survival time of 204.1 days (n = 64, SD 274.6, Median = 94 days). No statistically significant difference in mortality was noted among patients with relation to gender (P = 0.6116), race (P = 0.5428), ESRD status (P = 0.9163), E/e' > 12 (P = 0.6740), medical treatment (P = 0.9310), BMI (P = 0.2295), diastolic heart failure (HF) (P = 0.5644), systolic HF (P = 0.5076) and combined systolic and diastolic HF (P = 0.6757)

In a sub-sample analysis among patients with systolic HF, there was a statistically significant difference in mortality (P = 0.0089) and survival (P = 0.0043) among patients with an EF of < 25%. Patients with EF < 35% revealed a trend towards decreased survival (P = 0.0920). The best-fit logistic regression model predicting mortality contained only age [P = 0.0203; odds ratios (OR): 1.0301, 95% confidence intervals (CI): 1.005–1.057] and an indicator variable for EF < 25% (P = 0.0306). The odds of death were 2.5 (95% CI: 1.091, 5.934) times higher for those with EF < 25% compared to those with EF > 25% (Figure 1 & 2).

In view of the above findings, the study demonstrates that among patients with uniformly severely elevated NT-proBNP, heart failure and ESRD, EF continues to be a significant predictor of mortality. While elevated NT-proBNP levels in patients with ESRD are partially due to renal clearance, values exceeding 70,000 pg/mL are unlikely to be due solely to renal dysfunction.[4] Evidence suggests renal clearance of BNP and NT-proBNP to be equivalent, while additional clearance of NT-proBNP is present in liver and skeletal tissue.[20,21] Previous studies have demonstrated that neither length of time of hemodialysis nor duration of

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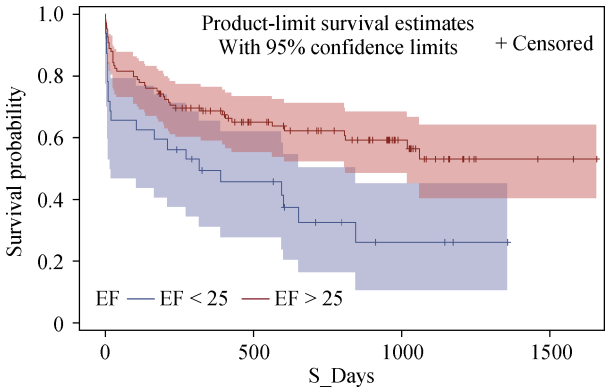

Figure 1. Survival estimates between patients with an EF < 25 versus those with an EF > or equal to 25 - Y-axis represents the probability of survival. The X-axis represents survival in number of days. The blue line represents those patients with an EF < 25%, while the red line represents patients with an EF > or equal to 25%. The shaded areas represent the 95% confidence intervals for the curves. Note the significant divergence between survival curves in the two populations. *P* = 0.0043. EF: ejection fraction.

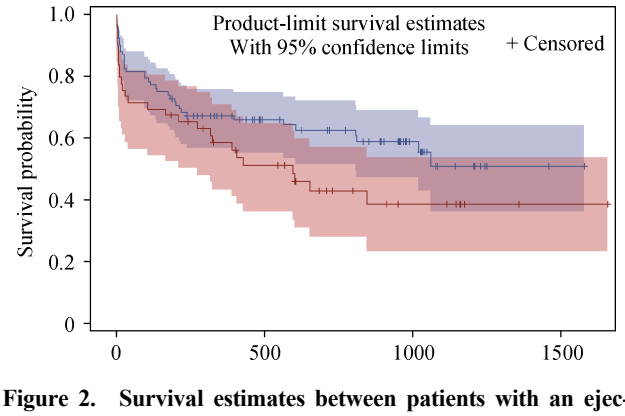

Figure 2. Survival estimates between patients with an ejection fraction of < 35% versus those with an ejection fraction > 35%. *P* = 0.0920 for the small but appreciable divergence between survival curves among the two different populations. Y-axis represents the probability of survival. The X-axis represents survival in number of days. The blue line represents those patients with an EF >35%, while the red represents those with an EF < 35%. The shaded areas represent the 95% confidence intervals for the curves. EF: ejection fraction.

Table 1. Association between mortality rate and clinical variables among patients with NT-proBNP > 70,000 pg/mL -Tabulation and statistical analysis of variables which may affect mortality rates among patients with NT-proBNP > 70,000 pg/mL.

Variable	Category	Alive	Dead	Overall	P-Value
Diastolic HF	No diastolic HF	42 (52.5%)	38 (47.5%)	80 (56.7%)	0.5644
	Diastolic HF	35 (57.4%)	26 (42.6%)	61 (43.3%)	
Systolic HF	No systolic HF	44 (57.1%)	33 (42.9%)	77 (54.6%)	0.5076
	Systolic HF	33 (51.6%)	31 (48.4%)	64 (45.4%)	
Combined systolic and diastolic HF	No	46 (56.1%)	36 (43.9%)	82 (58.2%)	0.6757
	Yes	31 (52.5%)	28 (47.5%)	59 (41.8%)	
E/e’	E/e'<12	9 (50%)	9 (50%)	18 (12.8%)	0.6740
	E/e' > or equal to 12	68 (55.3%)	55 (44.7%)	123 (87.2%)	
EF < 35%	EF ≥ 35%	55 (59.8%)	37 (40.2%)	92 (65.3%)	0.0909
	EF < 35%	22 (44.9%)	27 (55.1%)	49 (34.8%)	
EF < 25%	EF ≥ 25%	66 (60.6%)	43 (49.5%)	109 (77.3%)	0.0089
	EF < 25%	11 (34.4%)	21 (65.6%)	32 (22.7%)	
ESRD	No	8 (53.3%)	7 (46.7%)	15 (10.6%)	0.9163
	Yes	69 (54.8%)	57 (45.2%)	126 (89.4%)	
Gender	Female	43 (55.8%)	34 (44.2%)	77 (54.6%)	0.6116
	Male	33 (51.6%)	31 (48.4%)	64 (45.4%)	
Medical treatment	No	63 (54.8%)	52 (45.2%)	115 (81.6%)	0.9310
	Yes	14 (53.8%)	12 (46.2%)	26 (18.4%)	
All tests done using Chi-Squared					

Data were presented as *n* (%). Only EF < 25% is statistically significant. Medical treatment consists of angiotensin inhibitors, diuretics and beta blockers. ESRD: end-stage renal disease; EF: ejection fraction; E/e': Tissue Doppler from Echo; HF: heart failure; NT-proBNP: N-terminal pro-brain natriuretic peptide.

renal disease has significant correlation with NT-proBNP levels.[14] This suggests that while renal function plays a role in elevated NT-proBNP levels, left ventricular function is the most critical variable influencing mortality and NT-proBNP.

During the evaluation of renal function of our population, we incidentally discovered a large prevalence of ESRD. Previous studies diverge on a normal NT-proBNP in patients with ESRD.[15,19,23] The prevalence of heart failure among patients with ESRD is estimated to be 31%, while

the median survival is 36 months.[22] Despite the known decreased survival in patients with heart failure and ESRD, no previous study has demonstrated such a strong correlation between EF and mortality in patients with NT-proBNP > 70,000 pg/mL (Table 1).

Mortality rates in the studied population remained uniformly elevated in both systolic and diastolic HF. The subset of patients with severe systolic HF (< 25%) were noted to have 65.6% mortality over four years. We are unable to explain the occurrence of normal E/e' in 12.8% of patients with diastolic HF, despite elevated NT-proBNP levels. Possible reasons for such observation include operator error or poor acoustic windows at the time of imaging.

In view of the above findings, we assert that among patients with NT-proBNP > 70,000 pg/mL and ESRD, left ventricular EF < 25% is an indicator of increased mortality rate. Utilization of a uniform NT-proBNP level allows for better characterization of variables significant in mortality prediction among patients with ESRD. It is essential to emphasize the importance of aggressive medical management of heart failure patients with ESRD to prevent such magnitude of NT-proBNP levels and decrease mortality rates.

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