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

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. Although defined NT-proBNP cutoffs support the diagnosis of heart failure among patients with normal as well as impaired renal function, there is no consensus regarding specific NT-proBNP levels and their prognostic utility in patients with end stage renal disease (ESRD). In addition, no study to date has evaluated the significance of severely elevated NT-proBNP values in mortality rates.

In a sub-sample analysis among patients with systolic HF, there was a statistically significant difference in mortality and survival among patients with an EF of < 25%. Patients with EF < 35% revealed a trend towards decreased survival. The best-fit logistic regression model predicting mortality contained only age and an indicator variable for EF < 25%.

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. 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. Previous studies have demonstrated that neither length of time of hemodialysis nor duration of
renal disease has significant correlation with NT-proBNP levels. 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. The prevalence of heart failure among patients with ESRD is estimated to be 31%, while

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Table 1. Association between mortality rate and clinical variables 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%) | 46 (43.9%) | 92 (65.3%) | 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' ≥ 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 (54.4%) | 21 (45.6%) | 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.
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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