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Evaluation of NT-proBNP to Predict Outcomes in Advanced Heart Failure

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Abstract:

Aims: To determine which factors predict outcomes in a group of patients with advanced heart failure, and in particular if NT-proBNP provides additional clinical and prognostic information to other haemodynamic and biochemical data.

Methods and Results: 91 patients were studied who were being evaluated for heart transplantation, with 166 assessments. The patients had advanced heart failure as determined by median cardiac index of 2.0 L/min/m², left ventricular end-diastolic diameter 7.0 mm, and levels of NT-proBNP of 2473 pg/mL. Median follow up time was 359 days. Clinicians were blinded to NT-proBNP levels. NT-proBNP significantly correlated with cardiac index ($R=-0.44$, $P<0.001$), right atrial pressure ($R=0.40$, $P<0.001$), pulmonary arterial wedge pressure ($R=0.38$, $P<0.001$) and albumin ($R=-0.52$, $P<0.001$), and total bilirubin with right atrial pressure ($R=0.59$, $P<0.001$). Cardiac index was the most important independent predictor of outcome ($P=0.0001$), though bilirubin ($P=0.001$), and NT-proBNP ($P<0.05$) were also significant. In patients with a 50% increase in NT-proBNP 64% had adverse outcomes, whereas those in whom levels were stable 22% had adverse outcomes ($P<0.05$).

Conclusion: Cardiac index is the primary independent predictor of outcome in advanced heart failure when haemodynamic deterioration is evident. In situations where invasive haemodynamics are not available, total bilirubin (reflecting hepatic congestion), and NT-proBNP (related to haemodynamics) also provide important prognostic information.

What is already known about this topic?

There are numerous parameters that have been used to predict outcomes in advanced heart failure, including peak VO_2 and B type natriuretic peptide (BNP). Transplantation is increasingly being seen as benefiting only the sickest heart failure patients, so we wished to determine what predicts outcomes in such a cohort of patients and in particular if NT-proBNP provided additional prognostic information.

What does this article add?

The data presented shows that whereas NT-proBNP in single or serial measurements does provide important prognostic information in a group of patients where timely decisions are critical, other parameters such as cardiac index and total bilirubin are probably more important.

Introduction:

Predicting outcome in advanced congestive heart failure is critically important when considering urgent listing for transplantation or implantation of a ventricular assist device. As transplantation probably only provides a clear mortality benefit in the sickest heart failure patients¹, we need to know what predicts outcomes in these patients, as opposed to less sick heart failure patients. Numerous factors are thought to predict outcomes, particularly functional capacity as measured by peak VO_2 ^{2,3}, and B type natriuretic peptide (BNP)^{4,5}. Which factor is most important will depend on the population being studied. For instance, in more advanced heart failure, peak VO_2 may not be as predictive compared to less sick patients⁶, at least in part because the sickest patients are unable to exercise. Other factors such as haemodynamics⁷, serum sodium⁸ and circulating cytokines⁹ have also been shown to be important.

BNP, or its N-terminal fragment, NT-proBNP has been shown in a wide range of clinical heart failure settings to be able to predict outcomes, including patients being assessed for heart transplantation^{10,11}. In addition, both single and serial measurements of BNP provide important prognostic information^{12,13}. BNP relates to left ventricular wall stress¹⁴ and filling pressures in heart failure patients¹⁵, and it has been suggested that NT-proBNP provides more reliable prognostic information than haemodynamics¹⁶.

The purpose of this study was to determine which variables best predict outcomes in a group of patients with advanced heart failure being assessed for transplantation. We sought to determine the role of single and serial measurements of NT-proBNP in

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determining prognosis, and its relationship to other factors known to be abnormal in heart failure, including haemodynamics.

For Peer Review Only

Materials and Methods:

Patients. Ninety-one patients undergoing 166 heart transplant assessments at the Freeman Hospital were recruited to the study during the period between September 2005 and May 2008, and were followed until February 2009. Patient details are described in table 1. This indicates that the majority of patients were not on intravenous inotropes, but nevertheless had advanced heart failure with high pulmonary arterial wedge pressures, low cardiac index, and high levels of circulating NT-proBNP. Eight patients were studied as part of their first hospitalisation for heart failure, the rest had an established diagnosis prior to assessment. Patients gave signed informed consent and the study was approved by the local ethics committee.

Assessment. The heart transplant assessment consists of a right heart catheterization performed with a Swan Ganz catheter and measurement of thermodilution cardiac outputs with central venous access. Transpulmonary gradient is defined as mean pulmonary artery pressure minus pulmonary arterial wedge pressure, and pulmonary vascular resistance as transpulmonary gradient divided by cardiac output. A cardiopulmonary stress test for determination of peak VO_2 on a bicycle ergometer (Sensormedics, CA), a 2D echocardiogram acquired using British Society of Echocardiography guidelines¹⁷, and routine biochemical assessment. This consisted of urea and electrolytes, and liver function tests with all parameters measured using Olympus AU 2400 analysers with between batch CV of <3.0% for all parameters. Patients underwent a second or further assessment based on clinical need. Not all tests were necessarily performed at every patient assessment, though NT-proBNP levels were

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3 taken at every assessment. Blood samples for serum NT pro-BNP were drawn at the time
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5 of right heart catheterization from an internal jugular vein in those patients undergoing
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7 haemodynamic studies, and in those not having right heart catheterization. Blood samples
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9 were drawn by standard phlebotomy into plain tubes, centrifuged and serum was stored at
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11 -40 C until analysis. Serum NT pro-BNP was measured using a noncompetitive EIA
12
13 immunoassay kit (chemiluminescent technology, measuring range 0.5 – 4100 pmol/L run
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15 on an Elecsys 2010 platform using manufactures standards and controls (Roche
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17 Diagnostics, Indianapolis, Indiana) with between batch CV % of <6%. Clinicians were
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19 blinded to the results of NT-proBNP. Estimated glomerular filtration rate (eGFR) was
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21 calculated according to the abbreviated modification of diet in renal disease equation: 186
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23 $\times (\text{Creat} / 88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})^{18}$.
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32 **Data Analysis and Statistics.** Correlations between variables were determined by
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34 Spearman correlation coefficient. Patients were grouped into the following groups based
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36 on follow up events: deteriorated, death, alive and non urgent transplant: Those patients
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38 who required an in-hospital transplant, were nationally listed for urgent transplantation,
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40 or had implantation of a ventricular assist device were considered deteriorated patients,
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42 and these patients for analysis purposes were grouped with those that died, as they would
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44 have reasonably have been expected to die without intervention within a short period of
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46 time. Non-urgent transplant patients were censored at the time of transplant in the
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48 survival analysis as the timing of transplant in these patients was not necessarily related
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50 to impending death or deterioration. No patients were lost to follow up. Data are
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52 presented as median with 25th and 75th percentiles. Single comparisons were performed
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3 with the Mann Whitney *U* test, and proportions compared with the Exact test. Survival
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5 curves were assessed using the Tarone-Ware test comparing curves above and below the
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7 median, and Cox regression analysis used to determine influence of multiple factors on
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9 outcomes. Predictive power of variables was compared using receiver operator curves.
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13 SPSS 15 software was used and $P < 0.05$ was considered statistically significant.
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Results:

Correlation of NT-proBNP with other haemodynamic and biochemical variables: NT-proBNP was significantly correlated with several haemodynamic parameters (figure 1) with the strongest relationship to cardiac index. There was also a significant relationship to circulating levels of albumin. Right atrial pressure also significantly correlated with levels of bilirubin, suggesting that elevated levels of bilirubin were related to hepatic congestion.

Predictors of outcomes and survival curves: Thirty-seven patients were alive and stable at the end of the study period, and 19 were classed as deteriorated and 15 had died, these latter 2 groups being grouped together. Twenty patients had non-urgent transplants. Univariate predictors of outcome are shown in table 2. The most significant predictors of outcome were NT-proBNP, right atrial pressure, cardiac index, and bilirubin. Survival curves are presented in figure 2. Cardiac index clearly has the greatest separation of curves between those that survived without events, and those that died or deteriorated. Other significant factors were NT-proBNP, bilirubin, **transpulmonary gradient**, albumin, and right atrial pressure. Though not shown, survival curves for sodium were significant ($P<0.05$), systolic blood pressure were of borderline significance ($P=0.06$), and pulmonary arterial wedge pressure was not significantly related to outcome. The Cox regression analysis is presented in table 3, determining which variables independently predicted outcomes. Cardiac index, bilirubin and NT-proBNP were used in the model. Cardiac index showed the greatest significance and the greatest incremental change in outcome relative to unit change in its value, though bilirubin and

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3 NT-proBNP were also significantly related to outcome. When transpulmonary gradient
4 was added to the model, it was not significantly related to survival. Receiver operator
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6 curves showed the following areas under the curve: bilirubin 0.725, cardiac index 0.711,
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8 and NT-proBNP 0.683.
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15 **Serial measurements of NT-proBNP:** Significant increases in NT-proBNP were
16 associated with adverse outcomes. In the 43 patients with 2 or more NT-proBNP levels
17 outcomes and haemodynamic and biochemical correlates were studied (table 4). Patients
18 were divided into 3 groups based on those that increased levels by > 50% from the first to
19 second measurement, decreased by > 50%, or otherwise were stable ($\leq 50\%$ change). In
20 those with more than one sample, the lowest and highest values were taken. Fourteen
21 patients had a 50% increase in NT-proBNP, and in these patients 9 had adverse
22 outcomes. In the patients with a 50% decrease none out of 11 had adverse outcomes, and
23 in the stable patients 4 out of 18 had adverse outcomes ($P < 0.001$ and $P < 0.05$ vs increased
24 group respectively). In the > 50% increase and the stable groups, haemodynamics and
25 biochemistries were unchanged. In those patients with a 50% decrease, there were
26 significant reductions in right atrial pressure, pulmonary arterial systolic pressure
27 pulmonary arterial wedge pressure and bilirubin.
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46 In those patients with 3 or more levels of NT-proBNP a slope was derived and
47 this was related to outcome (N=18). Patients were divided into those with a slope > 1 (i.e.
48 increase, N=7) or ≤ 1 (i.e. stable or decrease, N=11). In those patients with a slope > 1, 4
49 out of 7 patients had an adverse outcome, and in those with a slope ≤ 1 , 1 out of 11 had
50 an adverse outcome ($P < 0.05$).
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3 Medications in patients with serial NT-proBNP data over the follow up period
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5 were used slightly more frequently then compared to the data presented for the initial
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7 assessment in table 1. At follow up, 86% of patients were on ACE inhibitors, 11%
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9 angiotensin receptor blockers, 72% β -blockers, 70% spironolactone or eplerenone, 95%
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11 diuretics, and 11% inotropes.
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Discussion:

Predicting outcome in patients with advanced heart failure is important when deciding timing regarding urgent listing for transplantation or implantation of a ventricular assist device¹. We demonstrate in a cohort of advanced heart failure patients that several factors are important in predicting outcome. Most important is cardiac index, though NT-proBNP, and bilirubin levels are also significantly and independently related to outcomes. We sought to determine the additive role of NT-proBNP to other haemodynamic and biochemical markers of heart failure when assessing advanced heart failure patients, and found that NT-proBNP, whether by single or serial measurements, is an important determinant of outcome, and also significantly correlates with invasive haemodynamics, especially cardiac index and pulmonary arterial wedge pressure. Potentially, in situations where invasive haemodynamics are not available (such as in the majority of heart failure patients that are not considered eligible for transplantation), levels of bilirubin or NT-proBNP might provide simple alternative prognostic information. Thus, refractory right heart failure resulting in secondary hepatic dysfunction and elevated NT-proBNP levels could be used to guide clinicians as to when to refer for heart transplantation. No patients with NT-proBNP levels below 421 pg/mL had adverse outcomes.

Pathophysiology of end-stage heart failure: These results provide some insight into the mechanism of deterioration in end-stage heart failure. Clearly, cardiac output is the major determinant of outcome, and patients with a cardiac index < 2.0 L/min/m² are at a high risk of adverse events, and underscores the importance of haemodynamics in

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3 advanced heart failure. Bilirubin provides a measure of the effects of right atrial pressure
4 and NT-proBNP correlates with haemodynamics and albumin. That bilirubin is an
5 independent predictor of outcome relates to the importance of right ventricular
6 dysfunction in the progression of heart failure. We know that right ventricular
7 dysfunction is an important predictor of outcomes in heart failure^{19,20}, and that elevation
8 of the jugular venous pulsation predicts all-cause mortality in a broad range of
9 cardiovascular diseases²¹. The relationship of albumin to NT-proBNP illustrates the
10 importance of metabolic abnormalities in these patients.
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25 **NT-proBNP, haemodynamics, and outcomes in advanced heart failure:**

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27 Several studies have shown the ability of BNP to predict outcomes in congestive heart
28 failure, including patients being assessed for heart transplantation. Our study provides
29 useful new information in that we have studied a sicker group of patients than most
30 previous studies^{10,11,16}, with median levels of NT-proBNP of 2473 pg/mL, cardiac index
31 of 2.0 L/min/m², and left ventricular end-diastolic diameter of 7.0 mm. It is in the sickest
32 patients that we derive the greatest benefits from transplantation and ventricular assist
33 devices¹. Whereas our study also shows the importance of measuring BNP, it also
34 demonstrates the primary importance of invasive haemodynamics, and this may be a
35 reflection of the severe nature of the heart failure in the current study. Gardner et al.¹⁶
36 have studied NT-proBNP and haemodynamics in patients being assessed for
37 transplantation, and found that NT-proBNP was the only predictor of all-cause mortality.
38 Compared to that study our patients have more deranged haemodynamics and higher
39 levels of NT-proBNP. Rothenberger et al.¹¹ studied a large group of patients being
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3 considered for transplantation and showed the importance of NT-proBNP in predicting
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5 outcomes – though these patients were also considerably less sick than the current study
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8 with mean cardiac indices of 2.9 ± 0.8 and 2.7 ± 0.7 L/min/m² for dilated cardiomyopathies
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10 and ischemic cardiomyopathies respectively. Recently the role of haemodynamics in
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12 predicting outcome has been highlighted^{7,22}, though these studies have not compared the
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14 relative predictive power of haemodynamics and BNP. Mullens et al.⁷ have shown in a
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16 large cohort of ambulatory heart failure patients undergoing right heart catheterisation
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18 that cardiac index was an independent predictor of outcome. The authors noted that most
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20 current studies of establishing prognosis in heart failure excluded haemodynamic
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22 measurements, though when they added invasive haemodynamics to the predictive
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24 models this provided incremental benefit. Consistent with this Lang et al²² have shown
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26 that non-invasive measurements of peak exercise cardiac output and cardiac power are
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28 independent predictors of outcome in patients with chronic heart failure.
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37 **Limitations:** There are a relatively low number of patients studied, and there will
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39 be a referral bias in patients being referred for transplantation, compared to patients that
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41 are not. However, the transplant assessment process allows us to collect a large amount of
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43 clinical, haemodynamic and biochemical data that is otherwise often not acquired. A
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45 relatively small number of patients underwent cardiopulmonary stress testing (N=41) at
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47 the time of the NT-proBNP assay, which at least in part, reflects the severity of the illness
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49 of the patients as they were often unable to exercise either due to heart failure symptoms
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51 or ventricular arrhythmias. The mean values of peak exercise oxygen consumption
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53 (13.4 ± 3.4 mL/kg/min) then likely reflect the less sick proportion of the total patient
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3 group, and is not reflective of the group as a whole. We have not assessed left ventricular
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5 function in detail, which has also been shown to provide important prognostic
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7 information²³.
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12 **Conclusions:** Cardiac index is an important significant predictor of adverse
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14 outcomes in advanced heart failure patients. In situations where this is not readily
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16 available, bilirubin, and NT-proBNP will provide important prognostic information.
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5 Newcastle upon Tyne Hospitals NHS Foundation Trust Biomedical Research Centre. We
6
7 are grateful to Roche Diagnostics for donating the NT-proBNP kits.
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12 **Author Contributions:**

13
14 MacGowan – all aspects of project.

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17 Neely: Concept, design, laboratory analyses, data interpretation, critical review of article,
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19 secure funding.

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22 Peaston: Concept, design, laboratory analyses, critical review of article.

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25 Wrightson: Concept, design, data analysis, critical review of article.

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28 Parry – all aspects of project.
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Figure Legends:

Figure 1: Correlations between \log_{10} NT-proBNP (pg/mL) and cardiac index (A, L/min/m²), pulmonary arterial wedge pressure (B, mmHg), right atrial pressure (C, mmHg), pulmonary arterial systolic pressure (D, mmHg), and albumin (E, g/L), and correlation of right atrial pressure with bilirubin (E, $\mu\text{mol/L}$) to illustrate that elevation of bilirubin was related to increased levels of right atrial pressure. As NT-proBNP is not normally distributed it is transformed to \log_{10} .

Figure 2: Kaplan-Meier survival curves based on variables divided into 2 groups based on median values, showing significant differences in survival for cardiac index (A), NT-proBNP (B), bilirubin (C), transpulmonary gradient (D), albumin (E), and right atrial pressure (RA, caption F).

Table 1: Baseline characteristics of patients. For patients with more than one assessment, these data are from the first assessment.

Variable:	
Number	91
Follow up duration (days)	359 (110,695)
Age	49 (40,58)
Gender	32% Female
Diagnosis	Idiopathic: 50%
	Ischemic 37%
	Congenital 2%
	Other 11%
NYHA class	2: 5%
	3: 66%
	4: 29%
Medication	ACEi: 74%
	ARB: 18%
	BB: 69%
	Spironolactone/Eplerone: 63%
	Diuretics: 99%
	Inotropes: 6%
LVEDD (cm)	7.0 (6.4,7.6)
Right Atrial Pressure (mmHg)	10 (6.0,13)
Pulmonary Arterial Systolic Pressure (mmHg)	46 (37,62)
Pulmonary Arterial Wedge Pressure (mmHg)	25 (17,31)
Cardiac Index (L/min/m²)	2.0 (1.7,2.4)
Heart Rate (beats/min)	80 (70,88)
Systolic Blood Pressure (mmHg)	100 (94,110)
Diastolic Blood Pressure (mmHg)	69 (60,74)
eGFR (ml/min/1.73m²)	62 (46,74)
Serum Sodium (mmol/L)	136 (133,138)
NT-proBNP (pg/mL)	2473 (1445,5278)

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: β -adrenergic receptor antagonist; LVEDD: Left ventricular end-diastolic dimension; eGFR: estimated glomerular filtration rate. Data are median (25th and 75th percentiles).

Table 2: Univariate predictors of outcome (alive patients versus those who deteriorated or died). The twenty patients that had non-urgent transplants are excluded from this analysis.

	Alive (N=37)	Deterioration (N=19) + Death (N=15)	P
Days Follow up	809 (475,969)	130 (31,413)	<0.0001
Age	48 (41,54)	55 (39,60)	NS
NT-proBNP (pg/mL)	1939 (788,3041)	3428 (2068,7163)	=0.001
Right Atrial Pressure (mmHg)	7 (4,10)	12 (9,18)	<0.0001
PA Systolic Pressure (mmHg)	45 (30,64)	46 (37,55)	NS
PA Wedge Pressure (mmHg)	20 (11,28)	25 (22,29)	<0.05
Cardiac Index (L/min/m ²)	2.3 (2.0,2.8)	1.8 (1.6,2.1)	<0.0001
Transpulmonary Gradient (mmHg)	10 (8,15)	6 (5,11)	<0.005
Pulmonary Vascular Resistance (Wood units)	2.4 (1.5,3.7)	2.0 (1.3,3.0)	NS
Heart Rate (beats/min)	76 (63,85)	79 (73,97)	NS
Systolic Blood Pressure (mmHg)	105 (98,119)	96 (90,105)	<0.005
Diastolic Blood Pressure (mmHg)	68 (60,75)	66 (59,72)	NS
LVEDD (cm)	6.9 (6.4,7.6)	7.1 (6.6,7.8)	NS
Peak VO ₂ (mL/kg/min)	14.3 (11.3,16.9)	12.3 (9.9,14.3)	NS
Sodium (mmol/L)	136 (134,138)	135 (130,137)	<0.05
Albumin (g/L)	44 (40,47)	41 (38,43)	<0.01
Haemoglobin (g/dL)	13.9 (12.6,15.2)	13.6 (12.6,14.3)	NS
Bilirubin (µmol/L)	13 (9,21)	26 (14,41)	=0.001
eGFR (ml/min/1.73m ²)	64 (51,77)	58 (44,68)	NS

Peak VO₂: peak exercise oxygen consumption; LVEDD: Left ventricular end-diastolic dimension; eGFR: estimated glomerular filtration rate;

Reference intervals: sodium:135-145 mmol/L; albumin 34-50 g/L; haemoglobin 13.0-18.0 g/dL; bilirubin 0-19 µmol/L. Data are median (25th and 75th percentiles).

Table 3: Cox regression analysis.

Variable	Significance	Exp(B)
Cardiac Index	0.0001	0.253
Bilirubin	0.001	1.031
NT-proBNP	0.036	1.001

Exp(B) is the predicted change in the hazard for a unit increase in the predictor

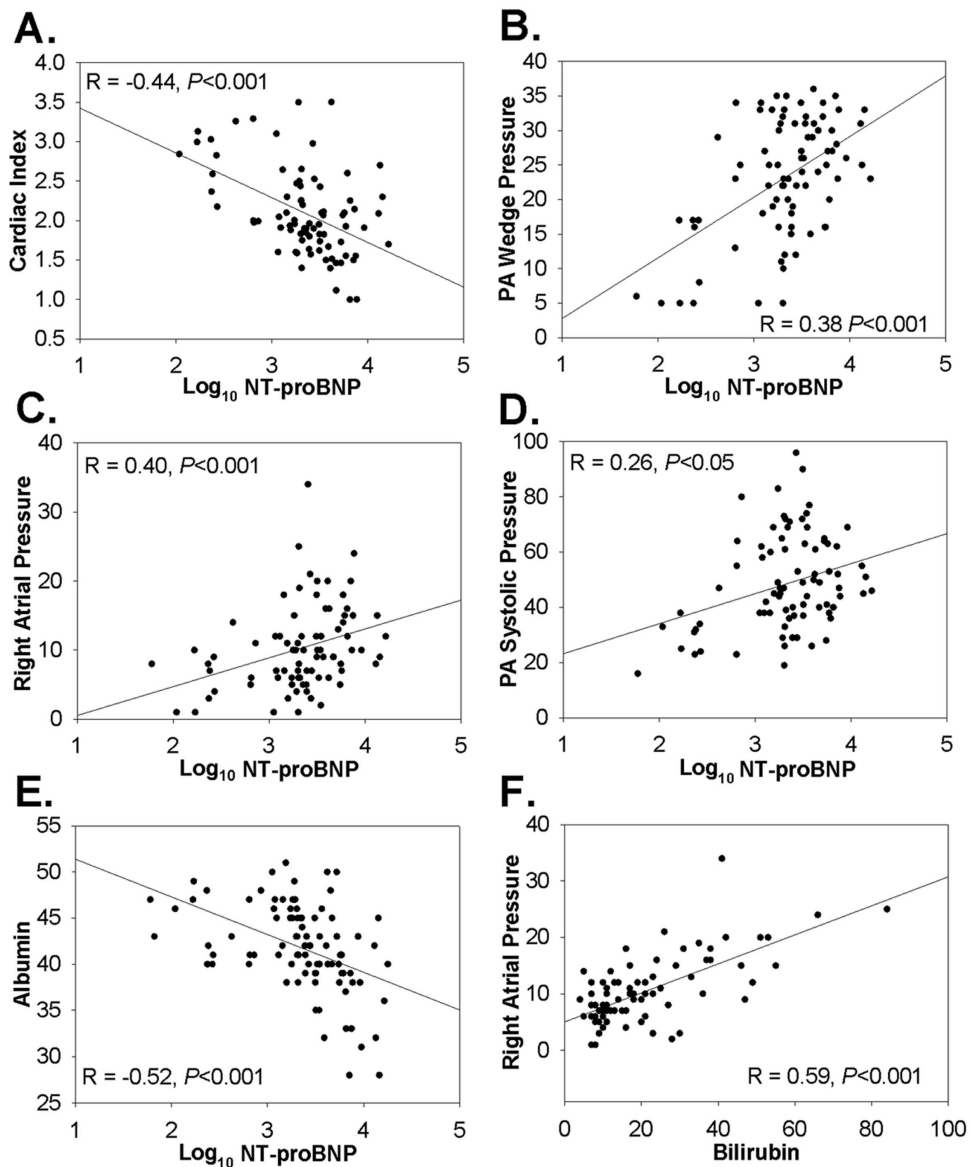
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Table 4: Serial Measurements of NT-proBNP and relationship to outcomes, haemodynamics and biochemistries. Groups are divided into those with increases of > 50%, decreases of > 50%, or otherwise stable levels.

Measurements	>50% Increase		>50% Decrease		Stable	
	First	Second	First	Second	First	Second
Median NT-proBNP	1863	5692	4694	1066	2962	2265
(25 th ,75 th quartiles)	(1409,3309)	(3755,7624)	(1815,14632)	(656,2274)	(1613,4654)	(1117,4097)
Interval between tests	207 (107,308)		120 (50,217)		110 (66,273)	
Adverse outcomes (x/N)	9/14		0/11††		4/18†	
Right Atrial Pressure	9 (6,12)	12 (5,14)	10 (9,15)	6 (3,11)*	10 (5,14)	5 (3,10)
PA Systolic Pressure	51 (42,61)	55 (45,64)	64 (49,73)	38 (28,68)*	44 (33,71)	44 (27,58)
PA Wedge Pressure	23 (22,27)	27 (23,32)	31 (23,31)	16 (5,22)*	21 (15,29)	19 (8,23)
Cardiac Index	2.0 (1.5,2.4)	2.0 (1.4,2.7)	2.3 (1.4,3.1)	2.6 (2.2,2.6)	1.9 (1.8,2.6)	2.0 (1.8,2.4)
Sodium	134 (131,138)	134 (130,136)	139 (137,141)	138 (137,141)	138 (134,139)	137 (136,139)
Bilirubin	14 (11,21)	19 (12,33)	21 (13,25)	11 (9,16)*	16 (10,21)	15 (12,19)
Albumin	43 (42,47)	42 (32,43)	40 (40,45)	43 (42,46)	43 (40,46)	43 (41,46)

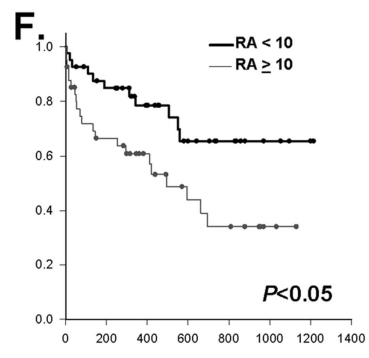
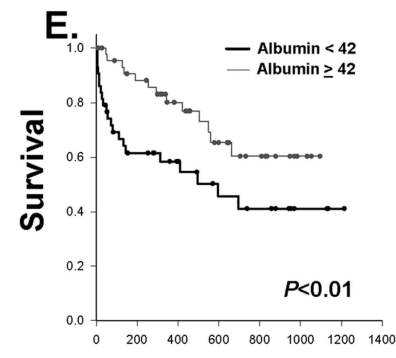
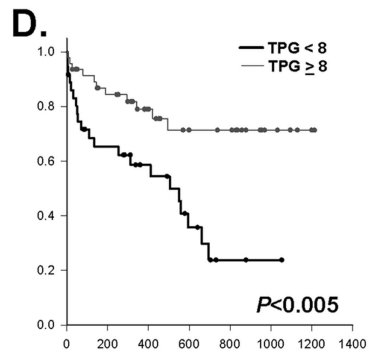
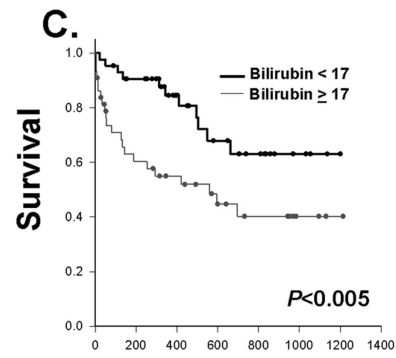
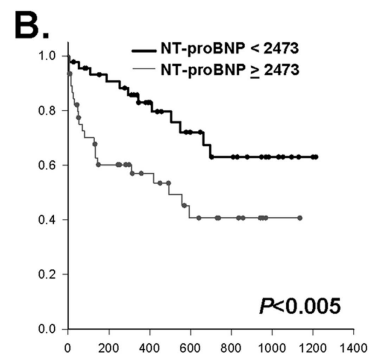
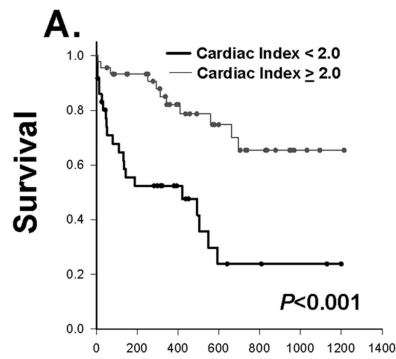
Data are median (25th,75th quartiles). NT-proBNP (pg/mL); Interval (days); Adverse outcomes: expressed as proportion of patients deteriorating or dying of total number; Right Atrial Pressure (mmHg); PA Systolic Pressure: pulmonary arterial systolic pressure (mmHg), PA Wedge Pressure: pulmonary arterial wedge pressure (mmHg), Cardiac Index (L/min/m²); Sodium (mmol/L), Bilirubin (μmol/L), Albumin (g/L). For haemodynamic and biochemistry data there are N=6-7 in the increased group, N=6-9 in the decreased group, and N=10-12 in the stable group, all paired data. * P<0.05 vs column to immediate left; † P<0.05 and †† P<0.001 vs outcomes for 50% increase group

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