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N-terminal pro Brain Natriuretic Peptide as predictor of outcome in scleroderma renal crisis

Running title: N-TproBNP in scleroderma renal crisis

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Abstract

Objectives: Although in scleroderma renal crisis (SRC) outcome has improved to a great extent with the introduction of ACE inhibitors, there remains significant mortality and morbidity with frequent requirement for renal replacement therapy. Therefore, novel biomarkers to identify patients at high risk of poor renal outcome would be invaluable. The aim of this study was to assess the role of the N terminal fragment of pro Brain Natriuretic Peptide (N-TproBNP) as predictor of renal outcome in SRC.

Methods: 20 subjects with confirmed SRC were retrospectively enrolled. Clinical data, full blood count, creatinine, eGFR and N-TproBNP at presentation were collected.

Results: Patients requiring renal replacement therapy presented significantly higher levels of N-TproBNP, creatinine and eGFR ($p<0.01$), shorter disease duration ($p<0.01$) and lower haemoglobin levels ($p=0.01$) compared to those who did not require dialysis. Whereas all the candidate variables significantly predicted renal outcome in univariate models, N-TproBNP was the only variable to hold significance in predicting renal outcome in a Firth's multivariate logistic regression model ($p=0.05$, OR 7.6). ROC curve of N-TproBNP to identify patients requiring renal replacement therapy provided a sensitivity of 88.9%, with a specificity of 81.8% at a cut-off value of 360 pmol/L (95% CI 0.84-1.00, area under the curve 0.94). In our cohort, this provided a positive predictive value of 80% and a negative predictive value of 90%.

Conclusions: N-TproBNP peptide may be a useful biomarker in risk-stratification of renal outcome in SRC, selectively identifying patients likely to require renal replacement therapy.

Indexing Terms: Systemic Sclerosis; Scleroderma Renal Crisis; N-TproBNP; renal outcome; dialysis

Word count: 3433 of 3500

Introduction

First described in 1863 by Auspitz, scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc)[1]. It is characterized by an abrupt onset of systemic hypertension with progressive renal failure [2,3]. SRC presents in 10-20% of patients with diffuse SSc (dcSSc), much less commonly in the limited subset (lcSSc). It occurs early in disease course, almost invariably within the first five years from diagnosis; up to 25% of patients are diagnosed with SSc at SRC onset [3]. Medium-high dose corticosteroids have been linked to SRC, with 60% of patients having received steroids prior to presentation [4]. Although there is variability between reports in the incidence of both SRC and anti-RNA polymerase III antibodies (ARA), recent studies suggest that 30-59% of SRC patients harbour ARA [3,5]. Several additional risk-factors have been identified as predictors of SRC in SSc population: rapidly progressive skin thickening, joint contractures, new-onset anaemia, recent cardiac events such as pericardial effusion and congestive heart failure [6,7]. The introduction of angiotensin converting enzyme inhibitors (ACEIs) has dramatically improved survival at 1 year from 15% to 76%[4,8]. However, prognosis remains poor, with a mortality rate at 5 years between 30 and 40%[3,9,10]. Penn et al showed that haemodialysis was instituted in 2/3 of patients presenting with SRC; approximately half of subjects on renal replacement therapy subsequently discontinued dialysis [3]. Median time to dialysis discontinuation was 11 months, the potential for renal recovery without long-term renal replacement therapy was low beyond 24 months [3].

To date, few authors have assessed the role of outcome predictors in SRC patients: most studies have focused on demographic and clinical variables associated with poor renal outcome; some investigators focused on the predictive role of pathologic features at renal biopsy, with conflicting results [3,11]. However, a non-invasive surrogate biomarker that predicted long-term outcome in SRC has not yet been proposed. Given the high mortality and morbidity SRC still heralds, the identification

of such prognostic tool would be valuable. This may facilitate stratification of patients at higher risk of poor outcome that may warrant more aggressive monitoring and treatment.

Brain Natriuretic Peptide (BNP) is a neurohormone released from cardiomyocytes in response to pressure overload. BNP opposes the effects of renin-angiotensin-aldosterone system, promoting vasodilatation and natriuresis and increasing glomerular filtration rate (GFR). It is synthesised as a 108-amino acid prohormone, proBNP, then cleaved into a biologically active peptide and an inactive fragment, the 76-residue N-TproBNP [12]. BNP is rapidly metabolised while N-TproBNP has a longer half-life resulting in a higher circulating level than BNP. Consequently, N-TproBNP assay is preferred as diagnostic and prognostic tool in cardiac failure and pulmonary arterial hypertension (PAH)[13,14]. Since N-TproBNP levels are elevated even in patients with end-stage renal disease receiving renal replacement therapy [15,16] and its long-term prognostic value is independent of cardiac mass and ejection fraction[17], N-TproBNP may act as biomarker in SRC. Therefore, the aim of this work was to retrospectively assess the role of N-TproBNP together with several clinical and biochemical parameters as a candidate predictor of renal outcome in a cohort of 20 SRC patients.

Patients and methods

- Patients

All patients included in this study fulfilled ACR preliminary classification criteria for SSc [18] and were recruited from a single UK centre. Patients were categorized into lcSSc and dcSSc according to LeRoy [19]. SRC was defined as a new-onset systemic hypertension $>150/85$ mmHg with a decrease in estimated GFR (eGFR) $>30\%$. Patients with normotensive SRC were also included; these patients demonstrate increased blood pressure (BP, even though not attaining standard hypertensive levels), with reduction in renal function as measured by serum creatinine as described for hypertensive SRC [20]. Demographic data were retrospectively collected through review of records, clinical data were

recorded: disease subset, modified Rodnan skin score (mRSS), heart involvement, PAH, autoantibody specificities (antibodies against centromere [ACA], topoisomerase I [ATA], U₃RNP [anti-U₃RNP], ARA). Additional parameters such as left ventricular ejection fraction (LVEF), systolic and diastolic BP (sBP and dBP) were recorded at the time of SRC.

- *Blood sampling and assay*

Serum biochemistry including full blood count and creatinine was assessed at the time of SRC presentation. eGFR was computed using the modification of diet in renal disease equation. All patients had N-TproBNP levels tested at the time of SRC presentation; twelve subjects had a repeat N-TproBNP at six-month follow-up. Serum N-TproBNP levels were measured with Roche Modular Analytics E-170. Normal N-TproBNP levels were less than 20 pmol/L.

- *Statistical analysis*

Renal outcome was defined upon dialysis requirement (“dialysis” and “no dialysis” group). Given the number of variables included in this study, principal components analysis (PCA) was applied to ascertain multivariate relationships by clustering groups of variables into components that accounted a common effect. A correlation matrix approach was used as these variables bore different measure units and magnitude orders. N-TproBNP levels were considered after log-transformation in order to achieve normality. The scree-plot of eigenvalues and Kaiser criterion were used to determine the components to retain. Absolute and relative contributions were estimated and a scatter plot was drawn. Mann-Whitney test was used to compare candidate variables in two subgroups of patients identified upon renal outcome and disease subset. Fisher’s exact test was performed to investigate the distribution of renal outcome between disease subsets. Kruskal-Wallis test was used to compare

clinical and biochemical variables between groups with specific autoantibody profile (ARA, ATA and anti-U₃RNP).

Associations between variables (N-TproBNP, creatinine, systolic and diastolic BP, LVEF, haemoglobin (Hb), disease duration and mRSS) were determined by Spearman's coefficient (r). Linear univariate regression analyses were performed to investigate the relationship between continuous variables and renal outcome. Quantile classification method was used to initially identify cut-off points for creatinine, eGFR, N-TproBNP, Hb and disease duration; the optimal cut-offs were then set based upon receiver operating characteristic (ROC) curves.

To overcome the quasi-complete separation phenomenon, we applied Firth's penalized maximum likelihood. This procedure has been proven to significantly reduce the small sample bias of maximum likelihood estimates. Firth's penalization logistic univariate regression analyses were performed to investigate the relationship between dichotomic variables and renal outcome. A Firth's penalization multivariate logistic regression model was also built to predict renal outcome inserting as dichotomic variables N-TproBNP, creatinine, Hb and disease duration with a step-wise approach. eGFR was not inserted in the model because a parsimony model was adopted to explain most variability, according to Occam's razor.

The likelihood ratio test (LRT) was used to compare the saturated model comprising four variables (N-TproBNP, creatinine, Hb and disease duration) against a model considering N-TproBNP only; the most restrictive model is considered the nested "null" while the general model provides the alternative hypothesis: when $p < 0.05$, the more restrictive model should be rejected.

The ROC curve was drawn to assess the diagnostic value of N-TproBNP in patients who required dialysis compared to those who did not.

Serial levels of N-TproBNP were compared using Wilcoxon matched-pair signed rank sum test. Due to the limited sample size and multiple nonparametric variables, continuous variables were expressed as median values (25°-75° percentile).

Statistical analysis was performed using SAS 9.1.5.

Results

Twenty scleroderma patients with a diagnosis of SRC were enrolled in this study. Fourteen patients (70%) were female, 17 subjects (85%) had been diagnosed with dcSSc. Only one patient presented with normotensive SRC. None of the subjects had received steroids at a dosage >7.5 mg daily prior to SRC onset. All patients were treated with ACEIs. Eleven patients (55%) did not require a renal replacement therapy (“no dialysis” group), while in 9 subjects (45%) dialysis was necessary (“dialysis group”). In the latter group, 5 patients recovered sufficient renal function to discontinue dialysis, while 4 remained dialysis-dependent. ARA was the most common autoantibody specificity (9 subjects, 45%), anti-U₃RNP antibodies were demonstrated in 5 patients (25%). All patients had a systolic pulmonary artery pressure below 30 mmHg and a LVEF above 50% on echocardiogram. Clinical and biochemical variables of patients are presented in **Table 1**. One patient in the “non dialysis” group deceased during follow-up because of squamous-cell lung carcinoma.

- Principal components analysis

PCA identified two main components, accounting for 70.5% of the total variance. The two components were retained with the following eigenvalues: component I 3.57, component II 1.37. The factor maps from the PCA including the most relevant study variables are presented in **Figure 1**. Component I included renal function tests such as creatinine and eGFR, N-TproBNP, disease duration and Hb. Component II comprised age and LVEF.

Component I was the most prominent, accounting for 51% of the total variance. It correlated positively with disease duration ($r=0.70$; $p<0.01$), eGFR ($r=0.94$; $p<0.01$) and Hb ($r=0.81$; $p<0.01$) but inversely with N-TproBNP ($r=-0.81$; $p<0.01$) and creatinine ($r=-0.80$; $p<0.01$). Component II accounted for 19.5% of the total variance. Component II correlated positively with age ($r=0.88$; $p<0.01$) and negatively with LVEF ($r=-0.63$; $p<0.01$).

- *Association of renal outcomes and clinical and biochemical variables*

Patients requiring renal replacement therapy presented with higher creatinine, eGFR and N-TproBNP values ($U=10.00$, $U=12.00$, and $U=6.00$ respectively, $p<0.01$; **Figure 2**) but shorter disease duration and lower Hb levels compared to those not requiring dialysis ($U=13.50$ and $U=17.50$ respectively, $p<0.01$). No difference in renal outcome was observed based on disease subset. Nine of the 14 female patients had a worse renal outcome, while none of the males required dialysis, thus no analysis was undertaken for gender. No further analysis was performed for autoantibody subtypes due to small sample size. The two subgroups were similar for age at SRC onset, systolic and diastolic BP, LVEF and mRSS.

- *Identification of candidate clinical and biochemical variables predictive of renal outcome*

The above analyses prompted us to consider five candidate variables potentially predictive of renal outcome in SRC: N-TproBNP, creatinine, eGFR, Hb and disease duration.

- *Candidate predictor variables*

Female patients presented significantly higher N-TproBNP and lower Hb than males ($U=8.00$, $p<0.01$ and $U=15.50$, $p=0.04$), no differences were noted for the remaining three variables. No significant

difference in creatinine, eGFR, N-TproBNP, disease duration and Hb was observed for disease subset or autoantibody subtypes.

- Correlation between candidate predictors of renal outcome in SRC and other clinical and biochemical variables

As expected, significant correlations emerged between all the five variables identified as candidate predictors of renal outcome. A positive correlation was observed between N-TproBNP and creatinine ($r=0.62$, $p<0.01$), a negative correlation was reported between N-TproBNP and eGFR, Hb, disease duration and age ($r=-0.74$, $r=-0.70$, $r=-0.66$, $r=-0.10$, $p<0.01$). Noteworthy, the correlation between N-TproBNP levels and LVEF did not quite meet statistical significance ($r=-0.46$, $p=0.07$); similarly, N-TproBNP did not correlate with sBP or dBP.

Positive correlations emerged between eGFR and Hb as well as disease duration, and between Hb and disease duration; a negative correlation was reported between creatinine and eGFR, Hb and disease duration.

- Univariate linear regression analyses

N-TproBNP, creatinine and Hb significantly predicted the requirement of dialysis ($p=0.02$, $p=0.02$ and $p=0.03$ respectively). Conversely, eGFR and disease duration were not significantly associated with renal outcome.

- Identification of cut-off values

The following threshold values were identified: N-TproBNP 360 pmol/L, creatinine 259 $\mu\text{mol/L}$, eGFR 15 ml/min/1.73m², disease duration 8 months and Hb 11.7 mg/dl.

- *Firth's univariate logistic regression analyses*

A N-TproBNP value >360 pmol/L conferred an odds ratio (OR) of 21.5 for dialysis requirement ($p < 0.01$, 95% CI 2.9-294.9). Both creatinine above the threshold value of 259 $\mu\text{mol/L}$ and eGFR at the cut-off value of 15 mL/min/1.73m² significantly predicted the renal outcome ($p < 0.01$, 95% CI 1.9-171.6), with an OR for dialysis requirement of 13.7. Disease duration above 8 months significantly predicted renal outcome, the OR was 7.3 ($p = 0.03$, 95% CI 1.2-58.8). In contrast, Hb above the threshold value of 11.7 mg/dl was not predictive of dialysis requirement.

- *Firth's multivariate logistic regression analysis*

Multivariate logistic regression model identified N-TproBNP as the only variable to reach statistical significance in predicting renal outcome, with a more accurate CI for OR estimate ($p = 0.05$, OR 7.6, 95% CI 1.1-115.8).

- *Likelihood ratio test*

LRT analysis showed that N-TproBNP exerted a strong impact on the fitness of the model (LRT=9.76, $p < 0.01$); conversely, the variables creatinine, Hb and disease duration had little influence on the fitness of the saturated model (LRT=1.22, $p = \text{NS}$). However, considering the important biological role of these three variables, we believe that the saturated model offers a more reliable adjusted estimates of the OR of N-TproBNP to predict poor renal outcome compared to the model considering N-TproBNP only (OR 7.6 versus 21.5).

- *Sensitivity, specificity and predictive values of N-TproBNP*

Based on the ROC curve of N-TproBNP that identified patients likely to require renal replacement therapy, a sensitivity of 88.9% was achieved at a cut-off N-TproBNP level of 360 pmol/L, with a

specificity of 81.8% (95% CI 0.84-1.00, area under the curve 0.94). In our SSc cohort, 45% of patients presenting with SRC required dialysis, leading to a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%. Considering the lowest estimates of the rate of patients requiring renal replacement therapy (31%)[21], the PPV would be 67% with a NPV of 76%.

- *N-TproBNP levels at six month follow-up*

Twelve patients (60%) had their N-TproBNP levels repeated during a six-month follow up after SRC. There was a statistically significant reduction in N-TproBNP values among patients who did not require dialysis and those who discontinued it ($p=0.01$); the reduction in N-TproBNP levels observed in the “permanent dialysis” group did not achieve statistical significance.

Discussion

There is a major clinical need for serum or plasma biomarkers, beyond routine measures of kidney function, that may predict outcome or help with clinical management of SRC. In this study, we retrospectively identified 5 candidate biomarkers of renal outcome assessing their prognostic role in a cohort of 20 SRC patients. Overall, our data suggest that in this setting N-TproBNP is the most reliable predictor of renal outcome. Indeed, the high sensitivity and specificity in predicting the requirement of renal replacement therapy provided by N-TproBNP at a cut-off value of 360 pmol/L may confer important clinical implications. Considering also the good NPV and the strong OR for renal replacement therapy, N-TproBNP could be helpful in the risk-stratification of SRC patients at presentation, complementing renal function tests. Our data also suggest that N-TproBNP is even more reliable than kidney function tests in predicting renal outcome among SRC patients. Indeed, N-TproBNP levels above the threshold value of 360 pmol/L conferred a higher OR for dialysis than creatinine above 259 $\mu\text{mol/L}$ and eGFR lower than 15 mL/min/1.73m² (21.5 versus 13.7). In addition,

N-TproBNP but not creatinine significantly predicted renal outcome in a Firth's multivariate regression model. In addition, LRT clearly showed that N-TproBNP contributed to the significance of the model to a stronger extent compared to the other candidate variables. Interestingly, high serum creatinine at presentation has been reported to confer poor outcome, either early death or requirement for permanent dialysis[3,6,8]; however, serum creatinine greater than 270 $\mu\text{mol/L}$ did not significantly predict outcome in multivariate regression analysis[8].

Significant renal impairment (creatinine $>150 \mu\text{mol/L}$) has been demonstrated to affect N-TproBNP levels[22]; in particular, as N-TproBNP displays a lower extrarenal excretion than BNP, renal dysfunction influences N-TproBNP levels to a greater extent than BNP[23]. Thus, the role of N-TproBNP as cardiac biomarker in patients with renal insufficiency has been much debated: some authors have suggested that in renal insufficiency N-TproBNP elevations were merely reflective of reduced clearance. However, several investigators have demonstrated that N-TproBNP levels are not spurious even in renal failure setting[22,24]: in heart failure patients, N-TproBNP levels at presentation were a powerful predictor of 60-day mortality regardless of renal function[23]. These observations prompted us to hypothesize that N-TproBNP in SRC may represent a marker of overall haemodynamic status. Endothelial dysfunction of the renal small arteries and arterioles is regarded as the initial pathogenic trigger in SRC; it causes an impaired glomerular perfusion, thus inducing hyper-renaemia and subsequent angiotensin-II induced hypertension. Consequently, higher N-TproBNP levels may reflect a stronger activation of renin-angiotensin axis, in turn responsible for an increased production of natriuretic peptides by cardiomyocytes.

Besides renal function tests and N-TproBNP, we identified two other variables as candidate predictors of renal outcome in SRC, namely disease duration and Hb. In this regard, in our study population patients with lower disease duration presented a worse renal outcome, with a strong inverse correlation between N-TproBNP levels and disease duration. These data might thus suggest that

patients presenting with SRC earlier on disease course are at higher risk of requiring dialysis. Indeed, in most studies conducted among scleroderma patients, N-TproBNP levels were not correlated with disease duration [25,26], with an Italian group even observing a positive relationship between disease duration and N-TproBNP[27].

A recent onset of anaemia is not only a well-described precipitating factor for SRC but also a frequent finding in patients with acute renal failure. Accordingly, in our cohort a significant association between Hb and N-TproBNP emerged, with patients requiring dialysis presenting lower Hb levels. Creatinine, Hb and disease duration were not associated with renal outcome in our multivariate model. However, considering the biological importance of the above-cited variables, we believe the saturated model should be considered, with a net OR for N-TproBNP to predict renal outcome of 7.6.

We also assessed the role of demographic confounders potentially affecting the prediction of renal outcome, such as age, gender, BP, and LVEF. In contrast to previous studies reporting older age as an independent predictor of dialysis-free survival [8,10,28], in our cohort the age of patients requiring renal replacement therapy was similar to that of subjects not on dialysis. We observed a significant inverse correlation between N-TproBNP and age, even if N-TproBNP levels are described to increase with aging [29]. Similarly, past studies identified male sex to be associated with poor renal outcome [6,8]. Unfortunately, we could not investigate any potential statistical difference in the distribution of gender between the two subgroups, even though men displayed lower N-TproBNP levels compared to women, likely because none of the male subjects required dialysis. Nevertheless, it is rather unlikely that in this setting gender could display a confounding effect as any difference in N-TproBNP has ever been reported between female and male SSc patients [25,26]. Previous studies conducted in heart failure population have provided conflicting results, with some authors describing similar N-TproBNP levels[30,12] and others higher N-TproBNP either among male[31] or female subjects[24,32].

Interestingly, we did not report any variance in low BP and LVEF between patients requiring and those not requiring renal replacement. Conversely, several investigators have reported that patients requiring dialysis displayed a lower BP at presentation [3,11,25,33]. Possibly, our finding might be ascribed to the fact that only one patient presented with normotensive SRC. In addition, as previously described by Penn[3], we could not report any significant difference in LVEF between the two groups of patients stratified to renal outcome, in contrast to other reports of heart failure as risk-factor for poor outcome in SRC[8]. Accordingly, we couldn't demonstrate a significant correlation between N-TproBNP and LVEF, in agreement with a recent study showing that N-TproBNP levels, despite maintaining a prognostic role in patients presenting with acute renal failure, are not closely related to LVEF [34].

As a whole, our data suggest that N-TproBNP provides a reliable surrogate biomarker to identify SRC patients at higher risk of poor renal outcome, independently from cardiorenal function and other demographic, clinical and biochemical variables.

Noteworthy, a significant reduction in serial N-TproBNP levels among patients with better renal outcome was observed, suggesting N-TproBNP could be a useful tool in the follow-up of SRC patients. Changes in N-TproBNP levels may reflect the response to ACEIs: N-TproBNP may allow monitoring treatment response facilitating therapeutic management post-acute crisis. Indeed, several drugs including ACEIs may strongly affect N-TproBNP levels; patients with chronic heart failure in whom treatment was adjusted based on N-TproBNP levels had an improved outcome [30].

Several important issues may limit interpretation of this study. The retrospective design is acknowledged as a weakness; the relatively small sample size may have affected the wide range of CI for OR estimates of N-TproBNP in predicting renal outcome. This critical issue was overcome with Firth's penalized maximum likelihood, which led to a more accurate estimate of the relative risk provided by N-TproBNP.

In conclusion, our data suggest that N-TproBNP could selectively identify patients at highest risk of poor renal outcome at SRC onset. This may potentially allow more intensive treatment or earlier use of renal replacement therapy to try and improve outcome, although this would require a prospective study. As the assay is increasingly available as routine laboratory test, N-TproBNP may provide a practical prognostic biomarker in patients presenting with SRC. We believe that, considering SSc is a relatively rare disease and SRC an uncommon complication with high mortality, this study presents important relevance in clinical practice. N-TproBNP may add to current armamentarium in the management of this life-threatening aspect of SSc, even though future studies are required to prospectively evaluate its utility as outcome predictor in this setting.

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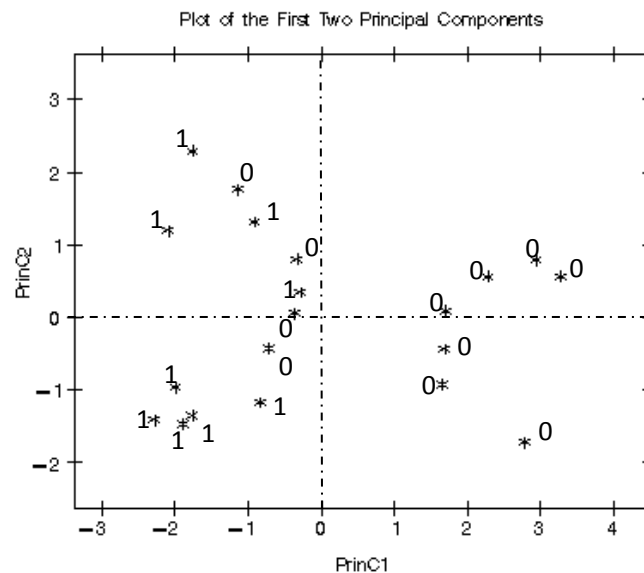
Table 1.

	No dialysis group (n=11)	Dialysis group (n=9)	Total cohort (n=20)
Disease duration (months)	12 (8.5-35)	6 (1-7)	9 (6-13)
mRSS	23 (18-24)	20 (15-23)	22 (16-24)
LVEF (%)	60 (58-66)	60 (55-62)	60 (58-62)
Systolic BP (mm Hg)	205 (170-227)	214 (165-225)	209 (169-227)
Diastolic BP (mm Hg)	110 (98-120)	115 (110-130)	110 (106-120)
Creatinine ($\mu\text{mol/L}$)	145 (129.5-250.5)	442 (297-676)	289 (143-441)
eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	37 (19.5-50)	15 (15-15)	15 (15-39)
Hb (g/dL)	11.7 (10.5-12.8)	9.3 (9-11.6)	11 (9-12)
N-TproBNP (pmol/L)	119 (63.5-194.5)	2052 (1494-4139)	305.5 (110-1987)

Clinical characteristics of patients enrolled in this study and N-TproBNP levels.

All variables are expressed as median (25° percentile – 75° percentile). mRSS = modified Rodnan skin score; LVEF = left ventricular ejection fraction; BP = Blood Pressure; eGFR = estimated glomerular filtration rate; Hb= haemoglobin.

Figure 1.



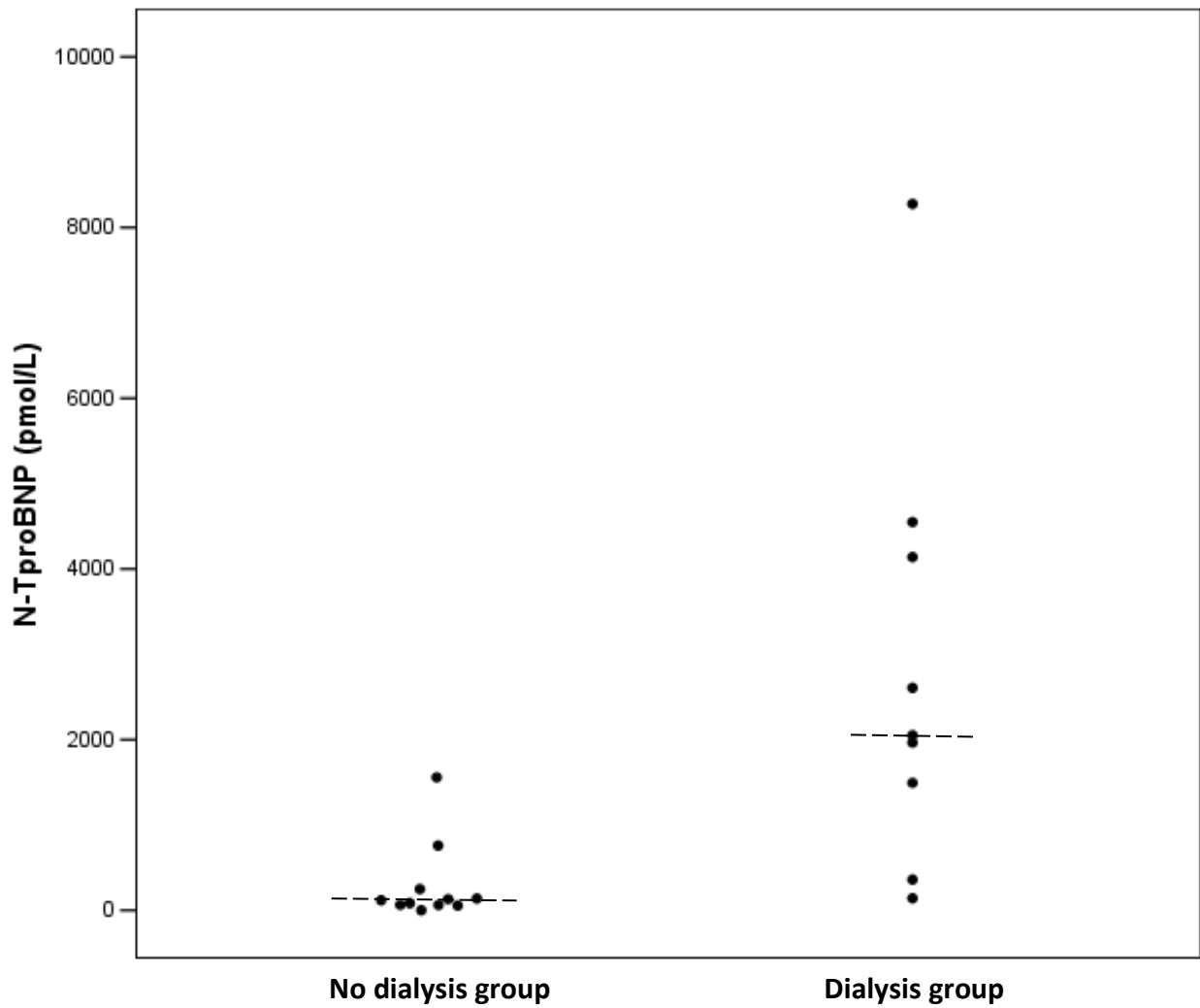
Scatter plot of Principal Component Analysis (PrinC) with patients stratified based on renal outcome (0= no dialysis; 1 = dialysis).

Subjects in the left portion of the graph (PrinC1<0) are characterized by medium–high levels of both N-TproBNP and creatinine, low disease duration, haemoglobin (Hb) and estimated glomerular filtration rate (eGFR). Seventy-five % (9/12) of these patients presented a poor renal outcome. Conversely, patients in the second group clustered in the right portion of the graph (PrinC1>0), presenting lower N-TproBNP and creatinine, a longer disease duration, higher eGFR values and normal Hb levels.

Levels of N-TproBNP and creatinine were defined high when above the cut-off values of 360 pmol/L and 259 μ mol/L respectively. Levels of eGFR, Hb and disease duration were defined low when below the following cut-off values: 15 ml/min/1.73m², 11.7 mg/dl and 8 months respectively.

Cut-off values were initially identified using the quantile classification method; the optimal cut-offs were then set based upon receiver operating characteristic (ROC) curves.

Figure 2.



Dot-plot of N-TproBNP in patients with scleroderma renal crisis based on renal outcome. Dotted lines indicate median values. Median values of N-TproBNP in 'no dialysis' group =119 pmol/L, in 'dialysis' group =2052 pmol/L (U=6.00, p<0.01).