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NT-proBNP predicts mortality in adults with transposition of the great arteries late after Mustard or Senning correction

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Abstract

Objective: The patients after Mustard and Senning corrections of transposition of the great arteries (TGA) are at an increased risk of unexpected death. The aim of this study was to identify markers allowing risk stratification of patients after atrial switch correction of TGA to provide them with optimum care.

Methods and Results: In this study, 87 patients were retrospectively evaluated after atrial switch correction of TGA followed-up between 2005 and 2015. The mortality during the follow-up was 9% (8 cardiac deaths). Markers significantly predictive of death using univariable Cox proportional hazard ratio survival analysis were: N-terminal pro-B-type natriuretic peptide (NT-proBNP), ejection fraction and end-diastolic dimension of the systemic right ventricle, mitral E, e', and s'. Surprisingly, the Doppler parameters of mitral valve in subpulmonary ventricle were more important for prognosis than those of systemic tricuspid valve. In multivariable analysis, the only independent predictors of mortality were NT-proBNP ($P = .00048$; AUC 0.97) and the velocity of early diastolic filling (mitral E) in subpulmonary ventricle ($P = .01815$; AUC 0.81). According to Kaplan–Meier survival analysis, patients with NT-proBNP > 1000 pg/ml are at high risk of death. Patients with mitral $E < 68$ cm/s are also at an increased risk of death.

Conclusions: NT-proBNP is the most reliable prognostic mortality factor and should be measured regularly in TGA patients after Mustard or Senning correction. Diastolic filling velocity of the subpulmonary left ventricle (mitral E) may be more important for prognosis than systolic function of the systemic right ventricle.

KEYWORDS
adult congenital heart disease, mitral E, mortality, Mustard and Senning operation, NT-proBNP, transposition of the great arteries

1 | INTRODUCTION

Transposition of the great arteries (TGA) used to be corrected by atrial switch operation according to Mustard or Senning in the 60s-80s of the 20th century.[1,2] This type of surgery leaves the morphologically right ventricle in the systemic position connected to the aorta. The systemic right ventricle becomes dilated and dysfunctional with increasing age. The systemic tricuspid valve is often regurgitating. The Mustard and Senning corrections are not used anymore; instead, arterial switch operation is performed, eliminating the problems with the systemic right ventricle.[3]

Presently, all patients with Mustard or Senning type of correction are adult and they are looked after and treated by adult cardiologists. These patients are usually well adapted and do not report excessive clinical problems, the majority being in functional class NYHA I-II.[4–8] However, several studies confirmed increased values of natriuretic peptides especially in patients after Mustard correction.[7,9] According to our experience, these patients do not report dyspnea even if they have severe dysfunction of the systemic right ventricle with low ejection fraction (EF) and a decreased exercise capacity. However, even without previous symptoms they may die unexpectedly due to severe heart failure or arrhythmias, often during respiratory infection or physical activities. The decision whether to add a patient to a waiting list for heart transplantation is difficult because these patients appear to be clinically stable for a long time and their deterioration may be quick

and unexpected. The risk stratification of patients after Mustard or Senning correction is therefore extremely important, although considered very challenging.[10]

The aim of our work was to analyze the possible predictors of death in adults after Mustard or Senning correction of the TGA. Reliable predictors may be used to identify patients at risk and enlist them for tricuspid valve surgery or heart transplantation with high priority.

2 | METHODS

We have evaluated the records of 87 adult patients after atrial switch operation (48 Mustard, 39 Senning) (Table 1), following-up these patients in the period 2005-2015. All patients were clinically stable during the first visit. All patients underwent repeated clinical and echocardiographic examination and N-terminal pro-B-type natriuretic peptide (NT-proBNP) assessment several times during the follow-up. Echocardiographic examination was performed using IE-33, Philips. Annular velocities (s', e') were measured by pulsed tissue Doppler echocardiography at lateral annulus of both ventricles. End-diastolic dimensions (EDD) of both ventricles were measured in 4-chamber apical projection. Ejection fraction (EF) was assessed by Simpson formula for the systemic right ventricle (RVEF)[11] and by Teichholz formula for subpulmonary left ventricle (LVEF). Evaluation of the ejection fraction of both ventricles by cardiac magnetic resonance (CMR) was performed in 18% of patients. Maximal exercise aerobic capacity (VO_2 max) was assessed in 44% of patients. All measurements were taken at regular check-ups in clinically stable outpatients without manifest heart failure, without arrhythmias, and without the need of hospitalization. In patients listed for transplantation, only the measurements before enlisting for the transplantation were included in this analysis. In the case a patient did not attend a planned check-up (e.g., because he has forgotten or has died), we contacted his local general practitioner, local cardiologist,

TABLE 1 Baseline characteristics of patients with TGA after Mustard vs. Senning correction.

	Mustard (n=48)	Senning (n=39)	*P* value
Men	32 (67%)	32 (82%)	0.10886
Pacemaker	9 (19%)	12 (31%)	0.21651
Age	30.00 (27.00–33.00)	21.00 (20.00–23.75)	< 0.00001 (***)
NT-proBNP	287.00 (165.35–628.05)	144.00 (85.00–217.85)	0.00058 (***)
NYHA	2.00 (1.75–3.00)	1.50 (1.00–2.00)	0.00344 (**)
LVEF	70.00 (60.00–80.00)	70.00 (65.00–75.00)	0.9894
RVEF	35.00 (28.75–45.00)	42.00 (37.00–45.75)	0.04284 (*)
LVEF CMR	58.00 (46.00–67.00)	53.00 (48.00–57.00)	0.60384
RVEF CMR	39.00 (30.00–51.00)	50.50 (42.00–57.00)	0.1835
LV-EDD	31.00 (26.00–40.00)	33.00 (29.00–36.00)	0.51048
RV-EDD	50.00 (41.75–57.25)	48.50 (42.00–54.00)	0.70935
TR	2.00 (1.00–3.00)	1.50 (1.00–2.00)	0.2153
Tric E	73.00 (58.00–85.00)	79.50 (69.00–90.00)	0.14107
Tric s'	5.00 (4.00–6.30)	8.00 (6.00–10.00)	< 0.00001 (***)
Tric e'	5.00 (4.00–6.00)	8.00 (6.00–10.00)	< 0.00001 (***)
Tric E/e'	13.60 (10.74–21.44)	9.27 (6.88–13.16)	0.00340 (**)
Mitr E	71.00 (58.00–84.00)	96.00 (72.25–113.25)	0.00057 (***)
Mitr s'	10.00 (8.00–12.00)	8.00 (7.00–10.00)	0.03146 (*)
Mitr e'	12.00 (8.75–16.00)	10.00 (7.00–14.00)	0.1835
Mitr E/e'	6.22 (4.64–9.40)	8.62 (7.41–12.42)	0.00133 (**)
VO_2 max	29.45 (24.00–33.50)	30.35 (27.35–35.55)	0.37998
Years since operation	26.00 (24.00–28.50)	21.00 (19.00–23.00)	< 0.00001 (***)

Values represent median (interquartile range) of the whole group of patients (first measurements). Difference between the two groups was measured with Mann–Whitney U test for continuous variables and Fisher test for binary variables. NYHA: functional class according New York Heart Association, LVEF: ejection fraction of the left (subpulmonary) ventricle, RVEF: ejection fraction of the right (systemic) ventricle, CMR: by magnetic resonance, Mitr: mitral = atrio-ventricular valve in the subpulmonary ventricle, Tric: tricuspid = atrio-ventricular valve in the systemic subaortic ventricle, TR: tricuspid regurgitation, RV: right ventricle, LV: left ventricle, EDD: end-diastolic dimension. Asterisks represent different significance levels: .001 (***), .01 (**), .05 (*) of *P* values.

family, or transplant center, so that we were able to gain mortality information about all our patients.

Informed consent from all patients and institutional research ethics approval were obtained (Ethical Committee of Na Homolce hospital). Blood samples for NT-proBNP were taken in a sitting position at rest from a peripheral vein together with blood samples for routine biochemistry and blood count evaluation. Serum samples were analyzed immediately after the transport to the laboratory. Serum levels of NT-proBNP were measured using commercially available electrochemiluminescence sandwich immunoassay (ELECSYS 2010; Roche, Mannheim, Germany).

2.1 | Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR, 25-75th percentile). In the case of repeated testing, the first (baseline) measurements were used in the main analysis. Differences between two groups (Mustard vs. Senning; survivors vs. deceased) were measured with Mann–Whitney *U* test for continuous variables and with Fisher test for binary variables. Benjamini–Hochberg correction was used on all *P*-values to correct for multiple testing. Differences were considered to be significant at a *P* value of less than .05. Pairwise Pearson correlation between all variables was computed. The Cox proportional hazard regression was performed to identify predictors of mortality. Variables with more than 15% missing values (VO_2 max, RVEF CMR, and LVEF CMR) were excluded from the univariable analysis. Nearest neighbor imputation of missing values was used for the included variables. Due to its non-normal distribution, NT-proBNP was dichotomized with cut-off value of 1000 pg/mL (based on expert opinion; see results for details of the cut-off choice). In multivariable analysis, a forward step-wise method with Akaike Information Criterion (AIC) for model selection has been used. Hazard ratios, with 95% confidence intervals, are reported. The two best predictors (NT-proBNP and mitral *E*) in multivariable Cox proportional hazard ratio analysis were explored in greater detail: Mortality prediction was assessed by receiver operating characteristic (ROC) curve analysis and area under curve (AUC) and three optimal operating points were

TABLE 2 Baseline characteristics of alive vs. deceased TGA patients.

	All (n=87)	Alive (n=79)	Deceased (n=8)	*P* value
Men	64 (74 %)	58 (73 %)	6 (75 %)	0.93104
Pacemaker	21 (24 %)	19 (24 %)	2 (25 %)	1.00000
Age	25.00 (22.00–31.00)	25.00 (21.25–31.00)	29.00 (25.00–31.00)	0.43719
NT-proBNP	203.00 (129.00–379.10)	186.10 (126.93–292.92)	1553.00 (1040.10–6348.50)	0.00032 (***)
NYHA	2.00 (1.50–2.50)	2.00 (1.50–2.00)	2.50 (2.00–3.00)	0.04197 (*)
LVEF	70.00 (63.00–77.75)	70.00 (63.00–77.00)	68.50 (40.00–85.00)	0.85236
RVEF	40.00 (30.00–45.00)	40.00 (33.50–45.00)	30.00 (21.00–35.00)	0.01693 (*)
LVEF CMR	55.50 (47.00–61.00)	56.00 (48.50–61.50)	42.00 (42.00–42.00)	0.44118
RVEF CMR	45.00 (34.25–57.00)	47.00 (38.00–57.00)	18.50 (18.50–18.50)	0.19139
LV-EDD	32.00 (27.00–39.75)	32.00 (27.00–40.00)	30.50 (25.00–33.00)	0.34007
RV-EDD	49.00 (42.00–55.00)	49.00 (41.00–55.00)	61.00 (57.00–66.00)	0.04197 (*)
TR	2.00 (1.00–2.50)	2.00 (1.00–2.38)	2.50 (2.50–3.38)	0.07457
Tric E	78.00 (60.75–88.25)	78.50 (60.00–87.00)	75.00 (70.00–102.00)	0.44567
Tric s'	6.00 (4.65–8.00)	6.00 (5.00–8.00)	5.00 (3.13–7.13)	0.2351
Tric e'	6.00 (4.75–9.00)	6.00 (5.00–9.00)	5.00 (3.70–7.50)	0.34316
Tric E/e'	11.23 (8.53–18.75)	11.17 (8.17–17.56)	15.00 (11.38–30.44)	0.19139
Mitr E	79.00 (66.00–103.25)	81.00 (67.00–104.75)	57.00 (42.00–63.00)	0.04582 (*)
Mitr s'	9.00 (7.00–11.00)	10.00 (7.20–11.00)	6.00 (4.00–8.00)	0.02610 (*)
Mitr e'	11.00 (8.00–14.00)	12.00 (8.00–15.00)	6.50 (4.00–7.00)	0.01693 (*)
Mitr E/e'	7.67 (5.94–10.40)	7.60 (5.75–10.03)	10.25 (7.71–12.33)	0.19139
VO_2 max	30.35 (26.20–34.00)	30.35 (26.20–34.00)	N/A	N/A
Years since operation	24.00 (21.00–27.00)	24.00 (21.00–26.00)	27.50 (21.00–28.00)	0.43719

Values represent median (interquartile range) of the whole group of patients (first measurements). Difference between the two groups was measured with Mann–Whitney U test for continuous variables and Fisher test for binary variables. Asterisks represent different significance levels: .001 (***), .01 (**), .05 (*) of *P* values.

computed: (1) sensitivity ≥80% and maximal specificity (corresponds to the expert-based), (2) slope based (returned by Matlab function perfcurve), and (3) maximal specificity + sensitivity. Log-rank statistical test was used for evaluation of differences in survival in Kaplan–Meier survival analysis. Finally, repeated measurements of NT-proBNP and mitral *E* were explored and the predictive value of the median measurements was compared with the first (baseline) measurements.

3 | RESULTS

Altogether 87 adult patients (64 men) with TGA after atrial switch operation in childhood were followed-up in our center between years 2005 and 2015 with the median of follow-up 6.4 years (4.2-8.2). Median age during the first measurement was 25.00 (22.00-31.00) years. Patients after Mustard correction were significantly older than Senning patients: 30.00 (27.00-33.00) versus 21.00 (20.00-23.75) years ($P < .0001$) with longer time passed since the operation: 26.00 (24.00-28.50) versus 21.00 (19.00-23.00) years ($P < .0001$). Mustard patients had significantly higher NT-proBNP and NYHA class and significantly lower RVEF, tricuspid *s*′, tricuspid *e*′, higher tricuspid *E*/*e*′, lower mitral *E*, higher mitral *s*′, and lower mitral *E*/*e*′ (Table 1). Pacemaker (PM) was implanted in 21 patients (9 Mustard and 12 Senning) (n.s.).

The mortality in the whole group was 9% (8 deaths out of 87 patients, 6 Mustard and 2 Senning patients) and the median survival of the deceased was 4 years (1.8-4.5). The mortality was 12.5% in the Mustard group and 5.1% in the Senning group without statistical significance ($P = .29$). The cause of death was heart failure in 7 patients and one early rejection after transplantation. Out of 12 patients enlisted for heart transplantation, 1 was successfully transplanted, 1 patient died after transplantation, 3 patients died on waiting list.

The differences between survivors and deceased are shown in Table 2. No significant difference was found between the age of survivors and deceased. The most significant differences were found in NT-proBNP. No Doppler or tissue Doppler parameters were significantly different for the systemic tricuspid valve. However, the Doppler and tissue Doppler parameters for mitral valve (*E*, *s*′, *e*′) differed significantly, with lower values in deceased. Parameters of the systemic right ventricle, RVEF, and RV-EDD, differed significantly between the groups, as well as NYHA class. The differences in EF assessed by CMR

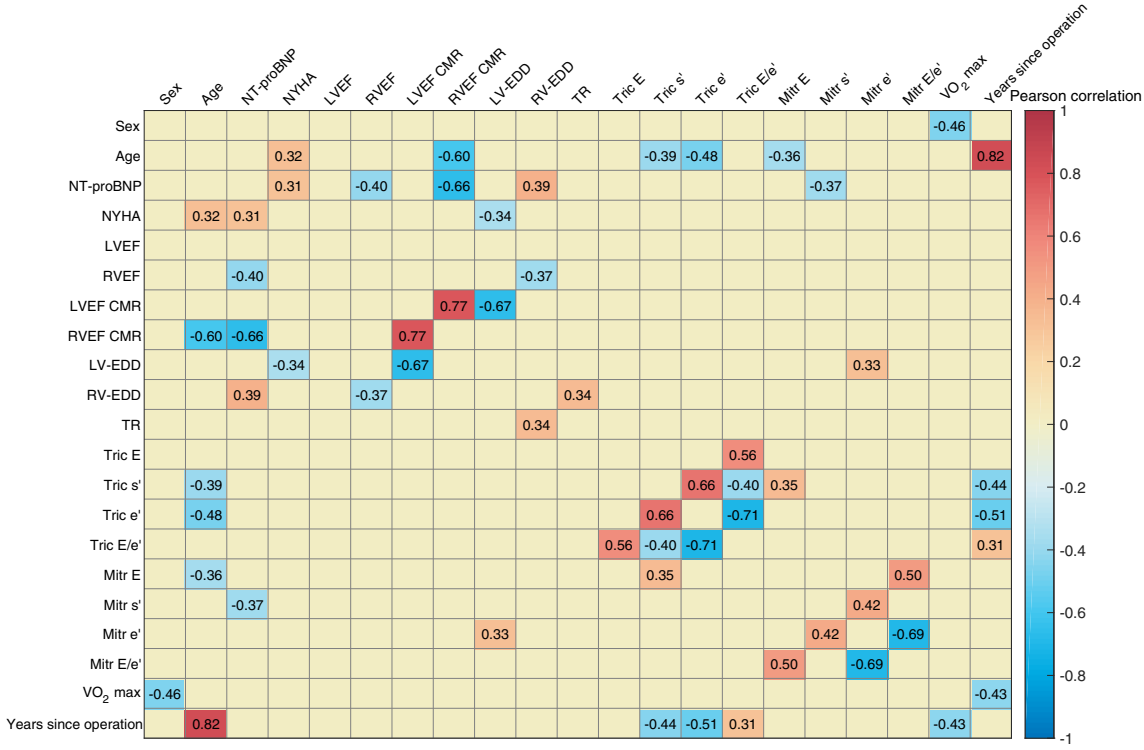

FIGURE 1 Pairwise correlations of variables (baseline values) in patients with TGA after Mustard/Senning correction. Only the significant correlations are shown. NT-proBNP, N-terminal pro-B type of natriuretic peptide; Mitr *E*, early filling velocity of subpulmonary ventricle via mitral valve assessed by Doppler echocardiography; Mitr *e*′, Tissue Doppler assessment of early diastolic annular velocity of mitral annulus in subpulmonary ventricle; RVEF CMR, ejection fraction of the systemic right ventricle assessed by cardiac magnetic resonance; RVEF, ejection fraction of the systemic right ventricle assessed by echocardiography (Simpson rule); Mitr *s*′, systolic annular velocity of mitral annulus in subpulmonary ventricle; LVEF, ejection fraction of the subpulmonary ventricle assessed by echocardiography (Teichholz); LVEF CMR, ejection fraction of the subpulmonary ventricle assessed by cardiac magnetic resonance; LV-EDD, end-diastolic dimension of the subpulmonary ventricle; RV-EDD, end-diastolic dimension of the systemic subaortic ventricle; TR, tricuspid regurgitation on the systemic tricuspid valve; VO_2max, maximal oxygen consumption during exercise test; Tric *s*′, systolic annular velocity by tissue Doppler on systemic tricuspid valve; Tric *e*′, early diastolic annular velocity by tissue Doppler on systemic tricuspid valve; Tric *E*, early filling velocity of systemic subaortic ventricle via systemic tricuspid valve by Doppler echocardiography

TABLE 3 Univariable Cox proportional hazard ratio analysis of mortality using baseline values

	Hazard ratio (CI)	*P* value
Sex	0.88 (0.17-4.49)	.87111
Age	1.06 (0.93-1.21)	.43461
NT-proBNP	96.16 (11.03-838.10)	.00044 (***)
NYHA	3.73 (1.11-12.54)	.07721
LVEF	0.97 (0.93-1.01)	.21988
RVEF	0.89 (0.82-0.96)	.00805 (**)
LV-EDD	0.95 (0.86-1.04)	.33137
RV-EDD	1.12 (1.03-1.23)	.03483 (*)
TR	2.19 (1.01-4.78)	.08803
Tric *E*	1.02 (0.99-1.04)	.25192
Tric *s*'	0.79 (0.58-1.07)	.20492
Tric *e*'	0.81 (0.62-1.07)	.20492
Tric *E/e*'	1.06 (1.00-1.12)	.08803
Mitr *E*	0.96 (0.93-0.99)	.04430 (*)
Mitr *s*'	0.48 (0.33-0.70)	.00092 (***)
Mitr *e*'	0.70 (0.55-0.90)	.01797 (*)
Mitr *E/e*'	1.03 (0.91-1.16)	.70326
Years since operation	1.11 (0.91-1.36)	.35563

Asterisks represent different significance levels: .001 (***), .01 (**), .05 (*) of *P* values.

and VO_2 max were not significant, possibly due to the large number of missing values. Out of 79 survivors, 19 had a PM (24%) and 2 patients out of 8 deceased had a PM (25%) (n.s.). Three patients had an ICD device, two of them with biventricular PM and epicardial leads, all in the survivor group.

NT-proBNP correlated significantly positively with NYHA (Pearson correlation $r = .31$) and RV-EDD ($r = .39$), while significant negative with RVEF CMR ($r = -.66$), RVEF ($r = -.40$), and mitral s' ($r = -.37$) (Figure 1).

In univariable Cox proportional hazard ratio analysis, a significantly increased hazard ratio of death was found in NT-proBNP, RVEF, RV-EDD, mitral *s*′, mitral *E*, and mitral *e*′. Interestingly, in neither mitral nor tricuspid valve was the parameter *E/e*′ significantly different (Table 3).

The step-wise AIC method of the multivariable Cox proportional hazard ratio analysis selected a model with two predictors: NT-proBNP ($P = .00048$) and mitral E ($P = .01815$) (Table 4). NT-proBNP was the most significant predictor in the univariable as well as in multivariable analysis and most of the other univariably-significant predictors were correlated with it (Figure 1), thus not significantly improving the predictions of the multivariable model. Conversely, mitral E appeared to be simultaneously predictive of mortality and sufficiently independent to NT-proBNP. Therefore, although the decrease of mitral *E* in deceased [57.00 (42.00-63.00)] compared with survivors [81.00 (67.00-104.75)] is only mildly significant ($P = .04582$; Table 2) and predicts mortality only moderately well on its own [hazard ratio 0.96 (0.93-0.99), $P = .04430$; Table 3], it contains independent information, improving predictions of the combined model.

ROC analysis for baseline NT-proBNP measurements predicting mortality gave AUC of 0.97 (Figure 2A). The expert-based cut-off 1000 pg/mL had 88% sensitivity and 95% specificity for the prediction of death and also represented the optimal operating point with sensitivity at least 80% and maximal specificity. The cut-off value of 628 pg/mL had the best sum of sensitivity (100%) and specificity (92%) and the cut-off value of 4263 pg/mL (slope-based optimal point by perfcurve) had 100% specificity and 38% sensitivity (Table 5). Using the expert based cut-off 1000 pg/mL for Kaplan–Meier analysis led to a very clear difference in survival (logrank $P < .0001$) (Figure 2C). The values of NT-proBNP over 1000 pg/mL were found mostly in deceased patients or in patients listed for transplantation (Figure 2B).

In the second best independent predictor (mitral *E*), the AUC was 0.81 and difference in survival using cut-off value of 68 cm/s was also significant ($P = .004$); however, less distinct than in the case of NT-proBNP (Figure 2D, E, F).

We have investigated how clinically useful it is to monitor the development of these two predictors of mortality over time. Patients had on average 3.1 ± 2.0 NT-proBNP measurements over the time of the study. Taking the median value compared with the baseline NT-proBNP improved AUC from 0.97 (Figure 2A, B) to 0.99 (Figure 3A, B) and similarly, median mitral *E* led to improvement from AUC 0.81 (baseline mitral *E*; Figure 2D, E) to 0.84 (median mitral *E*; Figure 3C, D). Importantly, NT-proBNP values of deceased patients were constantly high since the first measurement to their death (Figure 4), exhibiting striking and stable mortality predictions up to 6 years in advance. This shows both the potential of long-term mortality prediction even by the first NT-proBNP measurement and the importance of monitoring its values over time.

4 | DISCUSSION

Patients born with TGA had a minimal chance of survival before the Mustard and Senning operations were introduced. Presently, all patients with TGA after Mustard or Senning correction are adult and they represent one of the most frequent diagnoses among deceased adults with congenital heart disease (ACHD).[12,13] They have a relatively good quality of life, most of them being in the functional NYHA class I-II[4–8]; However, their mortality risk is increased,[14] although often not accompanied by any clear clinical deterioration. Therefore, the knowledge of parameters predicting death specifically in this group of

TABLE 4 Multivariable Cox proportional hazard ratio analysis of mortality using baseline values (using AIC model selection)

	Hazard ratio (CI)	*P* value
NT-proBNP	281.39 (13.06-6063.96)	.00048 (***)
Mitr E	0.95 (0.90-0.99)	.01815 (*)

Asterisks represent different significance levels: .001 (***), .01 (**), .05 (*) of p values.

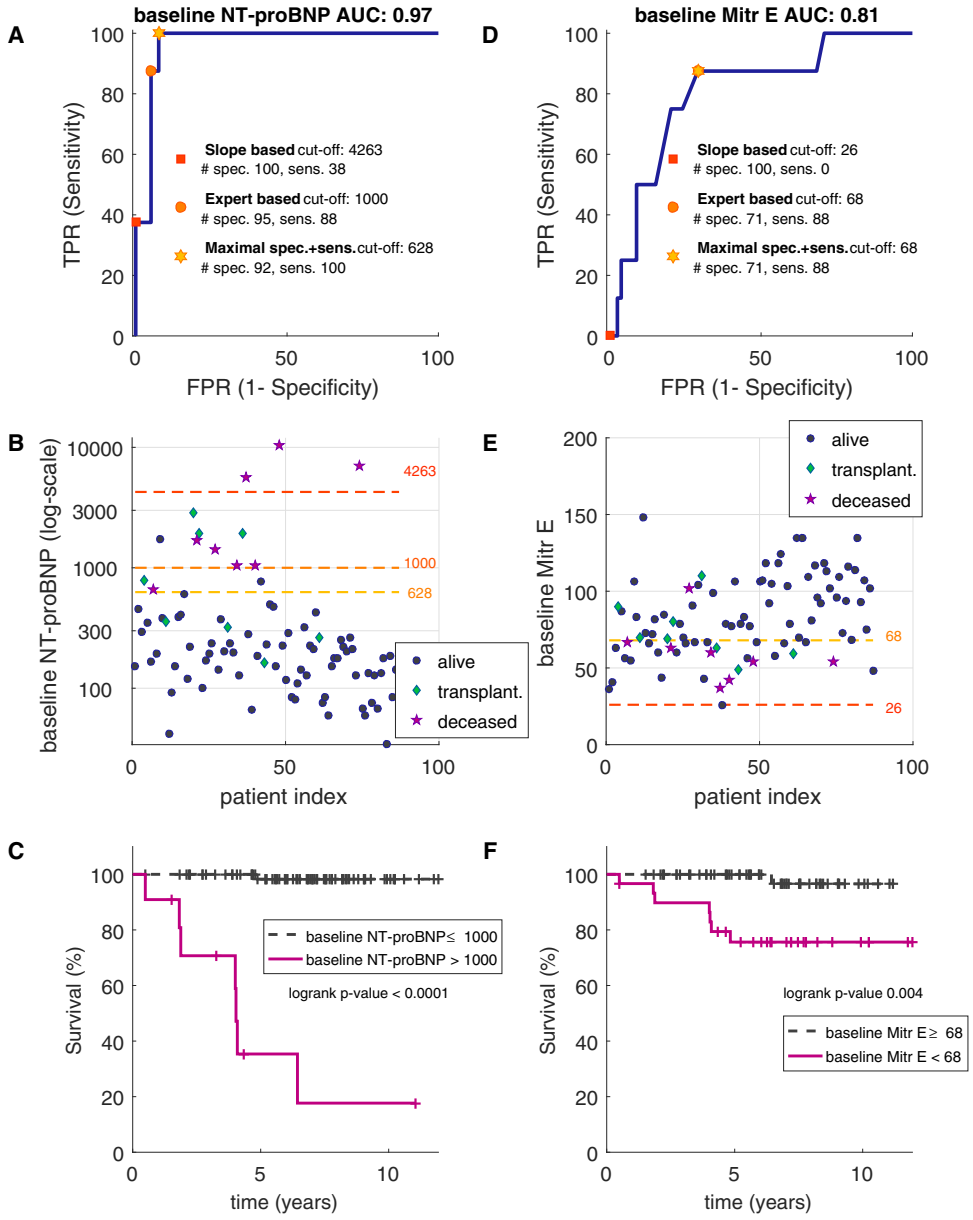

FIGURE 2 Survival analysis of patients with TGA after Mustard/Senning correction using baseline NT-proBNP (left column) and baseline mitral *E* (right column): receiver operating characteristic curve analysis (A, D), visualization of values of NT-proBNP/mitral E in survivors, deceased, and alive patients listed for heart transplantation (B, E), and Kaplan–Meier survival curves (C, F). For clarity, the y-axes in (B, E) are shown in log-scale

TABLE 5 The risk of death in adults with TGA after Mustard or Senning correction according to the level of baseline NT-proBNP with sensitivity and specificity for different cut-offs

NT-proBNP range (pg/ml)	Mortality risk	NT-proBNP cut-off (pg/mL)	Cut-off type	Sensitivity (%)	Specificity (%)
<628	Low risk (nobody died)	628	Maximal sensitivity + specificity	100	92
656-1000	Intermediate risk	1000	Expert based	88	95
1000-4263	High risk	4263	Slope based	38	100
>4263	Extremely high risk (everybody died)				

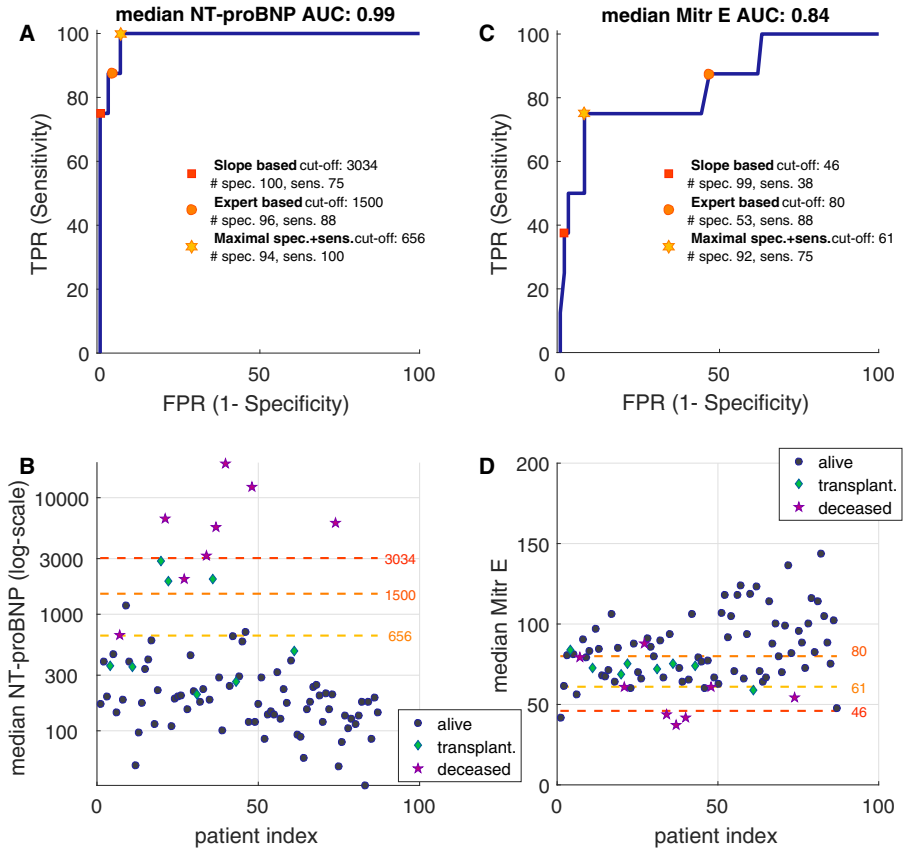

FIGURE 3 Survival analysis of patients with TGA after Mustard/Senning correction using median NT-proBNP (left column) and median mitral *E* (right column): receiver operating characteristic curve analysis (A, C), visualization of values of NT-proBNP/mitral *E* in survivors, deceased, and alive patients listed for heart transplantation (B, D). For clarity, the y-axes in (B, D) are shown in log-scale

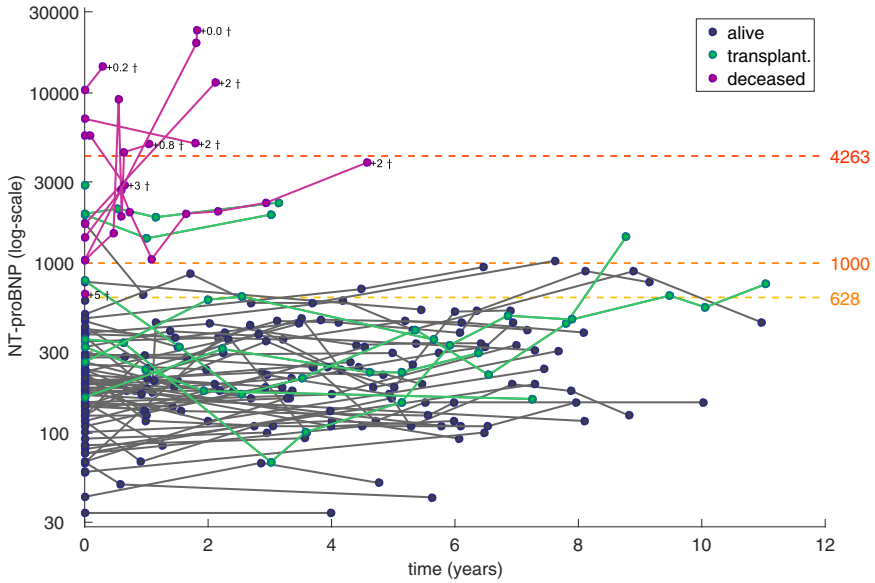

FIGURE 4 Development of NT-proBNP values over time in survivors, deceased, and alive patients listed for heart transplantation. For clarity, the y-axis is shown in log-scale. The last NT-proBNP values of the deceased patients shown in this figure represent the last NT-proBNP taken in the stable state during outpatient visit. The next values of NT-proBNP during hospitalization or after enlisting for transplantation are not shown in this figure and they were not analyzed in this study. The median follow-up of the deceased patients until their death was 4 years. That is not clearly apparent from this graph because of the abovementioned reasons. The time since last measurement till death is indicated by the small black number (years) next to the last measurement

patients is important for all cardiologists who may take care of them and mortality studies in this group are needed.

4.1 | *Mortality prediction—NT-proBNP*

Multivariable analysis in our study showed that NT-proBNP is the best independent predictor of mortality. These findings are in agreement with our previous study which assessed mortality risk for the whole large cohort of all types of ACHD.[12] Giannakoulas et al. were the first to assess cut-off values of natriuretic peptides for mortality prediction in ACHD in a small group of 49 patients. The number of patients was too small to specify the risk for individual diagnosis.[13] Other authors who studied prognostic factors in patients with TGA after Mustard or Senning correction found the importance of natriuretic peptides for the combined endpoints of mortality, transplantation and heart failure or hospitalization.[4,5] The numbers of deaths in these studies were insufficient to evaluate mortality alone.

A possible explanation of the predictivity of NT-proBNP may lie in the observation that BNP (for which is NT-proBNP a surrogate) is secreted predominantly in the setting of elevated cardiac wall stress, for example, to pressure overload.[15] An increased cardiac wall stress after atrial switch operation may be due to the increase in afterload found in patients after Mustard and Senning operations.[14] Pressure and volume overload of the systemic right ventricle may subsequently progress into myocardial dilation and heart failure when mechanisms compensating for the increased wall stress are exhausted.[16] I.e., high secretion of BNP may indicate the presence of uncompensated wall stress which will eventually cause heart failure via cardiac remodeling, but the BNP and thus also NT-proBNP will have been elevated before the start of the actual remodeling. Our study suggests that the predictive power of NT-proBNP is surprisingly long-term, as the deceased patients had greatly elevated levels of NT-proBNP several (a median of 4) years before the death, at time when they have not manifested deterioration or markers of poor prognosis.

4.2 | *Mortality prediction—NYHA class*

In our study, NYHA predicted mortality neither in univariable, nor in multivariable analysis. In the study of Westhof-Bleck et al., NYHA predicted the combined endpoint (heart failure, transplantation, and death) in multivariable analysis.[4] The majority of patients after Mustard or Senning correction are in functional class I-II.[4,5,17] They adjust their life-style, reduce physical activities, and do not report many problems until the manifest heart failure or arrhythmia occur. According to our study, NYHA class I-II does not warrant a positive long-term clinical outcome in contrast to low values of NT-proBNP.

4.3 | *Mortality prediction—systemic right ventricular function and tricuspid valve*

RVEF was predictive of death in univariate, but not in multivariate analysis in our study. Similar results were found in the study of Westhoff-Bleck et al.[4] Even though the systemic right ventricle and tricuspid valve function are believed to be the most important factors in TGA/atrial switch patients,[14] our data does not support their significance for mortality prediction. Interestingly, neither the Doppler and tissue Doppler parameters of the systemic tricuspid valve, nor the degree of tricuspid regurgitation were significantly predictive of mortality in our cohort.

In other studies with systemic left ventricle, the tissue Doppler derived parameter E/e' was shown to be an independent predictor of mortality in different clinical situations.[18–20] However, we did not observe such a prognostic value in patients after Mustard/Senning correction in the systemic right ventricle with tricuspid valve.

4.4 | *Mortality prediction—subpulmonary left ventricular function and mitral valve*

On the contrary, the parameters of the mitral valve in the subpulmonary left ventricle showed better prognostic value: mitral s', mitral e', and mitral E were significantly predictive in the univariate analysis. Moreover, the low mitral early diastolic filling velocity E (in the subpulmonary ventricle) was also significant in multivariable analysis. The cut-off $\leq$68 cm/s was predictive of mortality. This may be surprising, but corresponds well with the findings of Reich et al. almost 20 years ago.[21] He found abnormal left ventricular filling in 80% of patients after Mustard or Senning correction. This was caused not only by the diastolic properties of the ventricle, but mainly by the properties of the intra-atrial baffles. The left ventricular peak filling rate deteriorated with time.[21] Impaired left ventricular diastolic filling and inability to increase the flow over the intra-atrial baffle was considered a major factor in the inability to increase cardiac output on exercise in Mustard and Senning patients.[21]

Atrial function in TGA was studied also by CMR.[22] Franzoso et al. found diminished passive emptying fraction and loss of the atrial capacity to convert continuous venous flow into pulsatile ventricular filling.[22] Reduced atrial filling capacity detected by Doppler jugular venous flow velocity was described already in 1980 with more pronounced changes in the Mustard patients compared with the Senning patients.[23] The Mustard patients had significantly lower mitral E compared with the Senning patients in our study as well.

Slow early diastolic filling may reflect rigid intra-atrial baffles and increased pressure in the surrounding pulmonary venous atrium due to the tricuspid regurgitation. The low flow in systemic venous baffle decreases left ventricular systolic output. The significance of the low mitral E velocity for mortality prediction has to be confirmed in larger studies. However, besides NT-proBNP, it could represent a simple and easily accessible marker of adverse prognosis.

4.5 | *Mortality prediction—pacemaker*

In the study by Vejlstrup et al., the only prognostic factor in long-term survival of Mustard and Senning patients was the need of PM implantation.[14] We did not observe such a phenomenon among our patients. The rate of PM implantation was very similar among survivors and deceased. Patients after Senning correction had more PM than Mustard patients, probably due to more extensive atrial surgery. In patients

with severe right ventricular systolic dysfunction and the need of PM, we believe that the biventricular PM/ICD device with epicardial leads might be useful.

4.6 | Correlations

In our study NT-proBNP significantly correlated with NYHA class, RVEF, RV-EDD, and mitral *s′*. The association of natriuretic peptides with NYHA class and functional parameters and volumes of the systemic right ventricle in patients with TGA after atrial switch were described previously.[6,7,17,24–26] Similarly to Eindhoven et al., we have not found NT-proBNP to be significantly correlated with the Doppler parameters of the systemic right ventricle.[7] Larsson with co-authors expected low clinical value of natriuretic peptides because of their lack of relationship to ventricular function or exercise capacity.[26] On the contrary, our study has shown that NT-proBNP itself has higher mortality prognostic value compared with NYHA or ventricular function even for patients with systemic right ventricle.

In patients with TGA/atrial switch, the parameters of the systemic right ventricle and the tricuspid valve were historically considered the most important. However, our study is the first one to show the importance of the parameters of the subpulmonary left ventricle. The correlation of mitral systolic annular velocity *s′* with NT-proBNP was significant. This fact might be useful in estimating mortality risk in patients without NT-proBNP measurements. Furthermore, the significance of mitral *E* in the multivariate analysis including NT-proBNP suggests that mitral *E* provides information on patient risk beyond the correlation with NT-proBNP.

5 | LIMITATIONS OF THE STUDY

The main limitation of our study is the fact that CMR was performed in 18% of patients only. Similarly, the maximal aerobic exercise capacity was assessed in 44% of patients and moreover in the survivors only. Therefore, the correlations of these parameters with other variables are not reliable and the importance can be underestimated. These limitations are due to the retrospective character of our study. In echocardiographic evaluation we had not performed global longitudinal strain in those patients who died, therefore we cannot evaluate this parameter in our retrospective mortality study.

6 | CONCLUSION

In our study, the best independent predictor of mortality in patients with TGA after Mustard or Senning correction was NT-proBNP. The level of NT-proBNP stratified patients according to the mortality risk: low risk below 628 pg/mL and high risk above 1000 pg/mL. The NYHA class or echocardiographic parameters were not significantly predictive in multivariable analysis except for the early diastolic filling of the subpulmonary ventricle (mitral *E*). Mitral *E* was another significant predictor of death in multivariable analysis and patients with mitral *E* below 68 cm/s had significantly worse survival rate.

In conclusion, natriuretic peptides should be tested regularly in patients with TGA after atrial switch operation. Echocardiographically, not only the systolic function of the systemic right ventricle should be evaluated, but also the early diastolic filling velocity of the subpulmonary left ventricle might be also important.

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Concept/Design: J.R.P.; Data collection: J.R.P.; Data analysis and statistics: M.T. and J.T.; Results interpretation and drafting article: J.R.P., J.T., and M.T.

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