Cardiology in the Young

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Correlation between non-invasive to invasive right-heart data in paediatric heart transplant patients

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Original Article

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Abstract

Background: Paediatric studies have shown serum N-terminal pro b-type natriuretic peptide levels to be a valuable tool in the surveillance of myocardial function and an early biomarker for rejection in transplant patients. The correlation between low mean right atrial pressure and increased inferior vena cava collapsibility index is well studied in adults. Our study aims to assess correlation between non-invasive measurements (serum N-terminal pro b-type natriuretic peptide, inferior vena cava dimensions collapsibility, tricuspid regurgitation, and left ventricular remodelling index to invasive mean right atrial pressure in paediatric heart transplant patients). *Methods:* A single centre, retrospective chart review of the paediatric transplant patients from 0 to 21 years of age was performed between 2015 and 2017. Thirty-nine patients had complete data which includes cardiac catheterisation, transthoracic echocardiogram, and serum N-terminal pro b-type natriuretic peptide levels done within a two weeks of interval. *Results:* A higher inferior vena cava collapsibility index correlated with a lower mean right atrial pressure ($r = -0.21$, $p = 0.04$) and a larger inferior vena cava diameter in expiration indexed to body surface area (IVCmax/BSA0.5) correlated with a higher mean right atrial pressure ($r = 0.29$, $p = 0.01$). There was a correlation between elevated N-terminal pro b-type natriuretic peptide and inferior vena cava collapsibility index ($r = -0.38$, $p = 0.0001$), IVCmax/BSA0.5 ($r = 0.25$, $p = 0.0002$), and mean right atrial pressure ($r = 0.6$, $p = 0.0001$). *Conclusion:* Serum N-terminal pro b-type natriuretic peptide levels correlated to non-invasive measurements (inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$) and to the invasive mean right atrial pressure. Non-invasive (IVC-CI IVCmax/BSA$^{0.5}$) correlates with elevated mean right atrial pressure in this population. Together, these may serve as a reliable surveillance tool in assessing right heart filling pressures and cardiac function within the paediatric heart transplant patient.

Adult studies have demonstrated excellent correlations between the inferior vena cava collapsibility index and mean right atrial pressure, while paediatric data are less robust and even less conclusive.[1–7] Inferior vena cava diameter and degree of inspiratory collapse are used as echocardiographic indices in the estimation of right atrial pressure (RAP). Limited paediatric data are available in the intensive care setting, with the clinical goal of non-invasive inferior vena cava measurements aiding in the detection and management of hydration status. Neonates have shown a strong correlation between simultaneous echocardiogram measurements of inferior vena cava collapsibility index with central venous pressures measured from an umbilical venous catheter.[8–10] In older paediatric patients, Babaie et al showed negative correlation between inferior vena cava collapsibility index and mean right atrial pressure, while Ng et al showed no correlation.[11,12] Arya et al studied non-invasively to assess right-heart haemodynamics in paediatric pulmonary hypertension and cardiac transplant patients. They found that inferior vena cava collapsibility index did not correlate with mean right atrial pressure, while there was a modest relationship between inferior vena cava maximum diameter indexed to body surface area (IVCmax/BSA$^{0.5}$) and mean right atrial pressure.[13] These are the only data in the literature on paediatric heart transplant patients. Brain natriuretic peptide are established biomarkers of myocardial wall stress. Paediatric studies have shown serum NT-pro-BNP as a tool in surveillance of myocardial function and an early biomarker for evaluation of rejection in transplant patients. Given the paucity in the literature, we aimed to assess the correlation between non-invasive measurements (inferior vena cava dimensions and collapsibility, tricuspid regurgitation, left ventricular remodelling index, and serum NTproBNP to invasive mean right atrial pressure in paediatric heart transplant patients.

Methods

A retrospective, single centre, chart review of paediatric heart transplant patients from 0 to 21 years of age was performed. We identified the post-transplant cohort from our institutional

paediatric cardiology database. Institutional review board approval was granted. We identified patients who underwent cardiac catheterisation and echocardiogram within a maximum two week interval between June 2015 and June 2017 ("cath/echo encounter"). Patient demographics, indication for transplantation, postoperative course, and the time interval between the echocardiogram and catheterisation were collected. Cardiac catheterization data included the mean right atrial pressure, endomyocardial biopsy results, ventilation type during the procedure, and serum N-terminal pro b-type natriuretic peptide collected at the time of the catheterisation. The endomyocardial biopsy results were classified based on the International Society for Heart and Lung Transplantation.[14] Rejection is identified as grade 2R or higher or requiring augmentation of immunosuppressive therapies.[14] Our institutional inpatient cut-off point of 450 ng/dL was used to define an abnormal N-terminal pro b-type natriuretic peptide for confirming diagnosis of congestive heart faliure (CHF).

The echocardiographic studies were performed in the outpatient clinic with the patient spontaneously breathing, utilising a Phillips iE33ultrasound machine (Andover, Massachusetts) equipped with 5-, 8-, 12-MHz transducers. Standard echocardiographic imaging was performed by multiple sonographers. A retrospective measurement of the inferior vena cava diameter during inhalation (IVCmax) and the inferior vena cava diameter during exhalation (IVCmin) was obtained in the subcostal long axis, approximately 1 cm below the right atrium-inferior vena cava junction. Inferior vena cava diameter in inhalation was indexed to the patient's body surface area$^{0.5}$ per American Society of echocardiography paediatric guidelines.[15] Inferior vena cava collapsibility index was calculated: (IVCmax - IVCmin) / IVCmax. On two separate occasions, a single reviewer analysed the inferior vena cava measurements for all patients to account for intra-observer variability. The reviewer was blinded to clinical and haemodynamic data. Pulse-wave Doppler across the tricuspid valve was used to estimate the tricuspid regurgitation jet gradient using a modified Bernoulli equation. Tissue Doppler assessment was used to calculate the left ventricle remodelling index. Patients were excluded from the study if images of the inferior vena cava in the subcostal long axis during inhalation and exhalation were suboptimal and measurements could not be obtained.

Statistical analysis

The intraclass correlation coefficient was used to measure inter-reviewer reliability. An average of the reviewers' two data sets collected was used for statistical analysis. The relationships between mean right atrial pressure and inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$ were examined with linear models fit using generalised estimating equations to account for repeated measures. To assess whether clinical indication for heart transplant, type of anaesthesia used during catheterisation, and rejection status based on catheterisation biopsy pathology influenced these relationships, interaction tests from similar generalised estimating equations models that included inferior vena cava collapsibility index or IVCmax/BSA$^{0.5}$ by group interaction terms were used. Pearson's correlation coefficient (Pearson's r) was used to analyse the bivariable relationship between mean RAP and echocardiogram data including inferior vena cava collapsibility index, IVCmax/BSA, left ventricular remodelling index, and tricuspid regurgitation jet gradient. Within-cluster resampling was used to estimate correlations between serum NT proBNP and mean RAP, inferior vena cava collapsibility index, and IVC max/BSA$^{0.5}$ while accounting for repeated measures.[16] Serum N-terminal pro b-type natriuretic peptide was log-transformed prior to analysis. We analysed the sensitivity and specificity of using inferior vena cava collapsibility index of $\geq$0.5 to predict a mean right atrial pressure of $\leq$8 mmHg, based on previous paediatric literature investigating non-invasive inferior vena cava measurements accuracy in detecting and managing dehydration.[11,12] To evaluate multiple variables' ability to predict mean right atrial pressure, we fit a generalised estimating equations linear model of mean right atrial pressure with serum N-terminal pro b-type natriuretic peptide, inferior vena cava collapsibility index, IVC max/BSA$^{0.5}$, and their interactions, with backward elimination using the quasi-likelihood Akaike information criterion to select a final model that included serum N-terminal pro b-type natriuretic peptide, max/BSA$^{0.5}$, and their interaction. Analyses were conducted using R version 3.6.1 including the packages geepack version 1.3-1, pROC version 1.15.3, and irrNA version 0.1.4.[17–20]

Results

Patient characteristics

Forty-six patients with 106 cath/echo encounters were identified from the institutional paediatric cardiology database. Complete data were available in 39 patients who had 75 cath/echo encounters which formed the study cohort (Fig 1). Age ranged from 8 months to 18 years (mean 10.2 years ± 5.6 years) and 59% (n = 23) of patients were male. Patient indications for cardiac transplantation included complex CHD (n = 23, 59%), cardiomyopathy (n = 15, 38%), and myocarditis (n = 1, 3%) (Fig 1). Of the 75 cardiac catheterisations performed, general anaesthesia with positive pressure ventilation was used in 49% of the cases, and no general anaesthesia with spontaneous breathing (no general anaesthesia with positive pressure ventilation) was used in 51% of the cases. The mean time between cardiac catheterisation and echocardiogram was 2.6 days. The mean time between cardiac transplant and catheterisation was 4.8 years (± 4.7 years) and ranged from 6 days to 20.2 years (Table 1).

Cardiac catheterization data

The mean right atrial pressure was 8.5 mmHg (range 1–25 mmHg). Seventeen (23%) had mean right atrial pressure $\leq$5 mmHg, 39 (52%) had mean right atrial pressure 6–10 mmHg, and 19 (25%) had mean right atrial pressure >10 (Table 2a). Of the 75 encounters, 67 had biopsies and 5 biopsies (7%) showed signs of rejection on pathology (Table 2a).

Echocardiography data

Table 2a summarises the results of the inferior vena cava measurements, left ventricular remodelling index, and tricuspid regurgitation jet gradient. The results are an average of the two data sets collected by the single blinded reviewer. An intra-class correlation coefficient was used to measure intra-reviewer reliability and found excellent reliability for the raw measurements of the inferior vena cava (intra-class correlation coefficient 0.96).

Relation of Cath/Echo measurements

In our cohort statistical analysis demonstrated that a higher inferior vena cava collapsibility index was associated with a lower mean right atrial pressure ($r = -0.21$, $p = 0.04$), and a higher IVCmax/BSA$^{0.5}$ was associated with higher mean right atrial

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Table 1. Patient data

Patients	n = 39
Male patients	23 (59%)
Unique cath/echo encounter	n = 75
Mean age at cath/echo encounter	10.2y ± 5.6 years (range 0.67–18 years)
Mean time between cath and echocardiogram	2.6d ± 3.4 days (range 0–14 days)
Mean time between cardiac transplant and cath	4.8 ± 4.7 years (range 6 days – 20.2 years)

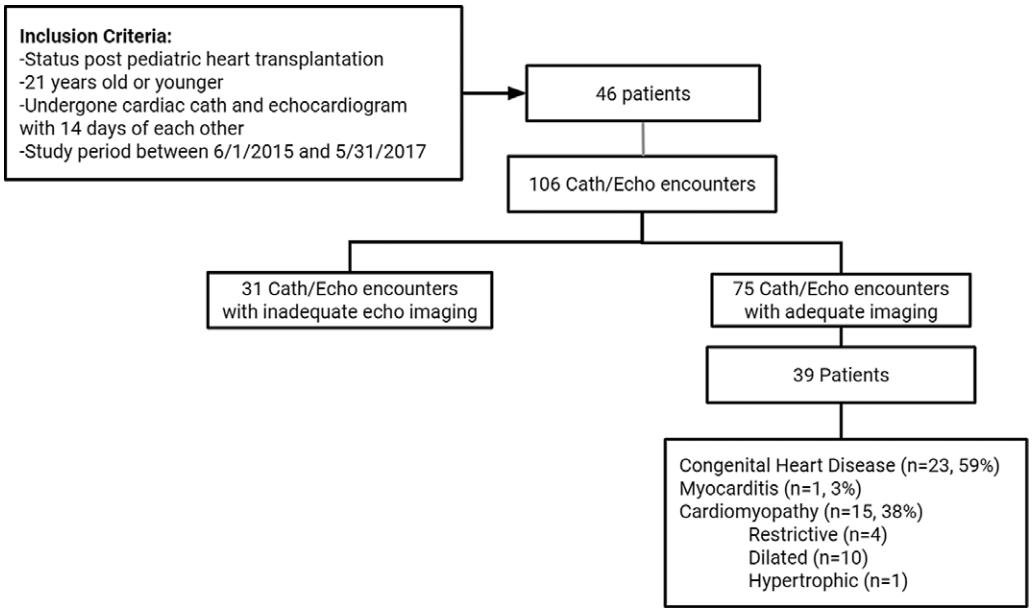

Figure 1. Study population.

pressure (r = 0.29, p = 0.01) (Fig 2a, 2b). There was no correlation between tricuspid regurgitation jet gradient and mean right atrial pressure or left ventricular remodelling index and mean right atrial pressure. Elevated serum N-terminal pro b-type natriuretic peptide correlated with inferior vena cava collapsibility (r = −0.38, p = 0.0001), IVCmax/BSA$^{0.5}$ (r = 0.25, p = 0.002), and mean right atrial pressure (r = 0.6, p < 0.0001) (Fig 2e, 2f, 2g).

We further analysed the sensitivity and specificity of a threshold inferior vena cava collapsibility index of ≥0.5 to predict a mean right atrial pressure of ≤8 mmHg (Table 2b). This threshold was chosen based on previous paediatric studies that aimed to predict dehydration using inferior vena cava dimensions.[11,12] An inferior vena cava collapsibility index threshold of 0.5 gives high specificity (if mean right atrial pressure >8 mmHg, probability that inferior vena cava collapsibility index <0.5) of 97% but very poor sensitivity (if mean right atrial pressure ≤8 mmHg, probability inferior vena cava collapsibility index ≥0.5) of 14%. We further assessed other inferior vena cava collapsibility index thresholds' ability to predict a mean right atrial pressure of ≤8 mmHg with better sensitivity and specificity (Fig 2d). The receiver operating characteristic curve shows that there is not an inferior vena cava collapsibility index threshold that will be both a sensitive and specific predictor of mean right atrial pressure ≤8 mmHg. Next we examined whether using multiple predictors together could improve our ability to predict mean right atrial pressure, with N-terminal pro b-type natriuretic peptide, inferior vena cava collapsibility index, and IVCmax/BSA$^{0.5}$ used as candidate predictors in a multiple regression model. The best model included N-terminal pro b-type natriuretic peptide, IVCmax/BSA$^{0.5}$ and their interaction is seen in the equation:

$$predicted\ mRAP = 14.32 - 16.49 \times IVC/BSA^{0.5} - 1.55 \times \log(NTproBNP) + 3.12 \times IVC/BSA_{0.5} \times \log_e(NTproBNP)$$

Figure 2c shows a contour plot that demonstrates predicted mean right atrial pressure from this model along with observed mean right atrial pressure values. The model explained 57% of the total variance in mean right atrial pressure, better than using serum N-terminal pro b-type natriuretic peptide alone (p = 0.009) or IVCmax/BSA$^{0.5}$ alone (p < 0.0001). However, substantial prediction uncertainty remains; for example, for an average patient with serum N-terminal pro b-type natriuretic peptide = 562 & IVC/BSA$^{0.5}$ = 1.059, predicted mean right atrial pressure is 7.9, with an 80% prediction interval of (3.7, 12.2) and a 95% prediction interval of (1.4, 14.5).

Discussion

In our retrospective analysis of paediatric heart transplant patients, we studied the relationship between non-invasive measurements (inferior vena cava dimensions and collapsibility,

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Table 2. (a) Catheterisation and echocardiogram data, (b) performance parameters of IVC-CI ≥0.5 as a predictor of mean right atrial pressure ≤8 mmHg

a	
Catheterization data	**n = 75 encounters**
mRAP (mmHg)	8.5 ± 4.8 (range 1–25)
mRAP ≤5 mmHg	17 (23%)
mRAP 6–10 mmHg	39 (52%)
mRAP >10	19 (25%)
Pathology Results from Biopsy	**n = 75 encounters**
No biopsy performed	n = 8
Indeterminate	n = 1
No rejection	n = 61
Rejection	n = 5
Echo data	**n = 75 encounters**
IVCmax (cm)	1.08 ± 0.37 (range 0.48–2.05)
IVCmin (cm)	0.84 ± 0.36 (range 0.28–1.75)
IVCmax/BSA	1.02 ± 0.4 (range 0.37–2.56)
TR jet gradient (mmHg)	23.4 ± 9.1 (range 7–58)
LVRI	1.1 ± 0.5 (range 0.4–2.7)
b	
	IVC-CI ≥0.5
Sensitivity	97% (30/31)
Specificity	14% (6/44)
PPV	86% (6/7)
NPV	44% (60/68)

PPV = positive predictive value; NPV = negative predictive value.

tricuspid regurgitation, left ventricular remodelling index and serum N-terminal pro b-type natriuretic peptide to invasive mean right atrial pressure. Serum N-terminal pro b-type natriuretic peptide is a neurohormone secreted from the ventricles in response to ventricular volume or pressure overload.[21,22] In adult heart failure patients, there has been a positive correlation between inferior vena cava diameter and NT-proBNP.[23,24] Paediatric studies have shown N-terminal pro b-type natriuretic peptide being a good predictor of the presence of congestive heart failure,[25,26] and rising serum N-terminal pro b-type natriuretic peptide in a patient is associated with increased risk of rejection. There are also associations between elevated serum N-terminal pro b-type natriuretic peptide and elevated filling pressures on cardiac catheterisations, as well as decreased ejection fraction on echocardiogram.[25,27] Both serum N-terminal pro b-type natriuretic peptide and echocardiography data are routinely used in the inpatient and outpatient management with rejection in heart transplant patients. The greatest use appears to be in following trends for an individual instead of using an absolute value. Our study, in addition to supporting previous literature on associations between elevated N-terminal pro b-type natriuretic peptideth elevated mean right atrial pressure, also adds to the paediatric literature in showing a modest positive correlation between N-terminal pro b-type natriuretic peptide with inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$.

Pediatric literature on the correlation between inferior vena cava measurements and mean right atrial pressure is limited and inconclusive. The majority of paediatric studies focus on inferior vena cava measurements to guide clinical decision making on volume status. While studies have found strong correlations between inferior vena cava collapsibility index and mean right atrial pressure, they failed to see a relationship between IVCmax and mean right atrial pressure.[8-10] Ng et al and Babaie et al have evaluated the correlations between the inferior vena cava collapsibility index and mean right atrial pressure, as well as identifying an inferior vena cava collapsibility index threshold that would predict a mean right atrial pressure ≤8 mmHg to suggest dehydration. The two studies offered mixed results. Ng et al showed a strong linear correlation between inferior vena cava collapsibility index and mean right atrial pressure, while Babaie et al showed no correlation. Both showed a low sensitivity and high specificity of using an inferior vena cava collapsibility index of ≥0.5 to predict a mean right atrial pressure of ≤8 mmHg.[11,12] Our data showed a low sensitivity and high specificity when using inferior vena cava collapsibility index of ≥0.5 to predict a mean right atrial pressure of ≤8 mmHg. We also demonstrated that there was no acceptable number for the inferior vena cava collapsibility index that would confidently predict with good sensitivity and specificity for a low mean right atrial pressure, demonstrated by the receiver operating characteristic curve in (Fig 2d). We also observed a modest negative correlation between inferior vena cava collapsibility index and mean right atrial pressure and a modest positive correlation between a IVCmax/BSA$^{0.5}$ and mean right atrial pressure. We did not observe a clear correlation between mean right atrial pressure and other echocardiogram measurements which include tricuspid regurgitation jet and left ventricular remodelling index. This is the first paediatric study to find correlations between mean right atrial pressure with both inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$.

Arya et al performed a prospective study in paediatric patients with pulmonary artery hypertension or post-cardiac transplant, focusing on inferior vena cava measurements guiding clinical decision making on right-heart haemodynamics. Patients underwent simultaneous catheterisation and echocardiograms. They demonstrated a correlation between IVCmax/BSA$^{0.5}$ and mean right atrial pressure, but failed to see a relationship between inferior vena cava collapsibility index and mean right atrial pressure.[13] Our study, evaluating a similar population with interest in right-heart haemodynamics, also found a correlation between mean right atrial pressure and IVCmax/BSA$^{0.5}$, and additionally saw a correlation between mean right atrial pressure and inferior vena cava collapsibility index. We believe the correlation being higher in our patient population is likely explained by the higher mean right atrial pressures noted in our cohort (8.5 ± 4.8 versus 6.7 ± 3.6 in Arya et al paper). This is also reflected in higher proportion in our cohort with a mean RA pressure greater than 5 mmHg (77% in our cohort versus 38% in Arya et al).

Clinical implications

Serum N-terminal pro b-type natriuretic peptide widely used as a marker for myocardial function, and serial monitoring is widely performed to monitor for rejection. Echocardiographic measurements like inferior vena cava collapsibility index and inferior vena cava diameter/BSA can provide additional clinical information along with N-terminal pro b-type natriuretic peptide levels to monitor cardiac function and rejection in heart transplant patients. With our data we have demonstrated correlation between serum N-terminal pro b-type natriuretic peptide, inferior vena cava

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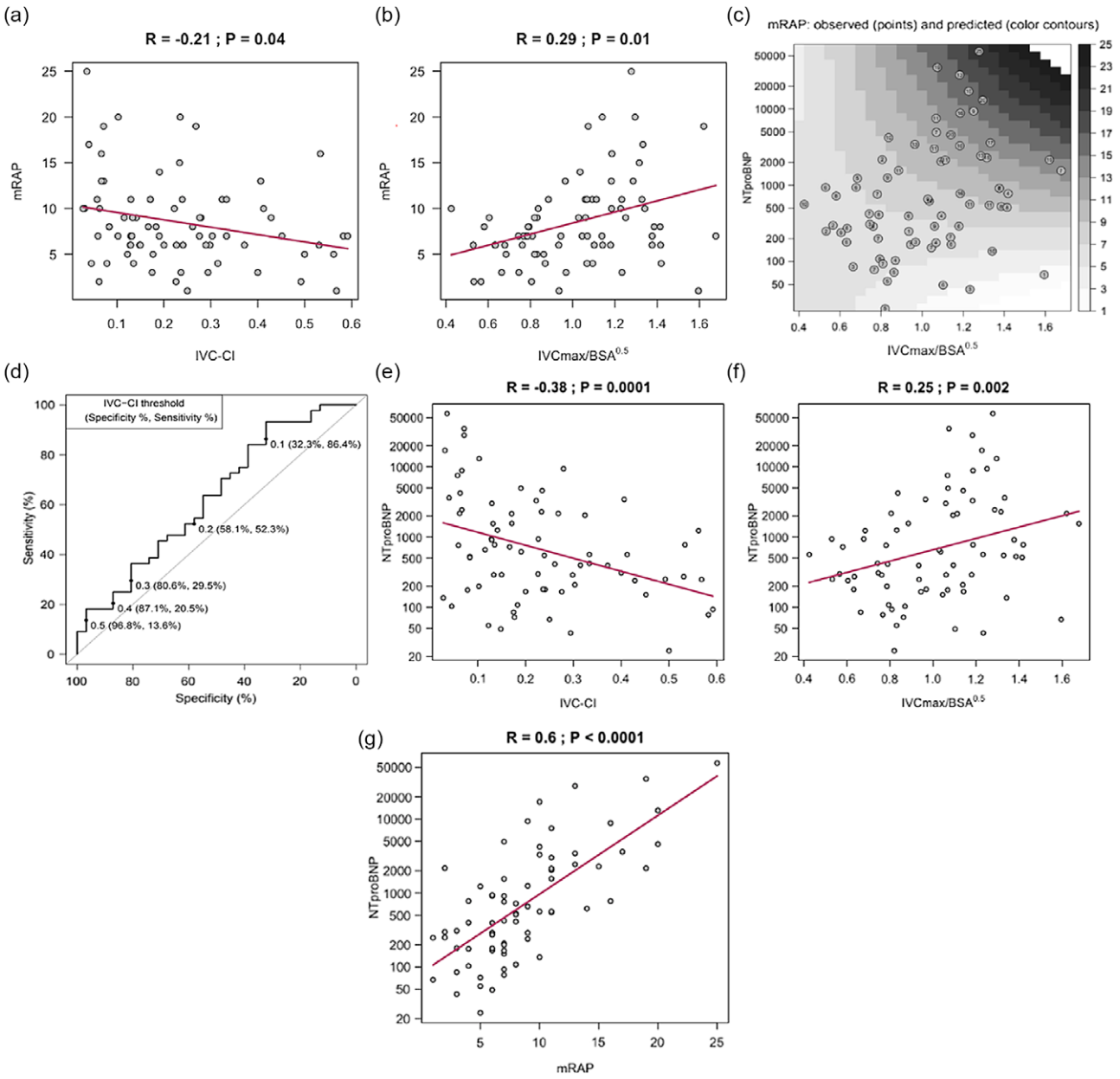

Figure 2 (***a***, ***b***). Associations between mRAP with IVC-CI and IVCmax/BSA0.5. (***c***) Contour plot showing predicted mRAP from a model using NTproBNP and IVCmax/BSA0.5 along with observed mRAP values. (***d***) ROC curve assessing the sensitivity and specificity of varying IVC-CI thresholds to predict mRAP ≤ 8mmHg. (*e-g*) Associations between NTproBNP with IVC-CI, IVCmax/BSA0.5, and mRAP.

collapsibility, and IVC/BSA$^{0.5}$ with mean right atrial pressure, which could offer an extra data point, in conjunction with laboratory, clinical, and more accepted echocardiogram measurements to completely assess cardiac transplant patients in outpatient and inpatient setting. Within the cardiac transplant population, knowledge of mean right atrial pressure offers a better understanding of right heart and pulmonary haemodynamics and oftentimes left-heart haemodynamics. Paediatric intensive care and emergency medicine clinicians are interested in elevated inferior vena cava collapsibility index to detect hydration status, while cardiac transplant clinicians are interested in a decreased inferior vena cava collapsibility index to detect poor ventricular compliance. The former assumes normal ventricular compliance, while the latter assumes a history of abnormal compliance, which in turn could signal diastolic dysfunction or graft rejection in this patient population. With this dichotomy in mind, a study on cardiac transplant patients should be used to inform clinical decisions being made on cardiac transplant patients, and hence our data should be cautiously interpreted outside of the paediatric heart transplant population. There is clinical benefit to a non-invasive technique estimating right heart filling pressures. By combining measurements from echocardiogram and blood draw we can obtain more accurate estimates of right heart filling pressure; however the level of uncertainty in these estimates remains too large to use it as an accurate surrogate for measured mean right atrial pressure.

Limitations

This was a retrospective analysis of catheterisation and echocardiogram data. All echo data were obtained while the patient

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was spontaneously breathing, while the catheterisation data varied. A prospective design would control for the timing between non-invasive and invasive measurements. It would also allow for collection of additional echocardiography measurements – including right atrial volume, systolic filling fraction of hepatic vein velocity, aorta dimensions – outside of our protocol that other studies have used to find relationships with mean right atrial pressure.[4,11–13,28] Echocardiographic measurements and cardiac catheterisation data were not simultaneously obtained on the same day and the haemodynamic state in an awake child is very different but given the fact that most echocardiograms in this patient population will be done awake, we think this study will help identify echo variables through outpatient echocardiogram that may predict invasive haemodynamic data in this patient population. Future prospective research needs to be undertaken to further analyse this relationship.

There is also significant heterogeneity within the cohort of cardiac transplant patients studied. The duration and type of pretransplant physiology has theoretic effects on inferior vena cava histology and elasticity. It is unknown if this physiology may affect inferior vena cava collapsibility in a similar way to adult studies that showed age-related decreases in maximum inferior vena cava diameter and increases in inferior vena cava collapsibility index.[29] We understand these limitations and a larger study group would allow for more complete data and the ability to better divide patients into specific subsets based on the pretransplant physiology.

Conclusion

Our study showed a correlation between the serum N-terminal pro b-type natriuretic peptide levels to non-invasive measurements (inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$) and to the invasive mean right atrial pressure. Echo parameters of inferior vena cava collapsibility index and IVCmax/BSA$^{0.5}$ in conjunction with N-terminal pro b-type natriuretic peptide are reliable tools for surveillance in assessing right heart filling pressures and cardiac function within the paediatric heart transplant population.

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Conflicts of interest. None.

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