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Utility of biomarkers in adult Fontan patients with decompensated heart failure

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Abstract

Background: The incidence of heart failure is increasing within the Fontan population. The use of serological markers, including B-type natriuretic peptide, has been limited in this patient population. *Methods:* This was a single-centre retrospective study of Fontan patients in acute decompensated heart failure. Fontan patients underwent a 1:2 match with non-Fontan patients for each heart failure hospitalisation for comparative analysis. A univariate logistic regression model was used to assess associations between laboratory and echocardiographic markers and a prolonged length of stay of 7 days or greater. *Results:* B-type natriuretic peptide levels were significantly lower in Fontan patients admitted for heart failure than that in non-Fontan patients [390.9 (±378.7) pg/ml versus 1245.6 (±1160.7) pg/ml, respectively, $p < 0.0001$] and were higher in Fontan patients with systemic ventricular systolic or diastolic dysfunction than that in Fontan patients with normal systemic ventricular function [833.6 (±1547.2) pg/ml versus 138.6 (±134.0) pg/ml, $p = 0.017$]. The change from the last known outpatient value was smaller in Fontan patients in comparison with non-Fontan patients [65.7 (±185.7) pg/ml versus 1638.0 (±1444.7) pg/ml, respectively, $p < 0.0001$]. Low haemoglobin and high blood urea nitrogen levels were associated with a prolonged length of stay. *Conclusion:* B-type natriuretic peptide levels do not accurately reflect decompensated heart failure in Fontan patients when compared to non-Fontan heart failure patients and should, therefore, be used with caution in this patient population.

The rate of survival into adulthood in babies born with univentricular heart defects and subsequently palliated by the Fontan operation has dramatically increased over the past several decades.[1,2] Despite these favourable mid-term outcomes, the expected trajectory to late adulthood for Fontan patients is less encouraging as they eventually develop many of the Fontan-related comorbidities such as arrhythmias, systemic venous congestion, and liver fibrosis and cirrhosis. Although this disease course is well described and expected by care providers, its insidious propagation makes impending Fontan failure difficult to recognise and manage in a timely manner.[3] Unlike systolic heart failure in patients with anatomically normal hearts, the systemic ventricle in a failing Fontan circulation is often under-filled, while the central venous pressures are chronically elevated, independent of the cardiac index.[3] Correspondingly, there is a relatively low incidence of significant systolic ventricular dysfunction, which further distinguishes these patients from those with anatomically normal hearts.[4–6] Decompensated heart failure in Fontan patients is driven by a reduction in pulmonary blood flow as opposed to a drop in the systemic cardiac output. In clinical practice, risk stratification and volume assessment in heart failure patients are evaluated not only by means of physical examination and imaging but also by obtaining relevant laboratory biomarkers. B-type natriuretic peptide, a marker of myocardial stretch and elevated cardiac filling pressures, is frequently used for these purposes in the general heart failure population.[7] Although serum levels of B-type natriuretic peptide were shown to be elevated in Fontan patients, its clinical utility at the time of acute decompensation is variable, and its prognostic ability remains in question.[8–10] In this study, we, therefore, sought to characterise the biomarker profile of Fontan patients hospitalised for acute decompensation and to evaluate the association between these markers and the overall length of the hospital stay. We also compared the biomarker profiles of Fontan patients to those of heart failure patients with anatomically normal hearts admitted in decompensated heart failure to assess whether these two different physiologic settings translate into different laboratory profiles during acute decompensation.

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Methods

Adult patients with a Fontan circulation, who were hospitalised for decompensated Fontan failure at a single quaternary care centre between January, 2013 and October, 2018, were retrospectively identified using International Classification of Diseases (ICD)-9 and ICD-10 codes for single ventricle diagnoses (ICD-9: 745.3, 746.01, 746.7 and ICD-10: Q20.4, Q22.0, Q22.6, Q23.4). Identified patients underwent subsequent confirmation of a Fontan physiology by review of medical records and all available imaging studies. Given the different terminologies that may be encountered in this patient population, either "decompensated heart failure" or "decompensated Fontan failure" was considered to be a qualifying primary diagnosis on admission, and the medical chart was subsequently reviewed to verify a clinical diagnosis of decompensated heart failure with symptoms of dyspnea on exertion or volume overload for every patient encounter. Each Fontan-failure hospital encounter was 1:2 matched by age, gender, and renal function with a non-Fontan heart failure admission by the initial inpatient laboratory profile. Identical inclusion criteria were used for the matched population.

Patient demographic information and clinical data were extracted from each qualifying hospitalisation encounter. Laboratory data, including complete blood count, basic metabolic panel, liver function test, and B-type natriuretic peptide levels, were collected for each of the study patients at the time of admission. In addition, the last available corresponding outpatient laboratory values prior to admission were collected. Patient encounters without B-type natriuretic peptide values were excluded from the analysis. The Model of End-stage Liver Disease score without international normalised ratio, which has been shown to predict risk for cardiac complications and mortality in Fontan patient, was calculated for each study patient encounter.[11] Blinded review of two-dimensional echocardiograms performed during the hospitalisation for all included patients was critically reviewed by one of the authors (J.B.). Echocardiographic parameters assessed included systolic function of the systemic ventricle, systemic atrioventricular valve function, aortic valve function, and diastolic parameters.[12] Ventricular systolic dysfunction was defined as a systemic ventricle ejection fraction <45%.[13] Information regarding use of diuretics was gathered on the Fontan population. In addition to characterising the laboratory and echocardiographic profiles, we investigated associations among the biomarkers, the echocardiographic parameters, and the prolonged length of hospital stay. Prolonged length of stay was defined as ≥7 days. Biomarker profiles and the association among biomarkers, echocardiographic findings, and length of stay were compared between the Fontan failure and general heart failure patients.

Descriptive and comparative analyses are presented as the mean with the standard deviation reported. The continuous data had a normal distribution. Comparative analysis was done with independent t-test for continuous variables and Chi-square test for categorical variables. A univariate logistic regression model was used to evaluate the association between biomarkers and prolonged length of stay. Additional stratification was also done within the Fontan cohort by systemic ventricular function and Fontan type. A p-value of <0.05 was deemed statistically significant. Statistical analysis was done with STATA version 15 (StataCorp, College Station, TX). The University of Washington Institutional Review Board approved this retrospective study.

Results

The study cohort included 54 encounters for 20 Fontan patients and 108 encounters for 108 unique non-Fontan patients who were admitted to our hospital for decompensated Fontan failure or heart failure. Within the Fontan cohort, there were 5 patients with an atriopulmonary Fontan, 10 patients with a lateral tunnel Fontan, and 5 patients with an extracardiac Fontan. Four patients were admitted four or more times for Fontan failure symptoms, and the remaining were admitted three or less times within the study period. The quality of matching between the Fontan patients and the non-Fontan patients was adequate with no statistical difference between groups in age, gender, and admission creatinine (Table 1, Supplemental Table S1). The time from the most recent outpatient visit to inpatient heart failure admission was similar between the two groups with an average of 71.9 (±56.1) days for Fontan patients and 78.1 (±64.8) days for non-Fontan patients ($p = 0.574$). The mean hospital length of stay was not different between groups (10.6 ± 14.6 days for Fontan patients and 13.2 ± 12.6 days for non-Fontan patients, $p = 0.249$, Table 1). No deaths occurred during the recorded hospital admissions, and none of the patients underwent either mechanical circulatory support device implantation or heart transplantation.

Echocardiographic parameters of the Fontan and of the matched non-Fontan cohorts are presented in Table 1. Systemic ventricular dysfunction was present in a minority of the Fontan patients, whereas it was present in the majority of the non-Fontan heart failure patients. Aortic valve dysfunction (i.e., stenosis or regurgitation > mild) was not present in any of the Fontan patients, and greater moderate systemic atrioventricular valve regurgitation was more common in non-Fontan patients.

As shown in Table 1, admission levels of platelets, sodium, blood urea nitrogen, aspartate aminotransferase, and B-type natriuretic peptide differed between the Fontan failure and non-Fontan heart failure groups. The mean B-type natriuretic peptide level on admission was lower for the Fontan patients than the non-Fontan heart failure patients (390.0 ± 978.7 pg/ml versus 1245.6 ± 1160.7 pg/ml, $p < 0.0001$, Fig 1a). The mean change in B-type natriuretic peptide from the last known outpatient value was lower for Fontan patients than that for non-Fontan patients (65.7 ± 185.7 pg/ml versus 1638.0 ± 1444.7 pg/ml, $p < 0.0001$, Fig 1b). None of the Fontan patients were treated with angiotensin receptor/neprilysin inhibitors, which can cause B-type natriuretic peptide elevation, whereas 11 (10.2%) of the non-Fontan heart failure patients were treated with these agents.

Within the Fontan cohort, admission B-type natriuretic peptide levels were significantly higher in those with moderate or severe systemic ventricular dysfunction than those with mild or no systemic ventricular dysfunction (833.6 ± 1547.2 pg/ml versus 138.6 ± 134.0 pg/ml, $p = 0.017$, Fig 2). However, there was no difference in the degree of B-type natriuretic peptide change from the last recorded outpatient value to admission value by the presence or absence of systemic ventricular dysfunction (31.8 ± 59.5 pg/ml versus 120.1 ± 287.5 pg/ml, $p = 0.151$). In the patient subgroup with systolic dysfunction, the mean B-type natriuretic peptide levels on admission were not lower for the Fontan patients than in the general heart failure patients (833.6 ± 1547.2 pg/ml versus 1377.2 ± 1244.7 pg/ml, $p = 0.1241$); however, the mean change in B-type natriuretic peptide level from the last known outpatient value remained lower for Fontan patients than for non-Fontan patients (120.1 ± 287.5 pg/ml versus 1894.1 ± 1524.9 pg/ml, $p = 0.0001$). No differences were found in the admission B-type

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Table 1. Baseline characteristics

Patient characteristics	Fontan n = 54	Non-Fontan n = 108	p-value
Male gender (%)	31 (57.4)	62 (57.4)	
Age, years	34.1 + 11.2	34.6 + 11.0	0.802
Creatinine	1.06 + 0.45	1.08 + 0.42	0.847
Length of stay, days	10.6 + 14.6	13.2 + 12.6	0.249
Echo parameters			
Systemic ventricular dysfunction (%)	20 (37)	81 (75)	<0.0001
Atrio-ventricular regurgitation (%)	4 (7.4)	32 (29.6)	0.0012
Cyanotic shunts (%)	20 (37)	0 (0)	<0.0001
Diastolic parameters			
E/A ratio	1.57 + 0.23	2.42 + 1.63	0.0002
E/e′	10.3 + 2.2	13.9 + 6.1	0.0001
IVRT	102.2 + 12.0	77.7 + 22.8	<0.0001
Admission lab values			
Sodium	133.7 ± 4.7	135.4 ± 5.9	0.048
Potassium	4.0 ± 0.5	4.0 ± 0.7	0.848
BUN	29.0 ± 16.5	22.6 ± 23.0	0.043
Haemoglobin	12.9 ± 2.8	12.8 ± 2.4	0.702
Platelets	190.9 ± 76.2	219.0 ± 76.2	0.022
AST	48.2 ± 115.3	99.5 ± 211.8	0.115
ALT	30.8 ± 36.1	112.4 ± 269.8	0.035
Alk Phos	98.5 ± 39.2	91.2 ± 61.4	0.449
T Bili	1.2 ± 0.9	1.6 ± 1.3	0.082
BNP	390.0 ± 378.7	1245.6 ± 1160.7	<0.0001
MELD-XI	9.2 ± 5.7	10.7 ± 6.3	0.144

Baseline characteristics between Fontan and non-Fontan patients, reported as n (%) or mean value (± SD). ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptice; BUN = blood urea nitrogen; dL = deciliter; IU = international units; IVRT = isovolumetric relaxation time; L = litre; MELD-XI = model for end-stage liver disease without international normalised ratio. mEq = miliequivalents; mg = milligram; ng = nanogram; SD = standard deviation.

natriuretic peptide levels based on systemic atrioventricular valve regurgitation severity (t-test p = 0.989) or the presence of shunt in the Fontan pathway (t-test p = 0.081). The diastolic echocardiographic parameters, E/A ratio, E/e′ ratio, and isovolumic relaxation time had the strongest correlation with elevated B-type natriuretic peptide level in the Fontan patients (correlation R-values 0.602, 0.664, and −0.569, respectively), whereas these parameters were not associated with B-type natriuretic peptisde (BNP) levels in the general heart failure group (Table 2). The mean B-type natriuretic peptide level was 1623.7 (±2257.6) pg/ml in atriopulmonary Fontan patients, 158.3 (±115.1) pg/ml in lateral tunnel Fontan patients, and 200.4 (±212.0) pg/ml in extracardiac Fontan patients with a significant difference between the groups (p = 0.001). The change from last outpatient value to admission B-type natriuretic peptide level was not significantly different by Fontan type (p = 0.233).

Table 3 describes the association between admission laboratory values and a prolonged hospital length of stay. In Fontan patients, both a low haemoglobin level (OR 0.766, 95% CI 0.609–0.964, p = 0.023) and an elevated blood urea nitrogen level (OR 1.053, 95% CI 1.011–1.098, p = 0.013) were associated with a prolonged length of stay. These associations were not observed for non-Fontan patients. None of the other laboratory values were associated with prolonged length of stay in the Fontan population (Table 3). In contrast, elevated serum potassium, bilirubin, and The Model of End-stage Liver Disease score without international normalised ratio were associated with prolonged hospitalisation in non-Fontan patients (OR 2.597, 95% CI 1.100–5.699, p = 0.029; OR 2.079, 95% CI 1.281–3.375, p = 0.003; and OR 1.100, 95% CI 1.023–1.182, p = 0.009, respectively). Neither admission B-type natriuretic peptide level nor degree of change from baseline B-type natriuretic peptide level was associated with a prolonged hospitalisation in either group (Table 3). Similarly, none of the echocardiographic findings were associated with a prolonged hospital length of stay ≥7 days in either group. By specific Fontan type, neither atriopulmonary Fontan, lateral tunnel Fontan, nor extracardiac Fontan patients had a prolonged hospital length of stay predicted by their admission B-type natriuretic peptide level (log p = 0.640, log p = 0.075, and log p = 0.768, respectively) or a significant change in B-type natriuretic peptide level from most outpatient value (log p = 0.590, log p = 0.182, and log p = 0.372, respectively). Home diuretics were seen in 55.6% of the decompensated Fontan admissions. Home diuretic requirements did not impact the length of stay (log p = 0.805). The B-type natriuretic peptide level on admission and change in B-type natriuretic peptide level from outpatient to admission did not differ in Fontan patients depending on diuretic use (p = 0.274 and p = 0.507, respectively).

Discussion

While the appropriateness of use and the prognostic implications of biomarkers in heart failure patients with anatomically normal hearts are well established, little evidence exists on their use in decompensated Fontan failure patients. Systemic ventricular systolic dysfunction is more the exception than the rule in Fontan patients, and chronically elevated central venous pressures make traditional exam findings of volume overload less reliable. In this study, we, therefore, aimed to characterise the biomarker profile of Fontan patients admitted with Fontan failure and to evaluate for an association between biomarkers and the hospital length of stay. We found that patients with decompensated Fontan failure had significantly lower B-type natriuretic peptide levels and a smaller change from their outpatient baseline values than the patients with non-Fontan heart failure. In addition, within the Fontan patient population, the presence of atriopulmonary Fontan system, decreased systemic ventricular function, and diastolic dysfunction were all associated with higher B-type natriuretic peptide levels. There was no correlation between B-type natriuretic peptide levels and hospital length of stay, whereas such correlation did exist between lower haemoglobin and higher blood urea nitrogen levels. The non-significant finding by Fontan type is likely due to the lack of power by the small sample size of subgroups. Lastly, none of the echocardiographic parameters for Fontan types were found to correlate with hospital length of stay.

Myocardial dysfunction with increased wall stretch is only one of several etiologies for Fontan system failure. In a recently published summary of a conference proceedings on Fontan failure, the authors identified four phenotypes associated with this condition: patients with ventricular systolic dysfunction, patients with

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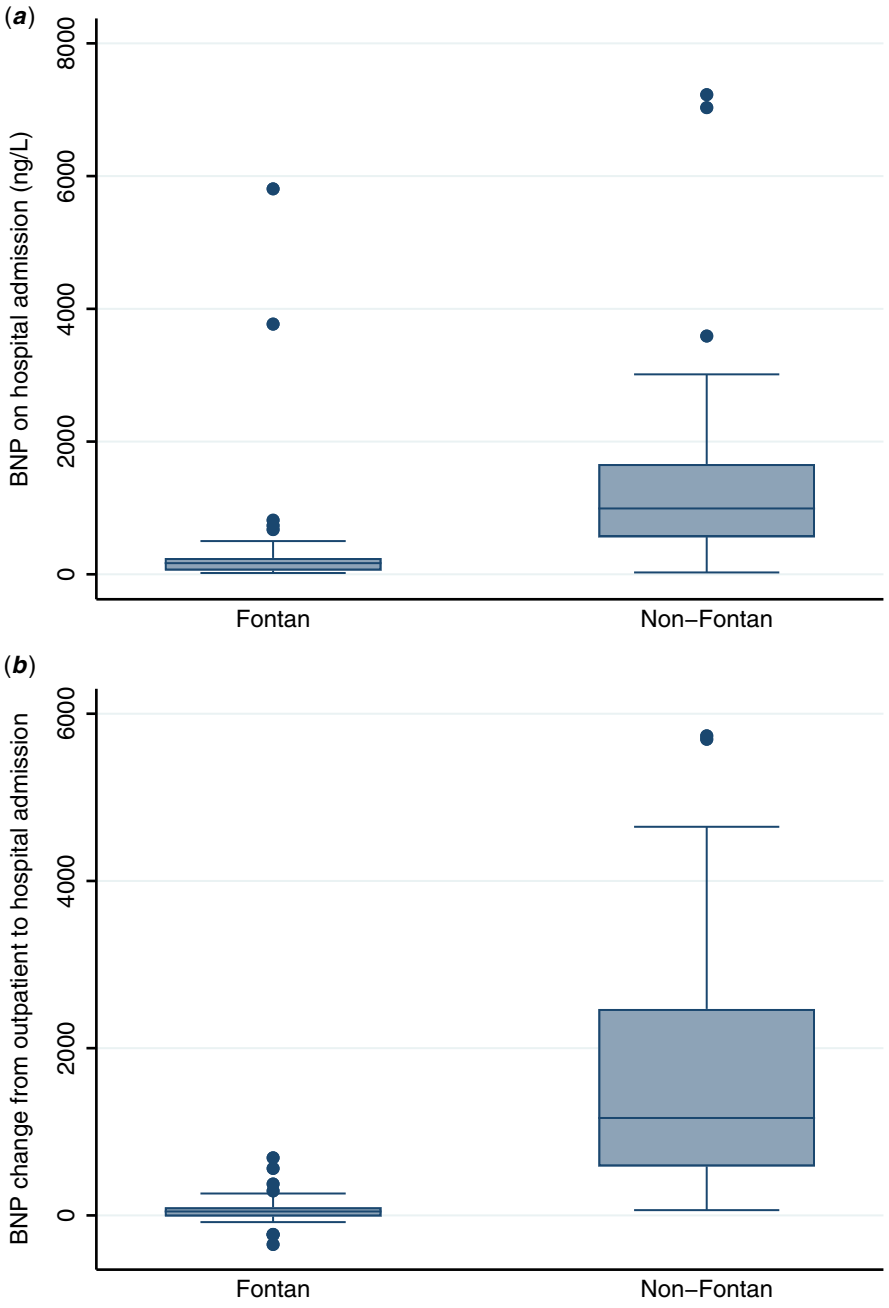

Figure 1. BNP levels between Fontan and non-Fontan heart failure patients. (***a***) Admission BNP level by Fontan status. (***b***) Change from outpatient BNP by Fontan status. Horizonal line represents the median. The box spans the 25th to the 75th quartile of values with whiskers extending to the 10th and 90th percentiles. Dots represent outliers. BNP = B-type natriuretic peptide.

ventricular diastolic dysfunction, with or without systemic atrioventricular valve regurgitation, patients with cardiac cirrhosis with preserved cardiac function, and patients with normal cardiac and liver function, but with significant lymphatic abnormalities.[3] Of these suggested phenotypes, it appears that high wall stretch and associated elevated BNP levels are expected to be present in the first two. The estimated prevalence of each of these phenotypes is largely unknown, and some overlap between the phenotypes may exist. In our study, 37% of the Fontan related admissions had systemic systolic ventricular dysfunction, and we found that B-type natriuretic peptide levels were higher in these patients as well as in those with diastolic dysfunction. These data suggest that elevated B-type natriuretic peptide levels at the time of admission can correctly identify those with systemic ventricular systolic or diastolic dysfunction at the time of decompensation-related hospitalizations. At this time, however, limited data exist as to whether phenotype-guided diagnostics and therapy should be utilised.[3,14]

We did not identify an association between elevated B-type natriuretic peptide levels and the overall length of stay in our study, yet the low number of patients included in this study precluded the possibility of performing a subgroup analysis to evaluate this association with Fontan patients with systolic or diastolic dysfunction only. Very little data exist on the prognostic implications of B-type natriuretic peptide during acute Fontan failure, whereas some data exist in the ambulatory outpatient setting. In paediatric Fontan patients, it was demonstrated that B-type natriuretic peptide levels are rarely elevated and are only weakly associated with worse outcomes such as a low chronotropic index, diastolic dysfunction by echo, and high ventricular mass.[15] In ambulatory adult Fontan

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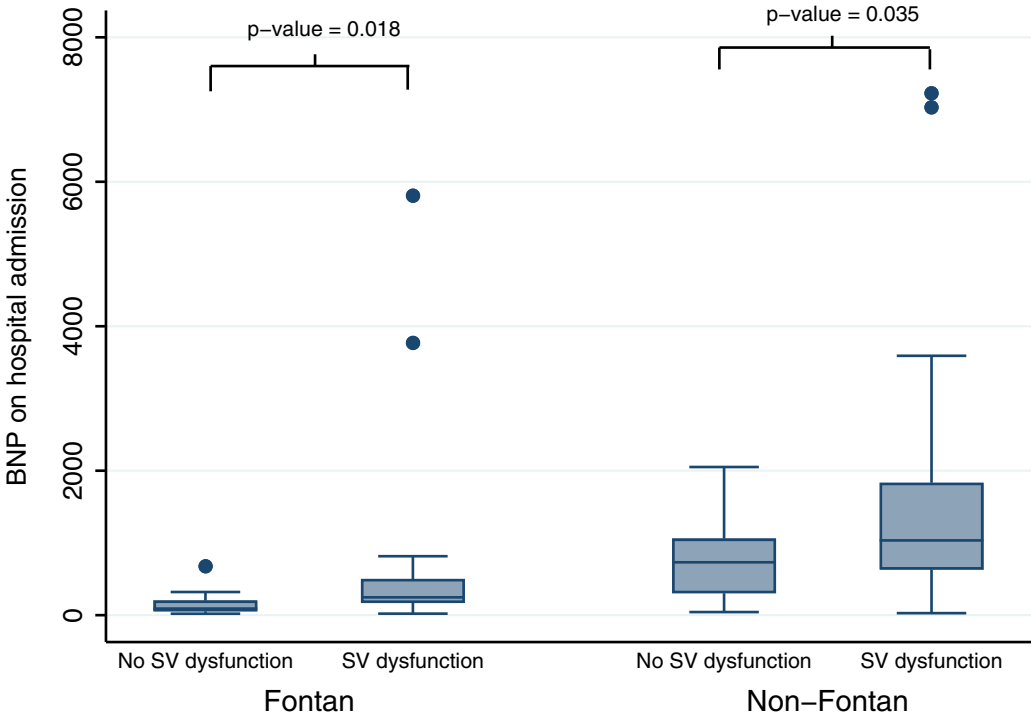

Figure 2. Admission BNP value by SV dysfunction stratified by Fontan status. Horizonal line represents the median. The box spans the 25th to the 75th quartile of values with whiskers extending to the 10th and 90th percentiles. Dots represent outliers. BNP = B-type natriuretic peptide. SV = systemic ventricle.

patients, one study found a correlation between elevated B-type natriuretic peptide levels and heart failure mortality.[9] N-terminal pro-hormone B-type natriuretic peptide levels were also found to be elevated in Fontan patients independent of volume status and cardiac function.[10] Thus, it appears that differences in the prognostic implications of elevated B-type natriuretic peptide levels may exist between the acute inpatient admissions and the more chronic outpatient settings. Further studies are required to further delineate these differences and to address the issue of the prognostic and therapy-guiding implications of this biomarker.

Prolonged hospital length of stay in heart failure patients is a major driver of cost in many health care systems.[16] While baseline B-type natriuretic peptide was not associated with a prolonged hospital length of stay in our Fontan cohort, low haemoglobin and elevated blood urea nitrogen levels were the two laboratory studies that were found to correlate with this outcome. These laboratory values are likely proxies of co-morbidities leading to their association with prolonged hospitalisation due to a higher degree of illness severity. Anaemia is a well-recognised sequelae of chronic disease, and its association with decreased functional capacity and mortality in the Fontan population may have additional implications.[17,18] Elevated blood urea nitrogen, but not elevated creatinine levels, was associated with prolonged hospitalisation. Whereas the discrepancy between blood urea nitrogen and creatinine may seem counterintuitive, it may reflect a chronic low output state with decreased renal perfusion leading to blood urea nitrogen elevation. Admitted patients with elevated blood urea nitrogen levels may be more difficult to improve with diuresis alone and thus require assistance from inotropic therapy, prolonging their hospitalisation. A previous study noted that patients with a low glomerular filtration rate as assessed by cystatin C levels were at increased risk of hospitalisation, but this was not noted in creatinine-derived glomerular filtration rate in the same series, suggesting that creatinine may not provide as granular an estimation of renal function as would be ideal.[19] Organ dysfunction, as indicated by the presence of anaemia and chronic kidney dysfunction, reflects the peripheral chronic effects of the Fontan circulation. Recent studies have investigated other biomarkers in this challenging population. Saral et al. explored an extensive panel of potential biomarkers and found that Fontan patients have a higher level of inflammation markers, stem cell mobilisation, renin neurohormonal activation, cardiac injury, and abnormal metabolism, and although this provides the foundation for further study, the clinical utility of any specific marker still remains unclear.[20] Opotowsky et al. found that Galectin-3 is elevated in Fontan patients with an increased risk of cardiovascular admission or death; however, additional study is needed for this promising biomarker.[21] Serum amino-terminal procollagen type III reflects ventricular remodelling and fibrosis in Fontan patients and may provide another potential therapeutic target.[22] Angiopoietin-2 levels were shown to be associated with the burden of atrial arrhythmias.[23] Faecal calprotectin levels may be able to detect the development of protein losing enteropathy in Fontan patients; however, one should strive for earlier identification of Fontan failure as the disease process is difficult to reverse at this stage.[24] Overall, the Fontan circulation is characterised by complex interactions between multiple organ systems with continuous interplay among the heart, lungs, liver, kidneys, and vasculature. Deterioration of other organ systems, in addition to the heart, may result in a general decompensated state in Fontan patients, requiring longer hospitalizations. This area of study remains underexplored and deserved further attention in the field of CHD research.

Limitations

This study has several important limitations. Our single-centre retrospective study is subject to variations in care among patients, provider specific practices, institutional bias, and inherent confounders in the interpretation of data. ICD-9 and ICD-10 codes were used for identification of our Fontan patient cohort, and

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Table 2. Echocardiographic correlates with B-type natrieuretic peptide

	Fontan correlation R-value	p-value	Non-Fontan correlation R-value	p-value correlation R-value
Systemic ventricular dysfunction	0.3449	0.018	0.2155	0.035
>Moderate systemic atrioventricular valve regurgitation	0.002	0.989	0.077	0.454
Cyanotic shunts	−0.2567	0.082	~	~
Diastolic parameters				
E/A ratio	0.6018	<0.0001	0.1184	0.299
E/e′	0.6635	<0.0001	0.0761	0.489
Isovolumic relaxation time	−0.569	<0.0001	−0.1099	0.314

Table 3. Effect of laboratory characteristics on prolonged hospitalisation

	Fontan patients		Non-Fontan patients	
Admit lab	Odds ratio	p-value	Odds ratio	p-value
Sodium	0.992	0.873	0.953	0.255
Potassium	0.990	0.980	2.597	0.029
BUN	1.053	0.013	1.017	0.209
Creatinine	4.016	0.061	1.499	0.399
Haemoglobin	0.766	0.023	0.911	0.258
Platelets	0.996	0.341	0.997	0.266
AST	1.002	0.793	1.004	0.083
ALT	1.003	0.738	1.005	0.057
Alkaline phosphatase	1.009	0.251	1.009	0.111
Total bilirubin	0.732	0.346	2.079	0.003
BNP	1.000	0.975	1.000	0.045
MELD-XI	1.083	0.131	1.100	0.009
Echocardiography				
SV dysfunction	2.089	0.250	0.951	0.911
E/A	1.436	0.760	0.742	0.121
E/e′	1.072	0.583	1.027	0.443
Isovolumic relaxation time	1.001	0.963	0.990	0.275

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptice; BUN = blood urea nitrogen; MELD-XI = model for end-stage liver disease without international normalised ratio; SV = systemic ventricle

we sought to limit patient misclassification through a detailed chart review of each participant; however, incomplete patient capture may have occurred. Despite querying 5 years worth of admissions, we were only able to identify a small sample of unique Fontan patient at our large adult CHD centre, which limits the power of our analysis. To increase our sample size of hospital admission analysis, repeat encounters of the same patients were evaluated, which may lead to sampling bias. We, therefore, refrained from reporting on patient characteristics. Likewise, the data were not stratified by further comorbidities due to the limited power of the small sample. We ensured an adequate match quality, but our matched non-Fontan sample may have an inherent bias that is unaccounted for. Given these limitations, we did not study any clinical outcomes, such as death, major adverse cardiovascular events, or development of cirrhosis.

Conclusion

In conclusion, we found that the B-type natriuretic peptide levels were significantly lower in Fontan failure patients admitted with decompensation than that in non-Fontan heart failure patients and that there was no significant difference between outpatient baseline B-type natriuretic peptide levels and admission B-type natriuretic peptide levels for Fontan patients. Admission B-type natriuretic peptide levels were not associated with prolonged hospital length of stay, whereas anaemia and markers of chronic kidney injury were. These findings underscore the multi-organ involvement inherent in the pathophysiology of the failing Fontan circulation and highlight the difficulty in treating the ageing Fontan population, as there are currently no clear serologic markers to aid in the detection of failing Fontan physiology. B-type natriuretic peptide levels should, therefore, be used with caution in the assessment of decompensated Fontan failure.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951120001250

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