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Original Article

Lymphopenia in the Adult Population With Fontan Physiology: A Potential New Marker for Disease Assessment

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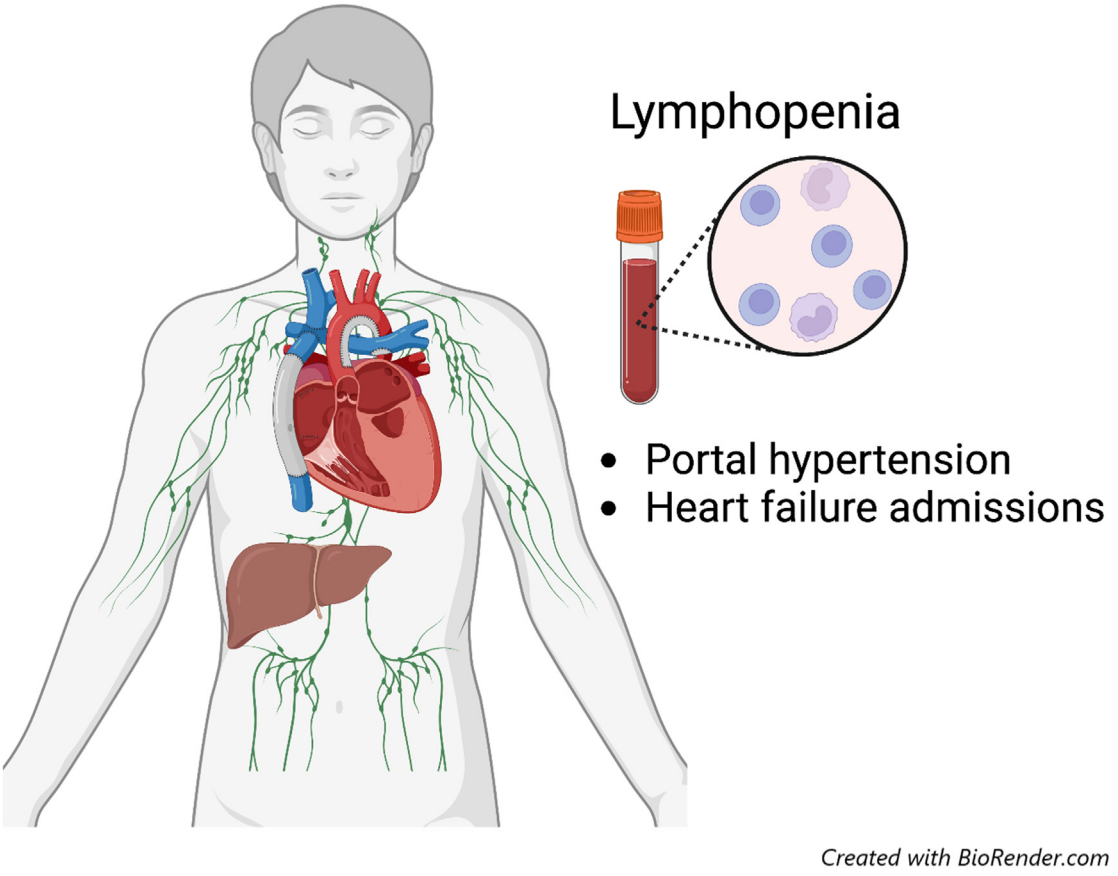

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ABSTRACT

Background: Patients with complex congenital heart disease and Fontan palliation frequently develop extracardiac disease, including hematologic abnormalities, such as lymphopenia. However, the clinical implications of this finding are poorly understood and are therefore the topic of this investigation.

Methods: Patients with Fontan physiology in our centre (1999-2018) were evaluated for the presence and impact of lymphopenia. The cohort was divided into a group with lymphopenia (L) (2 consecutive absolute lymphocyte counts $\leq 1*10^3$ K/ μL) and a group who had never had lymphopenia (NL). Clinical characteristics and hospital admissions (762 patient-years) were evaluated.

Results: In 62 adult patients with Fontan physiology (aged 34 ± 9 years; 32 women [52%]), the patients who developed lymphopenia earliest did so 8 years after Fontan completion, with up to 60% of patients developing lymphopenia by 30 years. Lymphopenia was found to be associated with portal hypertension (varices, ascites, splenomegaly, and thrombocytopenia [VAST] score)—NL: 0 (0-2) vs L: 2 (0-4), $P < 0.0001$). A total of 76 heart failure and 81 arrhythmia-associated admissions occurred per 1000 patient-years. At 40 years post-Fontan, the probability of a heart failure admission was higher in the L group (L: 51 [86%] vs NL: 8 [14%], $P < 0.01$).

Conclusions: Adult patients with Fontan physiology and lymphopenia demonstrated portal hypertension and lymphatic dysfunction more commonly, perhaps suggesting that this may be a marker of Fontan congestion and early Fontan failure. Further investigation into the relationship between lymphopenia, clinical outcomes, and Fontan function is needed.

RÉSUMÉ

Contexte : Chez les patients atteints d'une cardiopathie congénitale complexe ayant subi une intervention de Fontan, il est fréquent de voir apparaître des maladies extracardiaques, dont des anomalies hématologiques, comme la lymphopénie. Cependant, les implications cliniques de cette observation sont mal comprises et font donc l'objet de cette étude.

Méthodologie : La présence et l'impact d'une lymphopénie ont été évalués chez des patients présentant une physiologie de Fontan dans notre centre (1999-2018). La cohorte a été divisée en un groupe composé de sujets atteints de lymphopénie (L) (2 mesures consécutives du nombre absolu de lymphocytes $\leq 1 \times 10^3$ K/μL) et un groupe de sujets n'ayant jamais présenté de lymphopénie (NL). Les caractéristiques initiales et les hospitalisations (762 années-patients) ont été évaluées.

Résultats : Chez 62 adultes présentant une physiologie de Fontan (âgés de 34 ± 9 ans; 32 femmes [52 %]), la lymphopénie est apparue au plus tôt 8 ans après l'intervention de Fontan, avant 30 ans chez jusqu'à 60 % des patients. La lymphopénie a été associée à l'hypertension portale (score varices, ascite, splénomégalie et thrombocytopénie [VAST]) — NL : 0 (0-2) vs L : 2 (0-4), $p < 0{,}0001$. Au total, il y a eu 76 hospitalisations pour insuffisance cardiaque et 81 pour arythmie pour 1000 années-patients. Quarante ans après l'intervention de Fontan, la probabilité d'une hospitalisation pour insuffisance cardiaque était plus élevée dans le groupe L que dans le groupe NL (L : 51 [86 %] vs NL : 8 [14 %], $p < 0{,}01$).

Conclusions : L'hypertension portale et la dysfonction lymphatique étaient plus fréquentes chez les adultes présentant une physiologie de Fontan et une lymphopénie, ce qui laisse peut-être entendre que ce pourrait être un marqueur d'une congestion et d'une défaillance précoce du système Fontan. D'autres recherches sur le lien entre la lymphopénie, les issues cliniques et la fonction du système Fontan sont nécessaires.

The Fontan operation was first performed in 1968 by Francis Fontan as a palliative procedure for patients with tricuspid atresia.[1] However, it has since been adopted as the palliation of choice for most single-ventricle congenital heart disease patients, and most recent data suggest that approximately 70,000 survivors have Fontan physiology (85% survival at 30 years).[2] Important to note is that this number is expected to double in the next 20 years.[3] Although children with the Fontan palliation are surviving to adulthood, they are at increased risk for both late cardiac and extracardiac disease,[3] in part due to passive subpulmonary ventricular flow, high central venous pressure, and low cardiac output. Heart failure, arrhythmia, and liver disease are significant causes of morbidity and mortality, with heart failure being the most common reason for hospital admission, and a predictor of poor outcomes.[4]

Lymphopenia has been observed in both human and animal populations[5] in conditions associated with heart failure.[6-9] Patients with Fontan physiology are known to develop lymphopenia[10-12]; however, the etiology and overall impact of this finding are not well understood. Many have postulated that the abnormal cardiovascular hemodynamics of single-ventricle physiology are contributory,[9,13,14] yet contrary to this hypothesis, in both pediatric and young adult patients with Fontan physiology, hemodynamic profiles at catheterization have not been shown to differ between patients with vs without lymphopenia.[11,14,15] Although prior work has identified that lymphopenia is associated with evidence of portal hypertension,[15] no group has reported the impact of persistent lymphopenia and hospital admission in the adult Fontan population. Here, we aimed to characterize lymphocyte levels and identify potential relationships to disease status and hospital admission in adult patients with Fontan physiology.

Methods

Utilizing the institutional imaging software system (Synapse Cardiovascular 6.2.1, Fujifilm, Tokyo, Japan, 2007-2018), we identified adults with single-ventricle (ie, Fontan) physiology (1999-2018). Inclusion criteria were as follows: age $\geq$ 18 years; results available from at least 2 absolute lymphocyte counts

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See page 780 for disclosure information.

(ALCs), collected at least 12 hours apart, drawn on ≥ 2 separate occasions. We excluded subjects with a primary hematologic disease. The final cohort was described by "Fontan phenotype" as having either (i) an atriopulmonary connection (including Fontan-Kreutzer procedure and Bjork modifications) or (ii) a total cavopulmonary connection (TCPC; including lateral tunnel and extracardiac conduits). A total of 8 subjects underwent Fontan conversions and were included in the TCPC group. If a subject underwent orthotopic heart transplant, only pre-orthotopic heart transplant data were analyzed. A waiver of informed consent was requested from and approved by the institutional review board.

Demographic, anatomic, and laboratory data were collected from the hospital's electronic medical record. When available, we also collected invasive hemodynamic results, cardiac echocardiographic data, and exercise testing results. The severity of Fontan-associated liver disease (FALD) required a review of available data, including from imaging studies (abdominal ultrasound, computed tomography, magnetic resonance imaging), liver biopsy, and assessment of the VAST score (varices, ascites, splenomegaly, thrombocytopenia) to evaluate for portal hypertension.[16] Finally, local hospital admissions data were collected and included, when available.

Data analysis

Lymphopenia was defined as 2 consecutive ALCs of ≤ 1 x 10^3 /μL ≥ 12 hours apart. *Persistent lymphopenia* was defined as meeting the above criteria for lymphopenia and never having another subsequent ALC value above the cutoff threshold. *Intermittent lymphopenia* was defined as satisfying criteria for lymphopenia but subsequently having at least one ALC at or above the cutoff. Both subjects with persistent vs intermittent lymphopenia were analyzed together in a single group with lymphopenia (L). We analyzed data in both the group with lymphopenia (L) and the group who had never had lymphopenia (NL). All data were inspected to assess their distributions. Continuous variables are reported as means and standard deviation (SD) or median (25th, 75th percentiles), depending on the normality of their distributions. Differences between the groups with respect to continuous variables were assessed using unpaired *t*-tests or Wilcoxon rank-sum tests, as appropriate depending on their distributions. Comparison between groups with respect to categorical variables was made using χ^2 tests or Fisher's exact tests when expected cell counts were less than 5. The Kaplan-Meier estimator was used to assess the time to lymphopenia, first heart failure admission, first arrhythmia admission, and first infection admission, relative to the date of Fontan completion. The log-rank test was used to compare Kaplan-Meier survival curves between groups. Poisson regression was used to compare groups with respect to hospitalization admission rates. All hypothesis tests were 2-sided, and all analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC) or R software (R Foundation for Statistical Computing, Vienna, Austria). A type I error (α) of $\leq$ 0.05 was considered significant.

Results

A total of 62 subjects were included in this study (age 34 ± 9 years; 32 female patients (52%), 9 (15%) with atriopulmonary Fontan, and 53 (85%) with TCPC, 8 of which were Fontan conversions; Table 1). A total of 24 subjects (39%) were in the L group (age 33 ± 10 years; ALC range 0.6, 3.27), and 38 subjects (61%) were in the NL group (age 35 ± 8 years, $P = 0.61$; ALC range 0.57, 3.16). In the L group, 17 subjects (71%) had *persistent lymphopenia,* and 7 (29%) had *intermittent lymphopenia*. Two patients in our cohort had protein-losing enteropathy; both were in the lymphopenic group, and one met our criteria for persistent lymphopenia. Four deaths, and one combined heart-liver transplant in the cohort, occurred within the duration of the study (3 deaths in the L group (13%) and 1 (3%) in the NL group, $P = 0.29$). Freedom from lymphopenia in the years post—Fontan completion was analyzed, and we found that the earliest cases of lymphopenia occurred ~8 years after Fontan completion, and that freedom from lymphopenia worsened over time, with only 40% of adult Fontan patients being free from lymphopenia 30 years after Fontan conversion (Fig. 1).

In terms of description of the cohort, we found that the underlying anatomic congenital heart malformation presentation did not differ between the L and NL groups. Ventricular systolic function and valve function as assessed on echocardiography were also similar in the 2 groups, with most patients demonstrating normal systemic ventricular systolic function. Remarkably, although the incidence was not different between groups, up to 25% of all subjects had more than mild systemic atrioventricular valve dysfunction, an important characteristic, as it may contribute to the acceleration of Fontan Failure. A total of 50 subjects (81%) had cardiopulmonary exercise testing available for review (L group: 20 [83%]; NL group: 30 [79%]). The average time from Fontan completion to cardiopulmonary exercise testing was 24 ± 5.9 years for the NL group, and 25 ± 6.8 years for the L group. Subjects in the L group demonstrated resting hypoxia, compared to those in the NL group (medians 92% vs 95%, $P < 0.01$). However, objective exercise performance did not differ between groups (Table 1).

Given that white cell abnormalities may coincide with hepatic dysfunction, we next examined liver function and found abnormalities to be more likely in the L than in the NL group. The bilirubin level was slightly higher, and the serum albumin level was slightly lower, in the L group; however, both changes were not apparently clinically significant, whereas the international normalized ratio was insignificantly elevated in the L group. A minority of subjects (n = 17) were prescribed warfarin, and 2 were prescribed direct oral anticoagulants and therefore were excluded from international normalized ratio analysis. Of those on either warfarin or a direct oral anticoagulant, 12 were in the NL group, and 7 were in the L group. No statistically significant difference was found in other traditional liver-function testing (alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, gamma-glutamyl transferase (GGT), or alpha fetoprotein [AFP]). Portal hypertension severity as assessed by the VAST score was significantly higher in the L group (medians: 2 vs 0, $P < 0.001$), and additionally, for 3 of the 4 VAST components—varices, ascites, splenomegaly, and thrombocytopenia—rates were higher in the L group. Finally, to determine if invasive data supported a congestive presentation, we analyzed hemodynamic data from 30 subjects who underwent cardiac catheterization, 17 (71%) from the L

Table 1. Basic demographic data

Variable	All patients 62 (100)	Patients who never had lymphopenia 38 (61)	Patients with lymphopenia 24 (39)	*P*
Demographic data				
Female	32 (52)	22 (58)	10 (42)	0.21
Age, y	34 ± 9	35 ± 8	33 ± 10	0.61
Body mass index, kg/m^2	26.0 ± 6.6	26.3 ± 7.0	25.6 ± 6.0	0.65
AP Fontan	9 (15)	6 (16)	3 (12)	0.99
Anatomic data				
Transposition complexes	25 (40)	18 (47)	7 (29)	0.15
Heterotaxy syndrome	6 (10)	3 (8)	3 (13)	0.67
Hypoplastic right heart syndrome	26 (42)	14 (37)	12 (50)	0.31
Hypoplastic left heart syndrome	5 (8)	3 (8)	2 (8)	0.99
Left ventricle dominant	38 (61)	22 (58)	16 (67)	0.49
Right ventricle dominant	10 (16)	6 (16)	4 (17)	0.99
Common ventricle	14 (23)	10 (26)	4 (17)	0.38
Laboratory studies				
White blood cell count, K/μL	6.6 ± 2.1	7.3 ± 2.0	5.4 ± 1.9	< 0.001
Absolute neutrophil count, K/μL	4.36 ± 1.79	4.81 ± 1.81	3.64 ± 1.53	< 0.01
Absolute lymphocyte count, K/μL	1.29 (−0.95, 1.81)	1.64 (1.31, 2.18)	0.93 (0.73, 1.11)	< 0.001
Hemoglobin, g/dL	15.4 ± 1.8	15.3 ± 1.6	15.4 ± 2.2	0.77
Platelets, K/μL	161 (122, 216)	192 (149, 227)	130 (102, 173)	0.001
NT-ProBNP, pg/mL	282 (111, 680)	180 (94, 680), n = 31	404 (200, 773), n = 20	0.14
VO_2 exercise testing	**50 (81)**	**30 (79)**	**20 (83)**	
Resting oxygen saturation, %	94 (91, 96)	95 (93, 97)	92 (84, 95)	< 0.01
Age at time of VO_2 testing	31 ± 8	29 ± 8	32 ± 9	0.61
VO_2max (% predicted, mL/kg/min)	59 ± 17	62 ± 18	54 ± 14	0.12
VE/VCO_2	37.2 ± 6.4	35.8 ± 4.5	39.4 ± 8.2	0.10
Transthoracic echo	**62 (100)**	**38 (100)**	**24 (100)**	
Presence of ventricular systolic dysfunction	11 (18)	5 (13)	6 (25)	0.31
> Mild semilunar valve regurgitation	8 (13)	6 (16)	2 (8)	0.47
> Mild AV valve regurgitation	17 (27)	11 (29)	6 (25)	0.73

Values are frequency (%), mean ± standard deviation, or median (25th, 75th percentile), unless otherwise indicated. Each row in the Anatomic Data section represents a categorical response (yes/no), with the first 4 rows analyzed together, and the last 3 rows analyzed together. For example, a "yes" to Transposition complexes is associated with a "no" to the other 3 rows (Heterotaxy +HRHS + HLHS).

AP, atriopulmonary; AV, atrioventricular; HLHS, hypooplastic left heart syndrome; HRHS, hypoplastic right herat syndrome; NT-ProBNP, N-terminal pro hormone brain natriuretic peptide; TCPC, total cavopulmonary connection; VCO2, carbon dioxide production; VE, minute ventilation; VE/VCO_2 ventilator efficiency; VO2, volume of oxygen intake; VO_2max, maximal oxygen intake.

group, and 13 (34%) from the NL group. The average time to cardiac catheterization from initial Fontan completion was 21 ± 8.0 years for the L group, and 22 ± 6.6 years for the NL group. Only one L-group subject was found to have Fontan pathway obstruction during cardiac catheterization (Table 2).

With respect to hospitalizations, the cohort was followed for a total of 762 patient-years. The cohort had 76 cases of heart failure per 1000 patient-years, 81 arrhythmia cases per 1000 patient-years, and 18 infection cases per 1000 patient-years. The incidence of heart failure admissions was much higher in the L group (165 cases per 1000 patient-years), compared to that in the NL group (15 cases per 1000 patient-years; $P < 0.01$). Subjects with lymphopenia were more likely not only to be hospitalized with heart failure or congestion, but also to have the first hospitalization for heart failure occur earlier after the initial Fontan completion ($P < 0.01$; Fig. 2A). The incidence of arrhythmia admissions was higher in the L group (104 cases per 1000 patient-years) compared to that in the NL group (66 cases per 1000 patient-years); however, this difference was not significant ($P = 0.08$). A total of 21 unique patients had admissions associated with arrhythmia (11 [46%] in the L group, and 10 [26%] in the NL group), but this difference between the 2 groups was not statistically significant ($P = 0.11$). Further, only one arrhythmia case was coded as ventricular arrhythmia and/or cardiac arrest, and the remainder were coded as atrial tachyarrhythmia (Fig. 2B**).** The time to hospitalization for first arrhythmia did have a statistically significant earlier occurrence in the L group, compared to that in the NL group ($P = 0.04$). No difference between the groups occurred in use of anticoagulation, aspirin, pacemakers, or implantable cardioverter defibrillators. Sinus node dysfunction was not more prevalent in the L group (10 [42%]) than it was in the NL group (10 [26%], $P = 0.21$)

Hospital admission for infection occurred less frequently than heart failure overall; however, when present, it was more likely to occur in the L group than in the NL group (42 cases per 1000 patient-years vs 2 cases per 1000 patient-years, $P < 0.01$). Unique patient admissions for infections were more likely to occur in the L group than in the NL group (10 [42%] vs 1 [3%], $P < 0.001$). Hospitalizations for the first infection occurred earlier after initial Fontan completion in the L group ($P < 0.0001$; Supplemental Fig. S1). The most common infection documented was community-acquired pneumonia, which was observed in 5 of 14 admissions. All remaining infections were bacterial. The only opportunistic infection reported was a Nocardia brain abscess.

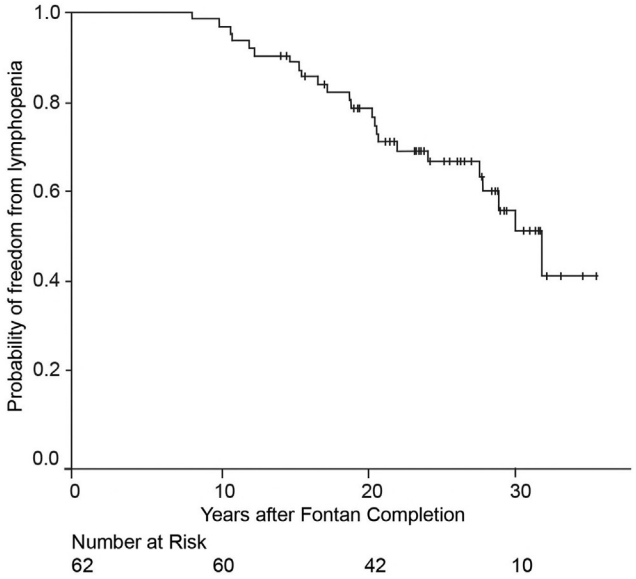

Figure 1. Post-Fontan conversion freedom from lymphopenia. In 62 adult patients with Fontan physiology followed for 762 patient-years post–Fontan completion, lymphopenic status was assessed over time. At 30 years of follow-up, 24 patients (39%) developed lymphopenia, the earliest case of which occurred 8 years after Fontan completion, with increasing numbers developing lymphopenia 20 years after Fontan completion. + represents censored data.

Discussion

This is the first natural history study of lymphopenia in an adult population with Fontan physiology, and we have shown that it develops as early as 8 years after Fontan completion, with diminishing freedom from lymphopenia for up to 30 years post-Fontan. Lymphopenia is tied to hepatic dysfunction, as demonstrated in the cohort here, shown by evidence of more significant portal hypertension as evaluated by the VAST score,[16] yet with clinically insignificant changes in bilirubin, albumin, or other traditional liver-function tests. This finding perhaps suggests that lymphopenia may be a better early marker of portal hypertension, compared with traditional markers of liver function (ie, liver function tests such as alanine transaminase (ALT), aspartate aminotransferase [AST] and/or MELD [model for end-stage liver disease] score). An interesting point to note is that, in this cohort, those with lymphopenia did not demonstrate significantly worse invasive hemodynamic parameters, which seems counterintuitive, as most experts postulate that worse hemodynamics (ie, higher resting Fontan pressure and congestion) contribute to liver dysfunction in a relatively linear fashion (higher pressure for longer duration = worse liver disease). However, those with lymphopenia did demonstrate higher rates of decompensated heart failure admission, suggesting that the hemodynamics measured invasively may not directly correlate with individual risk for worse outcomes, at least as it relates to liver dysfunction and Fontan failure. Although the difference was not statistically significant ($P = 0.14$), the N-terminal pro hormone brain natriuretic peptide (NT-ProBNP) level appeared to be elevated to a clinically meaningful degree (404 pg/mL) in the group with lymphopenia (vs 180 pg/mL in the group without lymphopenia). This finding may support the use of this biomarker to determine which patients with Fontan physiology are at risk of heart failure admission; however, this possibility needs to be studied in larger groups.

The great conundrum in caring for adults with Fontan physiology is in predicting which patients will continue to do well, and identifying those at risk for worse outcomes, mainly Fontan failure. If a method to determine this were better understood and could be accomplished reliably, then targeted therapies could be employed to modify this late risk. Critically important to this concept is better understanding of FALD, which currently has no reliable biomarker,[17,18] and we continue to lack understanding of its trajectory, and more importantly, why it differs among patients. Given the data we present here, lymphopenia should be investigated as a potential biomarker for FALD. Such investigation may provide some insight into the degree to which liver dysfunction is contributing to the overarching picture of Fontan failure, vs that which is due directly to dysfunction of the cardiac physiology itself (ie, worsening structural disease: valve dysfunction, collateral formation, etc.). The VAST score has been validated in FALD,[19] including the criteria for splenomegaly, which is a known consequence of right-sided heart failure and liver cirrhosis. However, the exact relationship of splenomegaly and lymphopenia in the population with Fontan physiology is unknown. Compared to the group without lymphopenia, the group with lymphopenia had a statistically significantly higher proportion of patients with splenomegaly—13% vs 57%, respectively. The cardiosplenic axis is a novel area of research in traditional heart failure, but it

Table 2. Hepatic assessment and hemodynamic characteristics

Variable	All patients	Patients who never had lymphopenia (NL)	Patients with lymphopenia (L)	P
Hepatic variables				
Varices (V)*	9 (19)	0 (0)	9 (39)	< 0.001
Ascites (A)*	12 (26)	4 (17)	8 (35)	0.15
Splenomegaly (S)*	16 (34)	3 (13)	13 (57)	< 0.01
Thrombocytopenia (T)†	20 (43)	5 (22)	15 (65)	< 0.01
VAST score	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	2.0 (1.0, 3.0)	< 0.001
Total bilirubin, mg/dL	0.90 (0.70, 1.30)	0.80 (0.60, 1.10)	1.15 (0.80, 2.45)	< 0.01
Albumin, g/dL	4.60 (4.30, 4.80)	4.70 (4.40, 4.90)	4.50 (4.30, 4.70)	0.02
INR*	1.20 ± 0.16	1.17 ± 0.15	1.24 ± 0.16	0.16
Cardiac catheterization characteristics				
Age at time of catheterization, y	29 ± 10	29 ± 10	28 ± 10	0.84
PA O_2 saturation, %	66 ± 7	67 ± 7	66 ± 6	0.74
Aortic O_2 saturation, %	90 ± 6	91 ± 4	89 ± 7	0.50
CVP, mm Hg	15 ± 5	15 ± 6	15 ± 5	0.80
PCWP, mm Hg	10 ± 6	10 ± 6	10 ± 5	0.90
mPA, mm Hg	15 ± 5	14 ± 6	15 ± 5	0.67
EDP, mm Hg	12 ± 6	13 ± 7	12 ± 5	0.66
SVR, Wood units	18.9 ± 8.6	18.9 ± 9.0	18.9 ± 8.6	0.98
PVR, Wood units	1.4 ± 0.8	1.2 ± 0.7	1.6 ± 0.9	0.20
Cardiac index, L/min/m^2	2.4 ± 0.8	2.4 ± 0.6	2.3 ± 0.9	0.93
Qp/Qs	0.96 (0.79, 1.00)	1.00 (0.83, 1.00)	0.89 (0.74, 1.00)	0.28
Right-to-left shunt	18 (64)	7 (58)	11 (69)	0.70

Values are mean ± standard deviation, n (%), or median (25th, 75th percentile).

CVP, central venous pressure; EDP, end diastolic pressure; INR, international normalized ratio; mPA, pulmonary arterial mean pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; VAST, varices, ascites, splenomegaly, and thrombocytopenia.

*INR was controlled for by warfarin use; data were available for a total of 47 patients, 24 in the NL group, and 23 in the L group.

†Data were available for a total of 46 patients, 23 in the NL group, and 23 in the L group.

has not been explored in the context of heart failure in the setting of congenital heart disease and needs to be the topic of future research.

The clinical impact of Fontan failure and/or FALD can at least in part be reflected in the impact upon hospitalizations. With both arrhythmia and decompensated heart failure being common in congenital heart disease, the latter remains a reasonable marker of overall disease burden. Here, we demonstrated that by 10 years after Fontan completion, a divergence in curves for heart failure and arrhythmia admission exists for patients with vs without lymphopenia. The burden increases significantly, especially at 20 years, when up to 40% of patients with lymphopenia have had a heart failure admission (vs 10% in the group without lymphopenia), and 30% of patients with lymphopenia have had admission for arrhythmia (vs 10% of the group without lymphopenia). This divergence worsens at up to 30 years post-Fontan and beyond, again highlighting the potential association of lymphopenia as one potential marker to consider when evaluating prognosis.

The association of lymphopenia with worse medium- and long-term outcomes is important, and we hypothesize that on some level, this association reflects the degree of liver dysfunction due to FALD more accurately than do traditional markers of liver disease. Only a few reports have been made of lymphopenia in single-ventricle congenital heart disease, and all have been in pediatric or young adult cohorts. In a study by Mattes, young children with Fontan completion (excluding those with protein-losing enteropathy [PLE]) and lymphopenia were hypothesized to have significant liver disease; however, no liver testing was reviewed.[14] In 178 young children studied by Morsheimer and colleagues, in 31 subjects with concomitant PLE, 21 (14%) demonstrated lymphopenia, the majority of whom also had PLE.[12] In this cohort, Fontan failure and liver disease were not assessed. A third and recent study on lymphopenia in the population with Fontan physiology demonstrated the prevalence of lymphopenia to be 32%, similar to our 38%.[15] They also found no correlation of lymphopenia with hemodynamics, cardiac imaging, or exercise testing, but they demonstrated that patients with lymphopenia had more signs of portal hypertension, similar to our findings. The differences between this study and ours is that subjects were older, presenting at age 34 ± 9 years, compared to age 25 ± 8 years, and in many cases, we reported data from up to 40 years post−Fontan completion.

In prior work, PLE has been implicated as the etiology of lymphopenia,[20,21] with the hypothesis that lymphocytes may leak from the gut. In support of this possibility, a report has been made on a subset of PLE patients with intestinal lymphangectasia for whom resection of the affected bowel improved lymphopenia.[22] In the Morsheimer study, the prevalence of lymphopenia exceeded 50% in the PLE subgroup.[12] However, our and other studies suggest that PLE is not the sole cause of lymphopenia, as it can occur in the absence of PLE.[12] In our cohort, only 2 of the 24 patients in the group with lymphopenia had PLE, one of whom met our criteria for persistent lymphopenia. We postulate that thinking of lymphatic dysfunction as being on a continuum may be helpful—with PLE at one extreme, and early lymphatic dysfunction at the other. With respect to Fontan physiology, lymphatic system abnormalities have been observed in patients both before Fontan completion,[23] and after,[24] and although no mechanistic link has been established between lymphatic dysfunction and Fontan failure,[25,26] thoracic duct decompression has been shown to be helpful

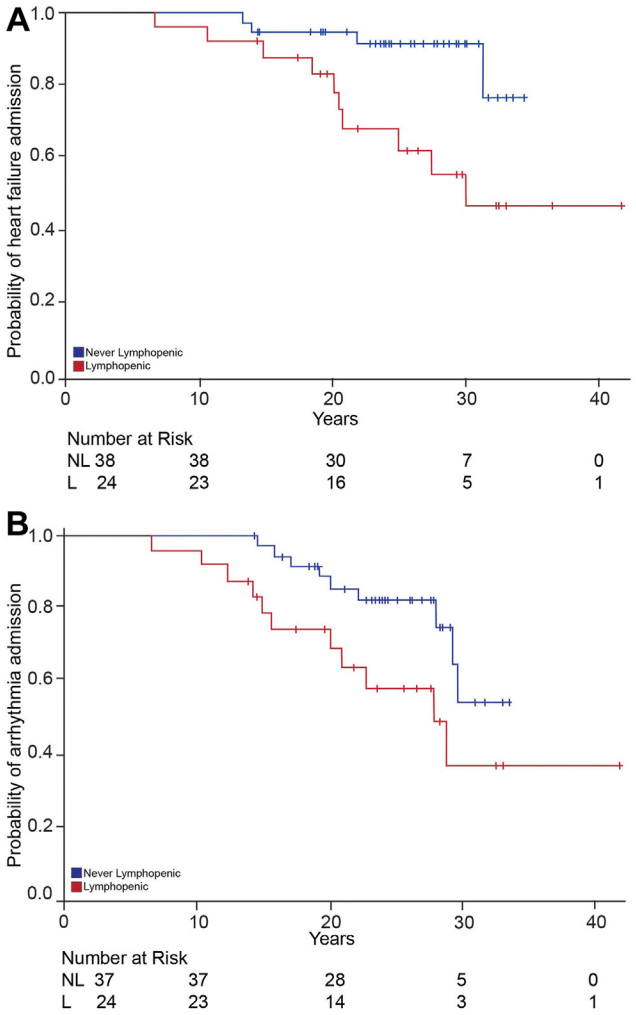

Figure 2. Heart failure and arrhythmia admissions adult patients with Fontan physiology. In 62 adult patients with Fontan physiology, 76 cases of heart failure per 1000 patient-years, and 81 arrhythmia cases per 1000 patient-years, were reported. Patients with lymphopenia (L) were more likely to be hospitalized with heart failure or congestion as well as to be admitted earlier for the first occurrence after the initial Fontan completion ($P < 0.01$) (**A**). A total of 21 unique patients had admissions associated with arrhythmia (11 [46%] in the group with lymphopenia (L), as did 10 patients (26%) in the group that had never had lymphopenia [NL]), a difference that was not statistically significant ($P = 0.11$); however, hospitalizations for first arrhythmia did occur earlier after the initial Fontan completion ($P = 0.04$) (**B**). + represents censored data.

in select pediatric patients suffering from PLE or plastic bronchitis,[27] one of the subtypes of Fontan failure. Certainly, the potential overlap of physiology responsible for lymphatic dysfunction, PLE, Fontan failure, and FALD requires more study. The data we present here, at least in part, suggest that lymphopenia may provide a clue to the link between these processes, and perhaps one day, aid in identifying the overarching mechanism of this disease.

Limitations

This study is retrospective, and data collection spanned more than 2 decades, highlighting the fact that the results may not necessarily be helpful prospectively, and that modern care approaches and contemporary large-scale analyses may provide a discordant story. Survival bias, and to some degree selection bias, may be an important confounder in the dataset. Those with more severe disease likely did not survive and therefore were not included. Alternatively, those who were doing well may not have been in active congenital heart disease care, as many are known to be lost to follow-up in adulthood.[28] Survival analysis could not be performed reliably due to the small number of deaths and transplants in this cohort. Hepatic wedge pressure was not collected routinely on every cardiac catheterization and was not included in our analysis.

Conclusion

Lymphopenia is present early after Fontan completion, often in childhood, and the incidence of lymphopenia increases up to 4 decades later. Those patients with lymphopenia have evidence of more significant portal hypertension, albeit with relatively normal traditional measures of liver function, suggesting that the relationship between lymphocyte count and the degree of FALD requires future study. In this study, patients with lymphopenia had higher hospitalization rates for decompensated heart failure and arrhythmia, at least in part, linking the clinical findings with disease burden.

Further studies evaluating the relationship between lymphatic dysfunction, FALD, and the impact upon adult Fontan morbidity and mortality are important to further advance our knowledge of this unique disease.

Ethics Statement

This is a retrospective chart review, and to adhere to ethical guidelines, institutional review board application was made and waiver of consent was granted.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective chart review, and a waiver of consent was obtained from the local institutional review board.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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