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Author for correspondence:
Tarek Alsaied, MD, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA. Tel: +513 6521226; Fax: +5136363952.
E-mail: tarek.alsaied@cchmc.org

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Lymphopenia in adults after the Fontan operation: prevalence and associations

Tarek Alsaied[1], Mathias Possner[1], Nicole Brown[1], Hassan Almeneisi[1], Cassandra Szugye[1], Andrew T. Trout[2,3], Omar Niss[4], Joseph J. Palermo[5], Faizeen Zafar[1], Jonathan R. Dillman[2,3], Gruschen R. Veldtman[1,6], Alexander R. Opotowsky[1,7] and Adam M. Lubert[1]

[1]Cincinnati Children's Hospital Heart Institute, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [2]Cincinnati Children's Hospital Medical Center, Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [3]Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [4]Division of Hematology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Centre, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [5]Cincinnati Children's Hospital Medical Center, Division of Gastroenterology, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [6]Adult Congenital Heart Disease, Heart Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia and [7]Boston Adult Congenital Heart Service, Boston Children's Hospital, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Lymphopenia is common in adults who have had a Fontan operation although its aetiology and clinical implications remain unknown. Previous work suggests an association between lymphopenia and both liver disease and splenomegaly. The objective of this study was to assess the prevalence of lymphopenia in adults with a Fontan circulation and evaluate its associations with risk factors and clinical outcomes. Using a retrospective cohort study design, we studied 73 adult Fontan patients (age 25.0 ± 8.4 years) who had a complete blood count and abdominal imaging performed. Patients with protein-losing enteropathy were excluded. Clinical data were extracted from hospital records. The mean white blood cell count was 6580 ± 220/ml with a mean lymphocyte count of 1223 ± 508/ml. Lymphopenia, defined as lymphocyte count <1000/ml, was present in 23 (32%) patients. Patients with lymphopenia had a lower total white blood cell count (5556 ± 2517 versus 7136 ± 1924/ml, $p = 0.009$) and a lower platelet count (162 ± 69 versus 208 ± 69 k/ml, $p = 0.008$). Lymphopenia was also associated with findings of portal hypertension, including splenomegaly (36 versus 14%, $p = 0.04$), varices (22 versus 6%, $p = 0.04$), and ascites (39 versus 14%, $p = 0.02$). Lymphopenia did not correlate with any cardiac imaging, haemodynamic or exercise testing variables. In conclusion, lymphopenia is common in adult Fontan patients and is associated with markers of portal hypertension. Larger studies are needed to better define the relationship between lymphopenia and clinical outcomes.

Introduction

The Fontan operation has improved survival of patients born with a single ventricle.[1,2] Nevertheless, the frequent insidious development of heart failure and multi-organ dysfunction in adults with a Fontan makes identifying high-risk patients a priority.[1,3–6] Lymphopenia in Fontan patients is common among those with protein-losing enteropathy or plastic bronchitis which rare complications hypothesised to be related to a lymphatic leak from the gastrointestinal or bronchial tract.[7–9] However, recent reports suggest a high prevalence of lymphopenia even in Fontan patients in the absence of a manifest lymphatic leak syndrome.[10] Further, lymphopenia appears to be associated with lower platelet count, suggesting a relationship with splenomegaly and Fontan-associated liver disease commonly seen in Fontan patients secondary to chronically elevated central venous pressure.[11] The objective of this study was to evaluate the prevalence and associations of lymphopenia in a group of adults after the Fontan operation.

Materials and methods

Patients

This retrospective study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act. Institutional electronic medical records were searched to identify all adult patients with a Fontan circulation (≥18 years of age) who had undergone a

complete blood count with differential and abdominal imaging by MRI or ultrasound between within 6 months of each other during the period between January 2012 and December 2018. Abdominal imaging is used as a routine clinical surveillance test for all adult Fontan patients at our institution using abdominal MRI or ultrasound examination every 1–3 years in agreement with the American Heart Association scientific statement for Fontan surveillance.[5]

We excluded patients with Fontan take down as well as those with clinical diagnosis of protein-losing enteropathy or plastic bronchitis as these conditions are associated with lymphatic leak and known to be associated with lymphopenia. Clinical protein-losing enteropathy was defined as any of the following clinical symptoms: oedema, abdominal distention and discomfort, diarrhoea, ascites, pleural and/or pericardial effusions in addition to hypoalbuminemia and evidence of enteric protein loss with stool alpha-1 antitrypsin.[12] Patients with other potential causes for lymphopenia, such as autoimmune disease, chronic steroid use, or infections around the time of the laboratory testing were excluded as well. Clinical findings, laboratory tests, liver imaging, and cardiac testing (including echocardiogram, cardiac magnetic resonance, exercise testing, and cardiac catheterisation) were compared between the groups of patients with and without lymphopenia. Since all testing were performed for clinical indications, not all the patients with data on lymphocyte count underwent all other testing.

Clinical data

Clinical and demographic data, including the underlying anatomic diagnosis and type of single-ventricle CHD, were abstracted from the electronic medical record (Epic Medical Systems Corporation, Verona, WI). The type of Fontan was classified as atriopulmonary connection, lateral tunnel, or extracardiac conduit. Additional parameters included age at the time of the evaluation, sex, age at Fontan operation, history of tachyarrhythmia defined as sustained atrial or ventricular tachycardia, and NYHA functional class. Clinical outcome measures were death, cardiac transplantation, unscheduled admissions, and heart failure symptoms requiring escalation of diuretics.

Laboratory tests

Laboratory data analysed included complete blood count with differential and liver transaminases, bilirubin, and gamma-glutamyl transferase. The laboratory data were obtained as part of the comprehensive assessment of the Fontan circulation according to our institutional recommendations for the surveillance of Fontan patients. Lymphopenia was defined as an absolute lymphocyte count below 1000 cell/ml and severe lymphopenia as <500 cell/ml. When more than one laboratory assessment was available, the assessment closest in time to the abdominal imaging was included.

Abdominal imaging

Liver stiffness by magnetic resonance elastography or by ultrasound shear wave elastography was measured per our institutional protocol.[13] Abdominal imaging reports were reviewed for the diagnosis of splenomegaly, presence of portosystemic shunts (varices), or ascites. When the patient had an ultrasound and magnetic resonance elastography, magnetic resonance elastography report was used. Splenomegaly was defined as a spleen size larger than 13 cm measured in the craniocaudal dimension. For this study, imaging findings of portal hypertension were defined as splenomegaly, ascites, or portosystemic shunts.[13]

Cardiac magnetic resonance

Cardiac magnetic resonance studies were performed on 1.5-T scanners (Ingenia; Philips Healthcare, Best, Netherlands) which are used for routine screening at our institution. All analyses were performed using commercially available software (QMass, Medis Medical Imaging Systems, Leiden, Netherlands).

Cardiac catheterisation

Cardiac catheterisation data collected included Fontan pathway pressure, ventricular end-diastolic pressures, aortic saturation, and pulmonary vascular resistance. Cardiac catheterisation was performed according to our standard institutional clinical protocol.

Cardiopulmonary exercise testing

Exercise testing was performed according to our institutional protocol using a calibrated cycle ergometer and a ramp protocol.[14] Gas exchange at rest, during exercise, and during recovery was analysed to determine peak VO_2.[15] Peak VO_2 was indexed to weight.[16] Exercise capacity was measured by percent of predicted oxygen consumption at peak exercise (% predicted VO_2) using the Wasserman equation.[17] Maximal exercise was defined as respiratory exchange ratio >1.09 or a heart rate >80% predicted. The relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) was recorded at peak exercise.

Statistical analysis

Two-sided Student's t-test or Mann–Whitney U-test were used to compare two groups of continuous variables if they were normally or non-normally distributed, respectively. Fisher's exact test was used to compare categorical variables between groups with and without lymphopenia. Univariate association between normally distributed variables was estimated using the Pearson correlation coefficient, while Spearman's correlation was used for non-normally distributed data. Odds ratio for adverse outcomes in patients with lymphopenia (death, unscheduled hospitalisation, and heart failure symptoms leading escalation of diuretics) were calculated from 2 x 2 tables. A two-tailed $p < 0.05$ was considered significant. Statistical analyses were performed using JMP® (version 12, SAS Institute Inc., Cary, NC).

Results

A total of 73 adult Fontan patients were included. The mean age at the time of lymphocyte count measurement was 27.8 ± 8.4 years, and 41 patients (56%) were women. The mean time since Fontan surgery was 18.8 ± 5.7 years. Demographic and clinical characteristics of the study cohort are detailed in Table 1. All patients had complete blood count with differential, abdominal imaging, echocardiogram, and laboratory liver function testing. The median absolute value of time between the complete blood count and liver imaging was 15 days (interquartile range: 7–156 days). Sixty-one patients (84%) had an abdominal MRI, 22 patients (30%) had an abdominal ultrasound, 52 patients (71%) had a cardiac catheterisation, 42 patients (58%) had a

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Table 1. Demographic and clinical characteristics of the study cohort

	All patients (n = 73)	Lymphopenia		p-Value
		Yes (n = 23)	No (n = 50)	
Age at time of lymphocyte measurement (years)	27.8 ± 8.4	26.4 ± 6.0	28.4 ± 9.2	0.25
Time since Fontan (years)	19.6 ± 5.7	19.5 ± 4.1	19.7 ± 6.3	0.83
Gender (female)	41 (56%)	10 (44%)	31 (62%)	0.11
Most recent BMI (kg/m^2)	24.8 ± 5.1	22.7 ± 3.6	25.8 ± 5.3	**0.005**
Cardiac diagnosis				0.13
Tricuspid atresia	23 (32%)	3 (13%)	20 (40%)	
Double-inlet left ventricle	11 (15%)	4 (17%)	7 (14%)	
HLHS	18 (25%)	8 (35%)	10 (20%)	
Unbalanced AV canal	6 (8%)	3 (13%)	3 (6%)	
Double-outlet right ventricle	5 (7%)	3 (13%)	2 (4%)	
Complex two-ventricle group*	4 (5%)	2 (9%)	2 (4%)	
Pulmonary atresia/IVS	3 (4%)	0 (0%)	3 (6%)	
Mitral atresia	1 (1%)	0 (0%)	1 (2%)	
Ebstein anomaly	2 (3%)	0 (0%)	2 (4%)	
Heterotaxy	3 (4%)	2 (8%)	1 (2%)	0.10
Type of Fontan circulation				0.24
Atriopulmonary Fontan	17 (23%)	3 (13%)	14 (28%)	
Lateral tunnel	37 (51%)	16 (70%)	21 (42%)	
Extracardiac conduit	19 (26%)	4 (17%)	15 (30%)	
Dominant ventricular morphology				0.12
Left	44 (61%)	11 (48%)	33 (67%)	
Right	29 (39%)	12 (52%)	17 (33%)	
History of tachyarrhythmia	28 (38%)	10 (44%)	18 (36%)	0.60
NYHA class				0.68
I	40 (55%)	12 (52%)	28 (56%)	
II	27 (37%)	10 (43%)	17 (34%)	
III	5 (7%)	1 (4%)	4 (8%)	
Ascites	16 (22%)	9 (39%)	7 (14%)	**0.02**
Portosystemic shunts (varices)	8 (11%)	5 (22%)	3 (6%)	**0.04**
Splenomegaly	15 (21%)	8 (36%)	7 (14%)	**0.04**
History of thromboembolism	15 (21%)	6 (26%)	9 (18%)	0.53

Results are presented as mean ± standard deviation or frequency (%).
AV = atrioventricular; BMI = body mass index; HLHS = hypoplastic left heart syndrome; IVS = intact ventricular septum.
*Complex two-ventricle group included two patients with superior-inferior ventricles (crisscross heart) and two patients with straddling tricuspid valve through an inlet ventricular septal defect.
p Value < 0.05 (statistically significant).

cardiac MRI, and 66 (90%) patients had a cardiopulmonary exercise stress test during the study period.

The mean white blood cell count in all patients was 6580 ± 220/ml with a mean lymphocyte count of 1223 ± 508/ml. There was a weak positive correlation between lymphocyte count and total white blood cell count (r = 0.32, p = 0.01). Lymphocyte count correlates neither with neutrophil, monocyte, or eosinophil count, nor with haemoglobin concentration or platelet count (Table 2). There was also no correlation between lymphocyte count and serum protein, albumin, liver function tests, liver stiffness derived from magnetic resonance elastography or kidney function markers (Table 2). There was no association between lymphocyte count and ventricular ejection fraction, the degree of atrioventricular valve regurgitation, Fontan pressures, percent-predicted VO_2, or ventricular end-diastolic volume (Table 2). Lymphocyte count had a weak positive correlation with the most recent body mass index (r = 0.27, p = 0.01).

Lymphopenia, defined as lymphocyte count <1000 cell/ml, was common and was seen in 23 (32%) of the patients. Only six patients (8%) had a severe lymphopenia defined as lymphocyte count <500 cell/ml. There was no statistically significant difference in age between patients with and without lymphopenia (26.4 ± 6.0 versus 28.4 ± 9.2 years, p = 0.252). Patients with lymphopenia

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Table 2. Correlation between lymphocyte counts and other variables

	Number of patients with each test	Correlation coefficient	p-Value
Body mass index (kg/m^2)	73	**0.27**	**0.01**
Ejection fraction (%, CMR)	42	−0.19	0.20
End-diastolic volume (mL/m^2, CMR)	42	0.13	0.35
End-systolic volume (mL/m^2, CMR)	42	0.24	0.10
Moderate or greater atrioventricular valve regurgitation (CMR/Echo)	73	0.01	0.85
Fontan pressure (mm Hg)	52	−0.08	0.51
Ventricular end-diastolic pressure (mm Hg)	52	−0.05	0.71
Pulmonary vascular resistance (iWu)	52	0.01	0.94
% predicted VO_2	66	0.07	0.59
VE/VCO_2 slope	66	−0.01	0.93
MRE shear liver stiffness (kPa)	61	−0.16	0.19
White blood cell count (/ml)	73	**0.32**	**0.01**
Neutrophils (/ml)	73	0.001	0.62
Monocytes (/ml)	73	−0.07	0.59
Eosinophils (/ml)	73	−0.12	0.35
Haemoglobin (gm/dL)	73	0.05	0.68
Platelet count (K/mcL)	73	0.01	0.91
Alanine aminotransferase (unit/L)	73	−0.11	0.80
Aspartate aminotransferase (unit/L)	73	−0.04	0.93
Total bilirubin (mg/dL)	68	−0.13	0.77
Gamma-glutamyl transferase (unit/L)	73	−0.11	0.81
Serum creatinine (mg/dL)	73	0.09	0.83
Serum cystatin C (mg/L)	43	−0.06	0.89
Serum BUN (mg/dL)	73	−0.06	0.89
Total protein (g/dL)	73	0.05	0.91
Albumin (g/dL)	73	−0.04	0.93

BUN = blood urea nitrogen; CMR = cardiac MRI, iWu = indexed Woods unit; MRE = magnetic resonance elastography.
p Value < 0.05 (statistically significant).

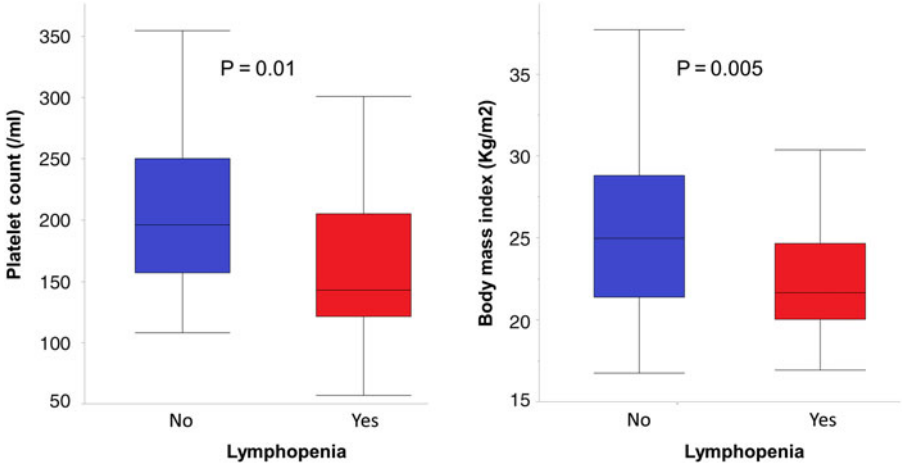

Figure 1. Lymphopenia and its association with findings of portal hypertension.

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Table 3. Medications used in the study population. Data are presented as number of patients (%)

	All patients (n = 73)	Lymphopenia		p-Value
		Yes (n = 23)	**No (n = 50)**	
Beta blocker	20 (27%)	4 (17%)	11 (22%)	0.79
Digoxin	6 (8%)	2 (8%)	4 (8%)	0.40
Angiotensin-converting enzyme inhibitor	34 (47%)	12 (52%)	22 (44%)	0.26
Aspirin	47 (64%)	15 (63%)	32(64%)	0.26
Warfarin	25 (34%)	8 (35%)	17 (34%)	0.89
Rivaroxaban	1 (2%)	0	1 (1%)	0.90
Amiodarone	2 (3%)	0	2 (4%)	0.35
Sotalol	1 (1%)	0	1 (1%)	0.90
Verapamil	1 (1%)	0	1 (1%)	0.90
Propafenone	1 (1%)	1 (4%)	0	0.30
Angiotensin-converting enzyme inhibitor	34 (47%)	12 (52%)	22 (44%)	0.26
Spironolactone	26 (35%)	8 (35%)	18 (36%)	0.95

had a significantly lower body mass index compared to patients without lymphopenia (22.7 ± 3.6 versus 25.8 ± 5.3 kg/m^2, p = 0.01) (Fig 1). Patients with lymphopenia had a significantly lower total white blood cell count (5556 ± 2517 versus 7136 ± 1924/ml, p = 0.01), lower monocyte count (445 ± 187 versus 679 ± 704/ml, p = 0.03), and lower platelet count (162 ± 69 versus 208 ± 69 k/ml, p = 0.01) (Fig 1). Patients with lymphopenia were more likely to have imaging findings of portal hypertension, including splenomegaly (8/23 patients [36%] versus 7/50 patients [14%], p = 0.04), portosystemic shunts (5/23 patients [22%] versus 3/50 patients [6%], p = 0.04), and ascites (9/23 patients [39%] versus 7/50 patients [14%], p = 0.02) (Fig 2). There was no difference in the type of medications used in patients with lymphopenia compared to patients without lymphopenia (Table 3). There was no difference between patients with and without lymphopenia in any laboratory liver or kidney function tests or in any of the cardiac imaging, catheterisation, or exercise testing measures (Tables 1, 4).

During a follow-up period of 3.6 ± 1.8 years from the time of lymphocyte count measurement, there were 4 deaths, 1 cardiac transplant, 23 unscheduled admissions, mostly for arrhythmia, and 13 patients developed symptoms consistent with progressive heart failure leading to escalation of diuretics, one of whom received a ventricular assist device. There was no association of lymphopenia or lymphocyte count with any of these clinical outcomes (Table 5).

Discussion

In this cohort of adults who have a Fontan circulation, lymphopenia was common and present in a third of patients. Lymphopenia was associated with lower total white blood cell count as well as lower platelet count and a lower body mass index. In addition, splenomegaly, ascites, and varices were common in the setting of lymphopenia suggesting a link with portal hypertension. There was no association of lymphopenia with kidney function, haemodynamic variables, exercise capacity, or clinical outcomes.

Prior reports suggest even higher frequency of lymphopenia, up to 47%, in patients with a Fontan circulation in a paediatric and adult Fontan population who underwent cardiac catheterisation for clinical haemodynamic assessment.[10] In line with results from prior analyses, we found an association between lymphopenia and lower white cell, lower monocyte, and platelet counts.[10,18]

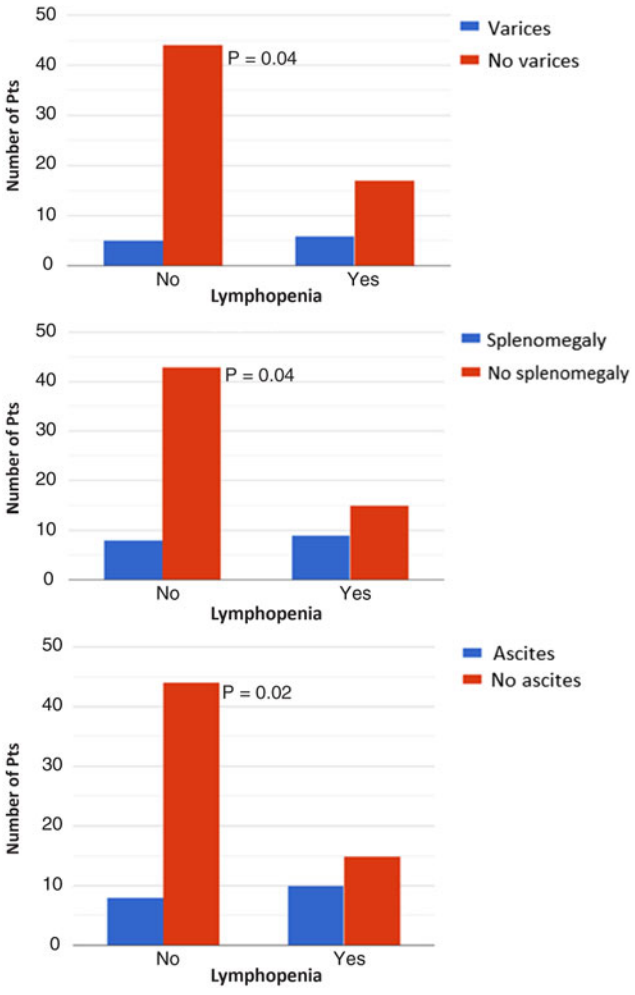

Figure 2. Lymphopenia is associated with thrombocytopenia and lower BMI.

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Table 4. Haemodynamic, cardiac imaging, laboratory, liver imaging, and exercise data in patients with and without lymphopenia

	Number of patients with each test	All patients (n = 73)	Lymphopenia		p-Value
			Yes (n = 23)	**No (n = 50)**	
Ejection fraction (%, CMR)	42	50 ± 8	50 ± 8	51 ± 10	0.87
End-diastolic volume (mL/m^2, CMR)	42	98 ± 32	97 ± 20	98 ± 37	0.92
End-systolic volume (mL/m^2, CMR)	42	51 ± 25	49 ± 16	52 ± 29	0.69
Moderate or greater atrioventricular valve regurgitation (CMR/Echo)	73	8 (11%)	3 (13%)	5 (10%)	0.63
Fontan pressure by catheterisation closest to the lymphocyte count (mm Hg)	52	13.6 ± 3.9	13.9 ± 3.4	13.2 ± 4.3	0.58
Ventricular end-diastolic pressure (mm Hg)	52	10.6 ± 3.8	10.5 ± 4.3	10.6 ± 3.9	0.91
Pulmonary vascular resistance (iWu)	52	1.5 ± 0.9	1.4 ± 0.7	1.6 ± 0.9	0.46
Aortic saturation (%)	52	91 ± 5	90 ± 7	91 ± 5	0.61
Peak VO_2 (mL/kg/min)	66	22.1 ± 6.5	24.5 ± 6.7	21.2 ± 6.3	0.07
% predicted VO_2	66	60.1 ± 15.5	58.7 ± 12.0	61.0 ± 15.3	0.54
VE/VCO_2 slope	66	37.7 ± 7.5	37.9 ± 6.0	37.4 ± 8.5	0.80
MRE shear liver stiffness (kPa)	61	4.5 ± 1.0	4.9 ± 1.1	4.4 ± 0.9	0.10
White blood cell count (/ml)	73	6587 ± 2292	5556 ± 2517	7136 ± 1924	**0.01**
Neutrophils (/ml)	73	4616 ± 2009	4278 ± 2451	4840 ± 1743	0.32
Monocytes (/ml)	73	608 ± 614	445 ± 187	679 ± 704	**0.03**
Eosinophils (/ml)	73	149 ± 119	132 ± 143	155 ± 104	0.49
Haemoglobin (g/dL)	73	16.1 ± 1.6	15.8 ± 1.4	16.2 ± 1.7	0.31
Platelet count (K/ml)	73	189 ± 71	162 ± 69	208 ± 69	**0.01**
Alanine aminotransferase (unit/L)	73	38 ± 19	40 ± 21	36 ± 17	0.47
Aspartate aminotransferase (unit/L)	73	25 ± 10	27 ± 12	25 ± 9	0.51
Total bilirubin (g/dL)	68	0.8 (0.6–1.2)	0.7 (0.5–1.0)	0.8 (0.7–1.2)	0.19
Gamma-glutamyl transferase (unit/L)	73	101 ± 102	123 ± 154	89 ± 62	0.30
Serum creatinine (mg/dL)	73	0.79 ± 0.19	0.78 ± 0.19	0.78 ± 0.20	0.92
Serum cystatin C (mg/L)	43	0.80 ± 0.23	0.88 ± 0.37	0.80 ± 0.20	0.52
Serum BUN (mg/dL)	73	14 ± 5	14 ± 5	14 ± 5	0.89
Total protein (g/dL)	73	7.8 ± 0.8	7.6 ± 1.0	7.8 ± 0.7	0.33
Albumin (g/dL)	73	4.3 ± 0.5	4.2 ± 0.6	4.2 ± 0.4	0.63

Data are presented as mean ± standard deviation or median (interquartile range).
Results are presented as mean ± standard deviation or frequency (%).
BUN = blood urea nitrogen; CMR = cardiac MRI, iWu = indexed Woods unit; MRE = magnetic resonance elastography.
p Value < 0.05 (statistically significant).

Table 5. Associations of lymphopenia with clinical outcomes

Clinical outcome	Clinical outcome odds ratio in patients with lymphopenia	Confidence interval	p-Value
Death	1.4	0.1–14.2	0.79
Unscheduled hospitalisation	1.2	0.6–3.2	0.31
Heart failure symptoms requiring escalation of therapy	0.6	0.2–2.4	0.74

We also found no association of lymphopenia with any invasive haemodynamic parameters.

Most patients in the present cohort had mild lymphopenia in the range of 500–1000/ml. Whether more pronounced lymphopenia is a risk factor for poor outcomes has to be addressed in future research, since the number of patients with this finding was low in the current cohort. A previous study reported an increased prevalence of cutaneous infections (molluscum

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contagiosum and human papillomavirus warts) in Fontan patients with lymphopenia, but more severe opportunistic infections have not been reported.[18]

While patients with protein-losing enteropathy commonly develop lymphopenia, we were able to demonstrate that lymphopenia is common even in patients without protein-losing enteropathy. It is possible that many patients have subclinical lymphatic leak causing lymphopenia even when protein-losing enteropathy is not apparent. Additional mechanisms could also play a role in the development of lymphopenia. One possible explanation is that many patients with Fontan circulation may have had a total thymectomy at a previous cardiac surgery, which is known to be associated with lymphopenia.[19] Unfortunately, available surgical reports are not consistent in reporting total versus partial thymectomy. Previous work, however, showed that thymectomy post-congenital heart surgery in children decreases T cell diversity and may increase the susceptibility to autoimmune disease in children.[20] Further studies are needed in adults with CHD.

The fact that patients in our cohort with lymphopenia were more likely to have splenomegaly, ascites, varices, and lower platelet counts suggests that portal hypertension may be an important contributor to the development of lymphopenia in Fontan patients. Splenomegaly, ascites, thrombocytopenia, and portosystemic varices are common in Fontan patients as a consequence of portal hypertension secondary to high central venous pressures and Fontan-associated liver disease. Cirrhosis in other populations is linked to lymphopenia by multiple mechanisms, including loss of memory B and T cells, decreased production of the T cells in the thymus, increased sequestration with apoptosis of the lymphocytes in the spleen, and decreased proliferation of the lymphocytes.[21] Portal hypertension is associated with mortality in the Fontan population; our findings suggest that screening for portal hypertension should be performed in Fontan patients with lymphopenia.[11]

A limitation of this study includes its single-centre retrospective study nature, and therefore, further studies are needed to validate our findings in other Fontan populations. Also, our study did not evaluate the impact of hepatic fibrosis on the development of lymphopenia due to the lack of liver biopsy data. The relationship between the change in lymphocyte count and the change in clinical status is not addressed by the current cross-sectional analysis and deserves further consideration. Furthermore, although we excluded patients with clinical protein losing enteropathy (PLE) from the study, a group of patients may have had subclinical PLE with protein losing from the intestine while still have no symptoms and normal albumin. This could not be evaluated as data for alpha-1 antitrypsin in the stool was not available for the majority of the population although albumin level was normal in all patients. Another limitation is that this study included very few patients with asplenia and it will be interesting to evaluate how heterotaxy may interact with the lymphocyte count. Finally, this study was underpowered to consider the relationship between lymphocyte count and clinical endpoints.[22]

Conclusions

Lymphopenia is common in adult Fontan patients without protein-losing enteropathy, with a prevalence of 32% in our study. Lymphopenia was not associated with Fontan failure (death, hospitalisation, or heart failure symptoms) in this cohort, but was significantly associated with findings of portal hypertension, including ascites, varices, low platelet count, and splenomegaly. The study design does not answer causality, but screening for portal hypertension with abdominal and liver imaging may be warranted in Fontan patients with lymphopenia.

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Conflicts of interest

None.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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