Received: 14 March 2024 | Revised: 16 July 2024 | Accepted: 28 July 2024

DOI: 10.1002/pbc.31251

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

RESEARCH ARTICLE

Treatments affecting splenic function as a risk factor for valvular heart disease in Childhood Cancer Survivors: A DCCSS-LATER study

Bente M. Houtman[1,2] | Iris Walraven[3] | Livia Kapusta[4,5] | Arco J. Teske[6] | Eline van Dulmen-den Broeder[7] | Wim J. E. Tissing[8,9] | Marry M. van den Heuvel-Eibrink[8,10,11] | A. B. Birgitta Versluys[8] | Dorine Bresters[8] | Margriet van der Heiden-van der Loo[8] | Cécile Ronckers[8,12] | Wouter E. M. Kok[13] | Helena J. H. van der Pal[8] | Saskia M. F. Pluijm[8] | Geert O. Janssens[8,14] | Nicole M. A. Blijlevens[15] | Leontien C. M. Kremer[8,11,16] | Jacqueline J. Loonen[1] | E. A. M. Lieke Feijen[8]

[1]Radboudumc Center of Expertise for Cancer Survivorship, Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

[2]Research Institute for Medical Innovation, Radboud University Medical Center, Nijmegen, The Netherlands

[3]Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

[4]Department of Pediatric Cardiology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, The Netherlands

[5]Department of Pediatrics, Pediatric Cardiology Unit, Tel Aviv Sourasky Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[6]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

[7]Department of Pediatric Oncology, Amsterdam UMC, VU University, Amsterdam, The Netherlands

[8]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[9]Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[10]Department of Pediatric Oncology, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

[11]Wilhelmina Children's Hospital, University Medical Center, Utrecht, The Netherlands

[12]Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[13]Department of Cardiology Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[14]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

[15]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

[16]Department of Pediatric Oncology, Emma Children's Hospital, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Bente M. Houtman, Center of Expertise for Cancer Survivorship, Radboud University Medical Center, Postbus 9101, In-House Postal Number 942, 6500 HB Nijmegen, The Netherlands.
Email: bente.houtman@radboudumc.nl

Abstract

Purpose: Splenectomy might be a risk factor for valvular heart disease (VHD) in adult Hodgkin lymphoma survivors. As this risk is still unclear for childhood cancer survivors (CCS), the aim of this study is to evaluate the association between treatments affecting splenic function (splenectomy and radiotherapy involving the spleen) and VHD in CCS.

Abbreviations: CCS, childhood cancer survivors; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; DCCSS-LATER, Dutch Childhood Cancer Survivor Study LATER; GP, general practitioner; HR, hazards ratio; ICCC3, Third edition of the International Classification of Childhood Cancer; TBI, total body irradiation; VHD, valvular heart disease.

Jacqueline J. Loonen and E. A. M. Lieke Feijen share senior authorship of this article.

Funding information
European Union's Seventh Framework Programme for research, technological development, and demonstration, Grant/Award Number: 257505; KWF Kankerbestrijding

Methods: CCS were enrolled from the DCCSS-LATER cohort, consisting of 6,165 five-year CCS diagnosed between 1963 and 2002. Symptomatic VHD, defined as symptoms combined with a diagnostic test indicating VHD, was assessed from questionnaires and validated using medical records. Differences in the cumulative incidence of VHD between CCS who received treatments affecting splenic function and CCS who did not were assessed using the Gray test. Risk factors were analyzed in a multivariable Cox proportional hazards model.

Results: The study population consisted of 5,286 CCS, with a median follow-up of 22 years (5-50 years), of whom 59 (1.1%) had a splenectomy and 489 (9.2%) radiotherapy involving the spleen. VHD was present in 21 CCS (0.4%). The cumulative incidence of VHD at the age of 40 years was significantly higher in CCS who received treatments affecting splenic function (2.7%, 95% confidence interval (CI) 0.4%-4.9%) compared with CCS without (0.4%, 95% CI 0.1%-0.7%) (Gray's test, $p = 0.003$). Splenectomy was significantly associated with VHD in a multivariable analysis (hazard ratio 8.6, 95% CI 3.1-24.1).

Conclusions and implications: Splenectomy was associated with VHD. Future research is needed to determine if CCS who had a splenectomy as part of cancer treatment might benefit from screening for VHD.

KEYWORDS
Childhood cancer survivors, heart valve diseases, late effects, spleen, splenectomy

1 | INTRODUCTION

A growing number of childhood cancer survivors (CCS) are confronted with the late effects of cancer treatment, leading to chronic morbidity and premature mortality.[1,2] One of these late effects is valvular heart disease (VHD).[3,4] VHD is associated with the development of congestive heart failure, reduced health-related quality of life, and early mortality.[5] As early detection and early intervention can improve the outcome of VHD treatment,[6] knowledge about risk factors for VHD in CCS is crucial and can inform surveillance guidelines.[5]

The prevalence of VHD in CCS is reported to be up to 43.1%.[3,4,7,8] The most important risk factor for VHD among cancer survivors is radiotherapy involving the heart area. The risk increases with radiation dose and time interval from exposure.[4,8–10] The association between anthracyclines and VHD remains unclear.[11]

Splenectomy was identified as an independent risk factor for VHD in adult Hodgkin lymphoma survivors.[12] Infective endocarditis could be an underlying mechanism for VHD, as asplenia is associated with an increased infection risk.[13] Several case reports described endocarditis caused by micro-organisms that are associated with asplenia.[14–16] Furthermore, splenectomy is associated with changes in blood composition, which might increase the risk for VHD.[17] The independent association between splenectomy and VHD, and the effect of splenic dysfunction after radiotherapy involving the spleen on the occurrence of VHD have not been studied before in CCS. We hypothesize that splenic dysfunction induced by treatments affecting splenic function, i.e., splenectomy or radiotherapy involving the spleen, impacts valvular function during long-term follow-up, irrespective of radiotherapy involving the heart area.

In this study, we investigate the cumulative incidence of VHD in CCS of the Dutch Childhood Cancer Survivor Study (DCCSS)-LATER cohort who received treatments affecting splenic function, compared with CCS without those treatments. We also investigate whether treatment affecting splenic function is a risk factor for VHD.

2 | METHODS

2.1 | Study population

The study population for this retrospective cohort study was obtained from the nationwide DCCSS-LATER cohort, previously described by Teepen et al.[18] This cohort includes 6,165 five-year CCS, who were diagnosed with a malignancy according to the third edition of the International Classification of Childhood Cancer (ICCC3)[19] and a few selected other conditions before the age of 18 years, and treated in one of seven Dutch pediatric oncology/hematology centers between January 1, 1963, and December 31, 2001. Data regarding cancer diagnosis and treatment were collected from patient files using a standardized protocol. Additional information was obtained from questionnaires.[18]

The current study included all patients with available data regarding treatments affecting splenic function and cardiac follow-up as described by Feijen et al.[20] Patients with known hemodynamically significant congenital heart disease, unknown cause of death, and patients lost to follow-up within five years from childhood cancer diagnosis were excluded.

2.2 | Data collection

Information regarding potential VHD was collected using questionnaires and validated using medical records as described by Feijen et al.[20] Two questionnaires were used: the DCCSS-LATER questionnaire, filled out by the survivor, and the general practitioner (GP) DCCSS-LATER questionnaire, filled out by the primary physician of nonresponders. Feijen et al.[21] developed an extraction-flowchart method for consistent and valid grading of VHD using a data extraction form and flowchart to grade VHD according to the Common Terminology Criteria for Adverse Events (CTCAE).[21] The outcome of interest was symptomatic VHD grade 3 (symptoms controlled with medication), grade 4 (valve replacement or valvuloplasty), or grade 5 (death due to VHD). The incidence date was defined as the date of a diagnostic test indicating VHD combined with symptoms. For known deceased CCS, the main cause of death and underlying diseases at the time of death were extracted from the medical records, as described by Kilsdonk et al.[21,22] Cardiotoxic therapy was defined as treatment with anthracyclines and/or radiotherapy involving the heart area. Treatments affecting splenic function were defined as splenectomy or radiotherapy involving the spleen.

The cumulative anthracycline dose was calculated by summing the doxorubicin-equivalent doses of each substance (daunorubicin [× 0.6], epirubicin [× 0.8], idarubicin [× 3], mitoxantrone [× 10.5]), based on the previously published equivalence ratio.[23]

The mean prescribed radiation dose to the heart area was estimated using 100% of the thoracic irradiation dose, 55% of the abdominopelvic irradiation dose, and 10% of the spinal irradiation dose, as described by Merkx et al.[24] If more than one of these body compartments was irradiated, the highest dose was assigned as the dose received by the heart area. If applicable, 100% of the total prescribed TBI (total body irradiation) dose was added to this dose, to estimate the final radiotherapy dose to the heart area. Radiotherapy involving the spleen includes irradiation to the spleen, left hemi-abdomen, left kidney, inverted-Y, para-aortic, total node, (total) abdominal irradiation, and/or TBI.

2.3 | Statistical analyses

Demographic, tumor, and treatment-related characteristics were summarized using descriptive statistics. Continuous outcomes were compared using the Mann-Whitney *U* test and categorical variables by the Chi-squared test or Fisher exact test.

End of cardiac follow-up was defined as the date of death, date of completion of the (GP) DCCSS-LATER questionnaire, or date of the last recorded patient contact that took place ≥5 years after diagnosis. Death due to another cause than VHD was considered a competing event.[25] VHD was evaluated with time at risk starting at 5 years after childhood cancer diagnosis, and ending on the incidence date of VHD or at the end of cardiac follow-up, whichever occurred first. Only VHD diagnosed ≥5 years after childhood cancer diagnosis was evaluated. We estimated the cumulative incidence of VHD overall and stratified by treatment affecting splenic function at several time points. Attained age at follow-up and time since diagnosis were used as a timescale. Between-group differences were analyzed using the Gray test.[26] To correct for the effects of other heart diseases on the occurrence of VHD, we also estimated the cumulative incidence of VHD if no previous cardiac events were diagnosed.

A multivariable Cox proportional hazards model was used to assess treatments affecting splenic function as a risk factor for VHD. Attained age was used as a timescale. The model was adjusted for sex. Other covariables were based on the literature and clinical knowledge and included radiation dose to the heart area (per 10 Gray) and cumulative anthracycline dose (per 100 mg/m^2). We selected variables to include in the multivariable model based on a p-value of < 0.2 in univariable analysis. Diagnosis was not included in the model to avoid over-adjusting due to overlap with treatment. A univariable analysis using quadratic and cubic polynomials was used to evaluate the linearity of variables. AIC model selection was used to select the best-fit model. A separate analysis to evaluate the association between splenectomy and VHD was performed that included CCS diagnosed with lymphoma only. Due to the limited number of events, we only corrected for radiotherapy exposing the heart, as this was observed to be the most important confounder.

Two-sided p-values were reported, and $p < 0.05$ was considered statistically significant. Analyses were performed using R (version 3.5.3; R foundation) and SPSS (version 24; IBM SPSS Statistics).

3 | RESULTS

3.1 | Study population, and events of valvular heart disease

Patient inclusion is shown in Figure 1. The DCCSS-LATER cohort included 6,165 CCS. For 5,286 (85.7%) CCS, data regarding cardiac follow-up and treatments affecting splenic function were available. A total of 548 CCS (10.4%) received treatments affecting splenic function. Data from participants versus nonparticipants are shown in Supplementary Table S1. A significant difference was noted in the number of CCS who received treatment including anthracyclines or radiotherapy involving the heart area.

Table 1 presents the characteristics of the included CCS. After a median follow-up time of 21.6 years (range, 5.0-50.4 years), 4,620 (87.4%) CCS were alive. The median attained age was 27.7 years (range, 5.1-65.2 years). In the total cohort, 58.0% of CCS received cardiotoxic treatment, which was 97.8% of the CCS who received treatments

TABLE 1 Patient, cancer, and treatment characteristics of the five-year CCS in the DCCSS-LATER cohort, comparing survivors with and without treatment affecting the spleen.

Characteristics	Cardiac follow-up *n* = 5,286 *n* (%)	Treatments affecting spleen *n* = 548 (10.4%) *n* (%)	No treatments affecting spleen *n* = 4,738 (89.6%) *n* (%)	*p*-value*
Sex				
Male	2,952 (55.8)	322 (58.8)	2,630 (55.5)	0.15
Female	2,334 (44.2)	226 (41.2)	2,108 (44.5)	
Primary childhood cancer (ICCC3)				
Leukemias, myeloproliferative diseases, myelodysplastic diseases	1,843 (34.9)	202 (36.9)	1,641 (34.6)	<0.01
Lymphomas and reticuloendothelial neoplasms	919 (17.4)	113 (20.6)	806 (17.0)	
CNS tumors	693 (13.1)	1 (0.2)	692 (14.6)	
Neuroblastoma	271 (5.1)	34 (6.2)	237 (5.0)	
Renal tumors	510 (9.6)	166 (30.3)	344 (7.3)	
Bone tumors	313 (5.9)	3 (0.5)	310 (6.5)	
Sarcomas	382 (7.2)	16 (2.9)	366 (7.7)	
Other	355 (6.7)	13 (2.4)	342 (7.2)	
Age at cancer diagnosis (y), median (IQR)	5.6 (2.8-10.5)	6.2 (3.1-12.0)	5.6 (2.8-10.4)	<0.01
Treatment period				
1960-1969	87 (1.6)	21 (3.8)	66 (1.4)	<0.01
1970-1979	794 (15.0)	131 (23.9)	663 (14.0)	
1980-1989	1,660 (31.4)	159 (29.0)	1,501 (31.l7)	
1990-1999	2,223 (42.1)	208 (38.0)	2015 (42.5)	
2000-2001	522 (9.9)	29 (5.3)	493 (10.4)	
Overall treatment modality				
No therapy	40 (0.8)	0 (0)	40 (0.8)	<0.01
Surgery only	448 (8.5)	1 (0.2)	447 (9.4)	
Chemotherapy ± surgery	2,605 (49.3)	6 (1.1)	2,599 (54.9)	
Radiotherapy ± surgery	402 (7.4)	39 (7.1)	350 (7.4)	
Chemotherapy and radiotherapy ± surgery	1,765 (33.4)	502 (91.6)	1,263 (26.7)	
Unknown	39 (0.7)	0 (0)	39 (0.8)	
Hematopoietic stem cell transplant				
No	4,843 (91.6)	320 (58.4)	4,523 (95.5)	<0.01
Autologous	146 (2.8)	54 (9.9)	92 (1.9)	
Allogenic	213 (4.0)	171 (31.2)	42 (0.9)	
Unknown	84 (1.6)	3 (0.5)	81 (1.7)	
Cardiotoxic treatment				
No cardiotoxic treatment	2,158 (40.8)	5 (0.9)	2,153 (45.4)	<0.01
Anthracyclines (including mitoxantrone) only	1,877 (35.5)	9 (1.5)	1,868 (39.4)	
Radiotherapy involving the heart only	576 (10.9)	194 (35.4)	382 (8.1)	
Anthracyclines (including mitoxantrone) and radiotherapy involving the heart	611 (11.6)	333 (60.8)	278 (5.9)	
Unknown	64 (1.2)	7 (1.3)	57 (1.2)	
Anthracyclines, median dose (IQR) (including mitoxantrone)	192 (132-320)	202 (150-300)	180 (132-330)	0.06
Radiotherapy involving the heart, median dose (IQR)	24.0 (19.3-36.0)	30.0 (21.0-40.0)	22.0 (19.3-35.0)	<0.01

(Continues)

TABLE 1 (Continued)

Characteristics	Cardiac follow-up *n* = 5,286 *n* (%)	Treatments affecting spleen *n* = 548 (10.4%) *n* (%)	No treatments affecting spleen *n* = 4,738 (89.6%) *n* (%)	*p*-value*
Treatments affecting splenic function				
No treatments affecting splenic function	4,738 (89.6)	0 (0)	4,738 (100)	<0.01
Splenectomy	59 (1.1)	59 (10.8)	0 (0)	
Radiotherapy involving the spleen	489 (9.2)	489 (89.2)	0 (0)	
Vital status				
Alive	4,620 (87.4)	431 (78.6)	4,189 (88.4)	<0.01
Deceased	666 (12.6)	117 (21.4)	549 (11.6)	
Attained age (y), median (min-max)	27.7 (5.1-65.2)	30.5 (5.8-59.7)	27.3 (5.1-65.2)	<0.01
Follow-up duration from primary cancer diagnosis (y), median (min-max)	21.6 (5.0-50.4)	22.6 (5.1-48.8)	20.0 (5.0-50.4)	<0.01
Valvular heart disease	21 (0.4)	8 (1.5)	13 (0.3)	<0.01
Other cardiac events				
Heart failure	104 (2.0)	15 (2.7)	89 (1.9)	0.17
Cardiac ischemia	19 (0.4)	8 (1.5)	11 (0.2)	<0.01
Arrhythmia	39 (0.7)	7 (1.3)	32 (0.7)	0.19

Abbreviations: CNS: central nervous system;ICCC3: third edition of the International Classification of Childhood Cancer; IQR: interquartile range.
**P*-value for difference between CCS with and without treatments affecting splenic function (Chi-squared test and Mann-Whitney *U* test).

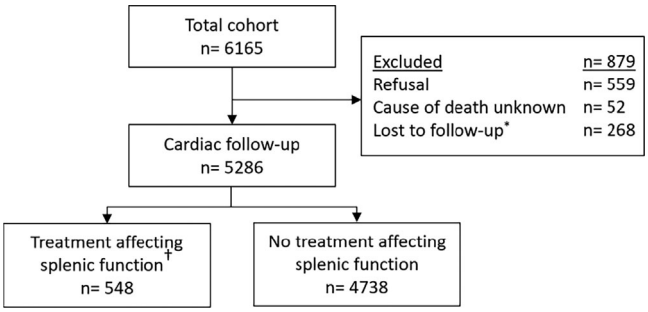

FIGURE 1 Flowchart of patient inclusion. *No visits recorded ≥5 years from a childhood cancer diagnosis. †Treatments affecting splenic function include splenectomy and radiotherapy involving the spleen.

affecting splenic function, and 53.4% of CCS without these treatments (Supplementary Table S2).

Symptomatic VHD was present in 21 CCS (0.4%), of whom 8 (38.1%) had received treatments affecting splenic function (6 splenectomy, 2 radiotherapy involving the spleen). No CCS died due to VHD. Table 2 shows characteristics of VHD by treatment group. Both age at VHD diagnosis and age at childhood cancer diagnosis were significantly higher in CCS who received treatments affecting splenic function compared with CCS who did not. However, the time from cancer diagnosis to VHD diagnosis was similar between groups. Furthermore, no significant differences were found in the involved valve, the grade of VHD, radiotherapy dose to the heart area or anthracycline dose. In all, 15 of 21 cases occurred among survivors of pediatric lymphoma. One CCS had aortic valve stenosis after endocarditis. Individual case information is given in Table 3.

3.2 | Cumulative incidence

The cumulative incidence of VHD at the age of 40 years was 0.8% (95% CI, 0.4%-1.3%) (Supplementary Table S3). This was 2.7% (95% CI, 0.4%-4.9%) for CCS who received treatments affecting splenic function compared with 0.4% (95% CI, 0.1%-0.7%) for CCS without these treatments (Gray test, $p = 0.003$), as shown in Figure 2. The cumulative incidence of VHD at 40 years follow-up since cancer diagnosis was 1.7% (95% CI 0.6%-2.9%) (Supplementary Table S4). This was 3.7% (95% CI 0.8%-6.7%) for CCS who received treatments affecting splenic function and 1.3% (95% CI 0.1%-2.50%) for CCS who did not (Gray test, $p = 0.003$). Cumulative incidence analyses only taking into account VHD if this was the first cardiac event yielded similar results (Supplementary Tables S3-S4 and Supplementary Figures S1-S2).

3.3 | Risk factor analysis

Table 4 shows the results of the multivariable analysis of risk factors for VHD (results of the univariable analysis are shown in Supplementary Table S5). Splenectomy (hazards ratio (HR) 8.6, 95% CI, 3.1-24.1), increasing dose of radiotherapy to the heart area (per 10 Gray) (HR 1.7, 95% CI, 1.4-2.1), and increasing dose of anthracyclines (per 100 mg/m^2) (HR 1.2, 95% CI, 1.1-1.5) were all independently asso-

TABLE 2 Characteristics of patients with symptomatic VHD by treatments affecting splenic function in the DCCSS-LATER cohort of five-year CCS.

Characteristics	Treatments affecting splenic function *n* = 8 (1.46%)* | *n* (%)	No treatments affecting splenic function *n* = 13 (0.27%)* | *n* (%)	*p*-value*
Age at VHD diagnosis (y), median (IQR)	37.7 (35.3-44.6)	28.2 (20.1-39.5)	0.04
Age at cancer diagnosis(y), median (IQR)	13.9 (9.7-14.7)	7.9 (3.5-11.7)	0.05
Follow-up duration from primary cancer diagnosis (y), median (IQR)	24.7 (22.7-31.3)	22.8 (14.5-28.8)	0.31
Radiotherapy field involving the heart, median dose (IQR)	36.0 (35.1-39.9)	25.0 (19.4-40.0)	0.19
Anthracyclines, median dose (IQR) (including mitoxantrone)	550 (140-918)	420 (167-478)	0.62
Involved valve			
Aortic valve	5 (62.5)[a]	3 (23.1)	0.24
Mitral valve	3 (37.5)	4 (43.8)	
Tricuspid valve	0 (0)	3 (23.1)	
Pulmonary valve	0 (0)	0 (0)	
Multiple valves	0 (0)	3 (23.1)[b]	
Grade (according to CTCAE)			
3	2 (25.0)	4 (30.8)	0.78
4	6 (75.0)	9 (69.2)	

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; IQR: interquartile range; VHD: valvular heart disease.
[a]One CCS had aortic valve endocarditis.
[b]Two CCS mitral valve + tricuspid valve involvement; 1 CCS aortic valve + mitral valve involvement.
*Percentage of patients treated with or without treatments affecting splenic function.

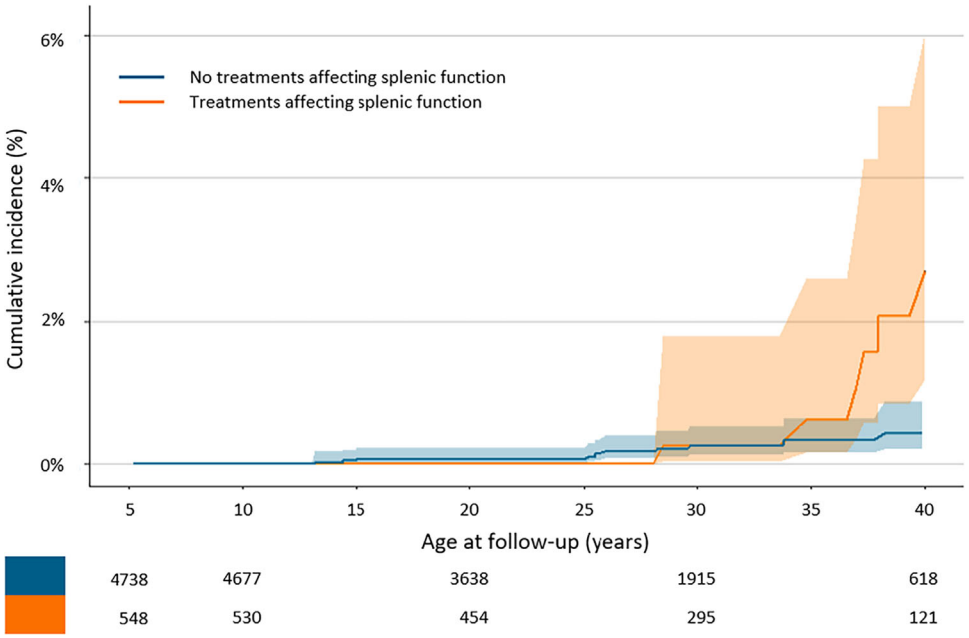

FIGURE 2 Cumulative incidence of symptomatic VHD for CCS who received treatments affecting splenic function and CCS who did not, with attained age as time scale. Shaded areas indicate 95% CI. Gray test $P = 0.003$.

TABLE 3 Individual case information for CCS diagnosed with VHD.

Patient	Sex	Deceased	Cancer diagnosis	Age at cancer diagnosis (y)	Age at VHD diagnosis (y)	Time since diagnosis (y)	Treatments affecting splenic function	Anthracycline dose (mg/m^2)	Chest radio-therapy dose (Gy)	Age at valve diagnosis	Affected valve	Grade	Type of defect
1	F	N	Malignant gonadal teratoma	12.5	29.7	17.7	None	NA	NA	29.7	Mitral	4	Regurgitation
2	M	N	Hodgkin lymphoma	4.8	43.6	38.8	None	NA	40.0	43.6	Aortic	4	Stenosis
3	M	N	Hodgkin lymphoma	4.9	40.7	35.8	None	NA	40.0	40.7	Aortic	4	Stenosis
4	M	N	Hodgkin lymphoma	8.6	38.3	29.8	None	NA	25.0	38.3	Aortic	3	Stenosis
5	M	Y	Hodgkin lymphoma	17.0	44.9	27.9	None	NA	25.0	44.9	Aortic + mitral	4	Stenosis
6	F	N	Hodgkin lymphoma	15.1	33.8	18.8	None	1,174	40.0	33.8	Mitral + tricuspid	3	Regurgitation
7[a]	M	N	Rhabdomyosarcoma	1.2	15.0	13.8	None	480	NA	15.0	Tricuspid	4	Unknown
8	F	Y	Hodgkin lymphoma	10.9	26.0	15.1	None	475	25.0	26.0	Mitral	4	Regurgitation
9	F	N	Ewing sarcoma	1.4	25.5	24.1	None	420	NA	25.5	Mitral	3	Regurgitation
10	F	N	Medulloblastoma	2.3	25.2	22.8	None	NA	13.8	25.2	Tricuspid	3	Unknown
11	M	Y	Rhabdomyosarcoma	6.1	14.4	8.3	None	NA	1.7	14.4	Mitral + tricuspid	4	Unknown

(Continues)

TABLE 3 (Continued)

Patient	Sex	Deceased	Cancer diagnosis	Age at cancer diagnosis (y)	Age at VHD diagnosis (y)	Time since diagnosis (y)	Treatments affecting splenic function	Anthracycline dose (mg/m^2)	Chest radio-therapy dose (Gy)	Age at valve diagnosis	Affected valve	Grade	Type of defect
12	F	N	Precursor cell leukemia	7.9	13.2	5.3	None	NA	NA	13.2	Tricuspid	4	Regurgitation
13	M	N	Hodgkin lymphoma	9.6	28.3	27.7	None	160	35.0	28.3	Mitral	4	Regurgitation
14	F	N	Hodgkin lymphoma	14.5	38.0	23.5	Radiotherapy	NA	40.0	38.0	Mitral	3	Regurgitation
15	F	N	Hodgkin lymphoma	14.8	37.3	22.5	Radiotherapy	944	35.0	37.3	Mitral	3	Regurgitation
16	M	Y	Hodgkin lymphoma	8.4	28.5	20.1	Splenectomy	260	25.2	28.5	Aortic	4	Regurgitation
17	F	N	Hodgkin lymphoma	13.7	46.2	32.5	Splenectomy	NA	40.0	46.2	Aortic	4	Stenosis
18[b]	F	Y	Hodgkin lymphoma	13.8	37.0	23.3	Splenectomy	100	35.5	37.0	Mitral	4	Regurgitation
19	M	Y	Hodgkin lymphoma	6.9	34.8	27.8	Splenectomy	NA	36.0	34.8	Aortic	4	Stenosis
20[c]	M	N	Non Hodgkin lymphoma	15.7	53.1	37.5	Splenectomy	NA	36.0	53.1	Aortic	4	Regurgitation
21	M	Y	Hodgkin lymphoma	14.1	40.0	25.9	Splenectomy	840	39.4	40.0	Aortic	4	Stenosis

Abbreviation: VHD: valvular heart disease.
[a]First cardiac event: CTCAE grade 4 heart failure.
[b]First cardiac event: CTCAE grade 4 ischemia.
[c]First cardiac event: CTCAE grade 3 ischemia.

TABLE 4 Multivariable Cox proportional hazards regression model for the analysis of potential determinants for VHD, with attained age as timescale.

Covariates	Cohort (*n*)[a] / cases (*n*)[b]	HR (95% CI)	*p*-value
Sex			
Male	2,884 / 10	Ref	
Female	2,994 / 10	1.4 (0.6-3.4)	0.49
Radiotherapy to the heart (per 10 Gy)		1.7 (1.4-2.1)	<0.01
Anthracyclines (per 100 mg/m^2)		1.2 (1.1-1.5)	<0.01
Treatments affecting splenic function			
None	4,652 / 12	Ref	
Splenectomy	58 / 6	8.6 (3.1-24.1)	<0.01
Radiotherapy involving the spleen	468 / 2	1.1 (0.2-4.8)	0.93

Note: Interaction between treatments affecting splenic function, radiotherapy dose to the heart, and anthracycline dose was tested, and no significant interactions were identified.
[a]Based on 5,878 CCS due to missingness.
[b]Based on 20 cases due to missingness.

ciated with a significant increase in risk for VHD. Sex and radiotherapy involving the spleen did not influence the risk of developing VHD.

In multivariable analysis that was limited to CCS who were diagnosed with lymphoma, a similar association was observed where splenectomy was associated with an increased risk of valvular heart disease. Nonetheless, due to a smaller sample size and less events, the association was not as robust as observed in the whole cohort.

DISCUSSION

This study represents the first investigation into the association between treatments affecting splenic function and symptomatic VHD in CCS. Our results indicate an increased cumulative incidence of symptomatic VHD in CCS who received treatments affecting splenic function. Specifically, we found that splenectomy was significantly associated with VHD after adjusting for radiotherapy to the heart area. Additionally, increasing anthracycline dose was associated with VHD. However, radiotherapy involving the spleen did not contribute to the risk for VHD.

Two studies previously reported on splenectomy as a risk factor for VHD. In agreement with our study, Cutter et al.[12] found that splenectomy was independently associated with the risk for VHD after adjustment for the mediastinal radiation dose and treatment with anthracyclines in adult Hodgkin lymphoma survivors.[12] In a study of 1,132 childhood Hodgkin lymphoma survivors, Schellong et al.[27] found no significant difference in the cumulative incidence of VHD between splenectomized and non-splenectomized survivors after 25 years of follow-up from cancer diagnosis, even though 5.2% of patients with a splenectomy had VHD, compared with 1.4% of patients without splenectomy.[27] This could potentially be due to a lack of power. Both studies report a higher cumulative incidence of VHD compared with our findings. This can be explained by the difference in study populations, and the use of different outcome definitions. Both studies report on VHD in Hodgkin lymphoma survivors, of which the majority received mediastinal irradiation, an important risk factor for VHD. Also, the patients in the study by Cutter et al. were adults at diagnosis and older at follow-up. In both studies, milder degrees of VHD were reported. Our study cohort included survivors of all childhood cancer diagnoses, of which a smaller proportion received radiotherapy involving the heart, and we only reported CTCAE grade 3-5 VHD cases. The findings in the current study represent the tip of the iceberg as only symptomatic VHD is reported. VHD is a progressive condition, thus it might be possible that patients with a shorter follow-up have milder, asymptomatic grades of VHD.

The mechanism of how splenectomy could be involved in VHD remains to be explored. Splenectomy and radiotherapy involving the spleen are associated with an increased infection risk.[13,28] In a previous study in CCS, an increased risk for late infection-related mortality was found for CCS who received ≥10 Gy splenic irradiation, though the risk remains the highest for CCS who had a splenectomy.[28] Several endocarditis-causing bacteria have been found to be more prevalent in asplenic individuals, such as Streptococcus Pneumoniae, Capnocytophaga Canimorsus, and Bordetella Holmesii.[14–16] Endocarditis can cause damage to the heart valves and subsequently result in VHD. Furthermore, loss of splenic filtration and sequestration is associated with increased platelet activation, persistence of abnormal erythrocytes in the circulation, and reduced levels of natural anticoagulants.[17,29–34] This might increase the risk of endocarditis causing bacteria to bind to the leaflet, which might be more prone due to preexisting endothelial valvular damage caused by radiotherapy involving the heart area.[11,35]

The spleen also has a role in inflammatory processes, and both protective and damaging effects of splenic leukocytes and cytokines in cardiac disease, such as myocardial infarction, atrial fibrosis, and heart failure, have been described.[36–38] One of these cytokines is IL-10, which might have a cardioprotective effect, and can be reduced in patients with splenic dysfunction. IL-10 could potentially have a protective role in valve inflammation. As all splenectomized patients with VHD also received radiotherapy to the heart, the loss of splenic function could potentially result in more valvular inflammation and fibrosis.[36,38,39]

Cardiac ischemia was more prevalent in the CCS with treatments affecting splenic function than those without. Two CCS with VHD had an ischemic cardiac event before they developed VHD, and both had a history of splenectomy. One of these CCS had CTCAE grade 3 ischemia nine years before the aortic valve replacement. As grade 3 ischemia does not include major myocardial infarctions,[21] and coronary artery disease is mostly related to mitral valve regurgitation, it is unlikely that these events were related. The other CCS hat CTCAE grade 4 ischemia seven years before the mitral valve replacement. These events could be related if the ischemic event resulted in cardiac remodeling.

Echocardiographic parameters did not match with a large infarction site. However, a relationship between these events could not be fully ruled out. In the group of CCS without treatments affecting splenic function, one CCS had CTCAE grade 4 heart failure 10 years prior to the tricuspid valve. Data were insufficient to determine whether there was a relationship between these events.

Current guidelines recommend screening for valvular dysfunction by echocardiography for CCS who received mediastinal irradiation, aiming to detect subclinical VHD, which will aid in timely intervention.[40] The significant association between splenectomy and VHD after adjustment for radiotherapy involving the heart in the current study could indicate that these patients are at even higher risk than after mediastinal irradiation alone. More research is needed to determine if patients with splenectomy or other treatments affecting splenic function should be considered as a population that needs screening for VHD.

The strengths of this study are the high follow-up rate of 85.7% CCS of the entire nationwide cohort, the nearly complete collection of treatment data, the validation of all cases of VHD, and the adjustments for several important confounders, including radiotherapy to the heart area. These strengths increase the reliability of the strength of the effect estimate and 95% confidence intervals and the validity of the study. It is worth noting that all CCS who received treatments affecting splenic function with symptomatic VHD also received radiotherapy to the heart area. Nevertheless, splenectomy remained significant in multivariable analysis after adjustment for radiotherapy to the heart area, which indicates that CCS treated with radiotherapy to the heart area and splenectomy constitutes the highest risk for VHD.

In this study, more participants received cardiotoxic treatments compared with nonparticipants. This bias could potentially lead to an overestimation of VHD. However, because this cohort comprises 85.7% of the underlying DCCSS-LATER cohort, we do not expect this to influence outcomes. Because only symptomatic cases of VHD were analyzed, the current study most likely underestimates the cumulative incidence of VHD among CCS. A large difference was found between the HR of splenectomy between the analysis of the full cohort and the lymphoma group. This is most likely due to the difference in the prevalence of the reference group without splenectomy, and the HR found in the lymphoma subgroup might give a more accurate representation of the actual risk. However, the power of the analyses was limited due to the small number of symptomatic VHD cases and CCS with splenectomy. There might have been some residual confounding. Nevertheless, we did observe a significant difference in cumulative incidence between the groups as well as a significant association between splenectomy and VHD in multivariable analysis, which implies that it is worthwhile to investigate the incidence of asymptomatic VHD in CCS after splenectomy by echocardiography.

4 | CONCLUSION

Splenectomy was associated with VHD in CCS independent of other risk factors, such as radiotherapy to the heart area. Future studies including analysis of echocardiographic data are needed in order to determine the exact incidence of VHD in this population and to reliably assess the association between treatments affecting splenic function and VHD more in depth. This can aid in determining whether survivors with splenectomy might benefit from screening for VHD, aiming at the timely identification of VHD, which would prevent delays in interventions.

AUTHOR CONTRIBUTIONS

Bente Houtman: Conceptualization; formal analysis; visualization; writing—original draft; writing—review and editing. **Iris Walraven**: Writing—original draft; writing—review and editing. **Livia Kapusta**: Writing—review and editing. **Arco Teske**: Writing—review and editing. **Eline van Dulmen-den Broeder**: Resources; writing—review and editing. **Wim Tissing**: Writing—review and editing. **Marry van den Heuvel-Eibrink**: Recruitment; funding acquisition; resources; writing—review and editing. **Birgitta Versluys**: Resources; writing—review and editing. **Dorine Bresters**: Resources; writing—review and editing. **Margriet van der Heiden**: Data curation; software; writing—review and editing. **Cécile Ronckers**: Investigation; methodology; writing—review and editing. **Wouter Kok**: Data curation; writing—review and editing. **Helena van der Pal**: Investigation; methodology; resources; data curation; writing—review and editing. **Saskia Pluijm**: Writing—review and editing. **Geert Janssens**: Writing—review and editing. **Nicole Blijlevens**: Supervision; writing—review and editing. **Leontien Kremer**: Conceptualization; investigation; methodology; funding acquisition; writing—review and editing. **Jacqueline Loonen**: Conceptualization; methodology; project administration; supervision; funding acquisition; writing—original draft; writing—review and editing. **Lieke Feijen**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing—original draft; writing—review and editing.

ACKNOWLEDGMENTS

We thank all participating patients for their contribution. We are also thankful to all the data managers and research assistants of the seven participating centers for contributing to the DCCSS-LATER study. This work was supported by the European Union's Seventh Framework Programme for research, technological development, and demonstration (Grant Agreement No 257505; PanCareSurFup). Cécile Ronckers was supported by grant funding from the KWF Kankerbestrijding.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the DCCSS-LATER Consortium under license. Data will be shared on request to the corresponding author with the permission of the DCCSS-LATER Consortium.

ORCID

Bente M. Houtman https://orcid.org/0000-0002-9242-5676
E. A. M. Lieke Feijen https://orcid.org/0000-0001-8930-3160

REFERENCES

1. Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970–99: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol*. 2018;19(12):1590-1601.
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. 2014;14(1):61-70.
3. Mulrooney DA, Armstrong GT, Huang S, et al. Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional study. *Ann Intern Med*. 2016;164(2):93-101.
4. Van Der Pal HJ, Van Dijk IW, Geskus RB, et al. Valvular abnormalities detected by echocardiography in 5-year survivors of childhood cancer: a long-term follow-up study. *Int J Radiat Oncol Biol Phys*. 2015;91(1):213-222.
5. Sitges M, Borregaard B, De Paulis R, et al. Creating a better journey of care for patients with heart valve disease. *Eur Heart J Open*. 2021;1(3):oeab034.
6. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J*. 2020;41(45):4349-4356.
7. Christiansen JR, Hamre H, Massey R, et al. Left ventricular function in long-term survivors of childhood lymphoma. *Am J Cardiol*. 2014;114(3):483-490.
8. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
9. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation*. 2013;128(17):1927-1995.
10. Bates JE, Rancati T, Keshavarz H, et al. Cardiac disease in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. *Int J Radiat Oncol Biol Phys*. 2023;119(2):522-532.
11. Leerink JM, de Baat EC, Feijen EAM, et al. Cardiac disease in childhood cancer survivors: risk prediction, prevention, and surveillance: JACC cardiooncology state-of-the-art review. *JACC: CardioOncol*. 2020;2(3):363-378.
12. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. *J Natl Cancer Inst*. 2015;107(4):djv008.
13. William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. *Hematology*. 2007;12(2):89-98.
14. Butler T. Capnocytophaga canimorsus: an emerging cause of sepsis, meningitis, and post-splenectomy infection after dog bites. *Eur J Clin Microbiol Infect Dis*. 2015;34(7):1271-1280.
15. De Egea V, Muñoz P, Valerio M, et al. Characteristics and outcome of Streptococcus pneumoniae Endocarditis in the XXI century: a systematic review of 111 cases (2000-2013). *Medicine (Baltimore)*. 2015;94(39):e1562-e1562.
16. Shepard CW, Daneshvar MI, Kaiser RM, et al. Bordetella holmesii bacteremia: a newly recognized clinical entity among asplenic patients. *Clin Infect Dis*. 2004;38(6):799-804.
17. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood*. 2009;114(14):2861-2868.
18. Teepen JC, Kok JL, Feijen EAM, et al. Questionnaire- and linkage-based outcomes in Dutch childhood cancer survivors: methodology of the DCCSS LATER study part 1. *Cancer Med*. 2022;12(6):7588-7602.
19. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer*. 2005;103(7):1457-1467.
20. Feijen E, Font-Gonzalez A, Van Der Pal HJH, et al. Risk and temporal changes of heart failure among 5-year childhood cancer survivors: a DCOG-LATER study. *J Am Heart Assoc*. 2019;8(1):e009122.
21. Feijen E, Van Der Pal HJ, Van Dalen EC, et al. A new method to facilitate valid and consistent grading cardiac events in childhood cancer survivors using medical records. *PLoS One*. 2014;9(7):e100432.
22. Kilsdonk E, Van Dulmen-Den Broeder E, Van Leeuwen FE, et al. Late mortality in childhood cancer survivors according to pediatric cancer diagnosis and treatment era in the Dutch LATER cohort. *Cancer Invest*. 2022;40(5):413-424.
23. Feijen EAM, Leisenring WM, Stratton KL, et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. *JAMA Oncol*. 2019;5(6):864-871.
24. Merkx R, Leerink JM, Feijen E, et al. Extensive cardiac function analyses using contemporary echocardiography in childhood cancer survivors. A DCCSS LATER study. *JACC: CardioOncol*. 2023;5(4):472-485.
25. Geskus RB. *Data analysis with competing risks and intermediate states*. CRC Press, Taylor & Francis Group; 2016.
26. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Statist*. 1988;16(3):1141-1154.
27. Schellong G, Riepenhausen M, Bruch C, et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. *Pediatr Blood Cancer*. 2010;55(6):1145-1152.
28. Weil BR, Madenci AL, Liu Qi, et al. late infection-related mortality in asplenic survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *J Clin Oncol*. 2018;36(16):1571-1578.
29. De Porto A, Lammers AJJ, Bennink RJ, Ten Berge IJM, Speelman P, Hoekstra JBL. Assessment of splenic function. *Eur J Clin Microbiol Infect Dis*. 2010;29(12):1465-1473.
30. Dennis Robinette C, Fraumeni J. Splenectomy and subsequent mortality in veterans of the 1939–45 war. *Lancet North Am Ed*. 1977;310(8029):127-129.
31. Frey MK, Alias S, Winter MP, et al. Splenectomy is modifying the vascular remodeling of thrombosis. *J Am Heart Assoc*. 2014;3(1):e000772.
32. Kimmig LM, Palevsky HI. Review of the association between splenectomy and chronic thromboembolic pulmonary hypertension. *Ann Am Thorac Soc*. 2016;13(6):945-954.
33. Kristinsson SY, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica*. 2014;99(2):392-398.
34. Thomsen RW, Schoonen WM, Farkas DK, Riis A, Fryzek JP, Sørensen HT. Risk of venous thromboembolism in splenectomized patients compared with the general population and appendectomized patients: a 10-year nationwide cohort study. *J Thromb Haemost*. 2010;8(6):1413-1416.
35. Liesenborghs L, Meyers S, Vanassche T, Verhamme P. Coagulation: at the heart of infective endocarditis. *J Thromb Haemost*. 2020;18(5):995-1008.
36. Hiraiwa H, Okumura T, Murohara T. The cardiosplenic axis: the prognostic role of the spleen in heart failure. *Heart Fail Rev*. 2022;27(6):2005-2015.
37. Kondo H, Takahashi N, Gotoh K, et al. Splenectomy exacerbates atrial inflammatory fibrosis and vulnerability to atrial fibrillation induced by pressure overload in rats: possible role of spleen-derived interleukin-10. *Heart Rhythm*. 2016;13(1):241-250.

38. Heusch G. The spleen in myocardial infarction. *Circ Res*. 2019;124(1):26-28.
39. Toli K, Paraskevas KI, Poulakou MV, et al. Association between plasma levels and immunolocalization of cytokines in heart valve lesions: a possible target for treatment? *Expert Opin Ther Targets*. 2008;12(10):1209-1215.
40. Ehrhardt MJ, Leerink JM, Mulder RL, et al. Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. 2023;24(3):e108-e120.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Houtman BM, Walraven I, Kapusta L, et al. Treatments affecting splenic function as a risk factor for valvular heart disease in Childhood Cancer Survivors: A DCCSS-LATER study. *Pediatr Blood Cancer*. 2024;71:e31251. https://doi.org/10.1002/pbc.31251