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Valvular Dysfunction in Lymphoma Survivors Treated With Autologous Stem Cell Transplantation

A National Cross-Sectional Study

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ABSTRACT

OBJECTIVES This study assessed the prevalence and associated risk factors for valvular dysfunction (VD) observed in adult lymphoma survivors (LS) after autologous hematopoietic stem cell transplantation (auto-HCT), and to determine whether anthracycline-containing chemotherapy (ACCT) alone in these patients is associated with VD.

BACKGROUND The prevalence of and risk factors for VD in LS after auto-HCT is unknown. Anthracyclines may induce heart failure, but any association with VD is not well-defined.

METHODS This national cross-sectional study included all adult LS receiving auto-HCT from 1987 to 2008 in Norway. VD was defined by echocardiography as either more than mild regurgitation or any stenosis. Observations in LS were compared with a healthy age- and gender-matched (1:1) control group.

RESULTS In total, 274 LS (69% of all eligible) participated. Mean age was 56 ± 12 years, mean follow-up time after lymphoma diagnosis was 13 ± 6 years, and 62% of participants were males. Mean cumulative anthracycline dosage was 316 ± 111 mg/m^2, and 35% had received radiation therapy involving the heart (cardiac-RT). VD was observed in 22.3% of the LS. Severe VD was rare (n = 9; 3.3% of all LS) and mainly aortic stenosis (n = 7). We observed VD in 16.7% of LS treated with ACCT alone (n = 177), corresponding with a 3-fold increased VD risk (odds ratio: 2.9; 95% confidence interval: 1.5 to 5.8; p = 0.002) compared with controls. Furthermore, the presence of aortic valve degeneration was increased in the LS after ACCT alone compared with controls (13.0% vs. 2.9%; p < 0.001). Female sex, age >50 years at lymphoma diagnosis, ≥3 lines of chemotherapy before auto-HCT, and cardiac-RT >30 Gy were identified as independent risk factors for VD in the LS.

CONCLUSIONS In LS, ACCT alone was significantly associated with VD and related to valvular degeneration. Overall, predominantly moderate VD was prevalent in LS, and longer observation time is needed to clarify the clinical significance of this finding. (J Am Coll Cardiol Img 2016;9:230–9) © 2016 by the American College of Cardiology Foundation.

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High-dose chemotherapy with auto-logous stem cell transplantation (auto-HCT) has for 30 years been a curative treatment option for patients with relapsed or refractory malignant lymphomas, or as consolidation after first-line therapy in selected patients at particularly high risk for relapse (1–4). Transplantation strategies and supportive care have improved, resulting in increased survival rates (5). Lymphoma survivors (LS) who remain in complete remission for ≥2 years after HCT have favorable long term prognosis, with 10 years survival rates exceeding 80% for certain subgroups (6). Compared with age-matched controls, survivors of HCT (autologous and allogeneic) for hematologic malignancies have a close to 3-fold increased risk of cardiovascular complications (7), and cardiovascular diseases are the leading nonmalignant cause of death (8,9). Consequently, there is an increasing focus on the risk for treatment-related late effects.

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Valvular dysfunction (VD) is a well-known complication after radiation therapy involving the heart (cardiac-RT) (i.e., mediastinal fields and mantle fields) (10,11). The reported prevalence of VD after cardiac-RT for lymphoma varies from 30 to >50% among survivors observed 10 to >20 years after primary treatment (10,12). The development of VD occurs over decades. Our group has previously demonstrated the slow evolving process with fibrosis, valve retraction, and calcification after cardiac-RT, finally causing mainly left-sided regurgitations and stenosis in Hodgkin lymphoma (HL) survivors (13). Other VD-associated risk factors have not been demonstrated consistently, although female sex and additional anthracycline treatment have been identified as aggravating the risk for VD in HL survivors (12,14).

The dose-dependent cardiotoxic potential of anthracyclines (i.e., doxorubicin) is well-documented. Doxorubicin has been reported to induce heart failure in up to 2% and 26% of the treated patients after cumulative doses of 300 and 550 mg/m^2, respectively (15). To the best of our knowledge, data on valvular function in LS after anthracycline exposure without cardiac-RT have not been reported. Hitherto, there are no robust data demonstrating the valvular function in adult LS after auto-HCT, and consequently the prevalence and risk factors for VD in this group of cancer survivors remains unknown.

Consequently, the aims of the present study were first to assess the general prevalence and associated risk factors for VD in adult LS after auto-HCT and second to determine if anthracycline-containing chemotherapy (ACCT) alone was associated with VD in these patients.

MATERIALS AND METHODS

Between March 2012 and March 2014, we performed a cross-sectional, national, multicenter survey in Norway on a broad spectrum of late effects inviting all adult LS treated with auto-HCT (16). Participants fulfilled questionnaires and a comprehensive clinical examination at the hospital where they received their HCT, that is, at 4 sites in Norway (**Figure 1**). The study protocol was endorsed by the Regional Committee for Medical and Health Research Ethics, and written informed consent was given by all participants.

PATIENT POPULATION. Eligibility criteria were treatment with auto-HCT for Hodgkin or non-Hodgkin's lymphoma from 1987, when auto-HCT was first introduced as a treatment option in Norway, until 2008, age ≥18 years at auto-HCT, and alive at time of the survey. The only exclusion criterion was current treatment for relapsed lymphoma. The LS were identified through medical records and registries at each university hospital, and cross-checked against reports from HCT meetings, the clinical quality register for lymphomas at Oslo University Hospital, and radiotherapy registries.

CONTROLS. Controls were drawn from a clinical echocardiographic database consisting of 1,266 participants without diagnosed cardiovascular disease, hypertension, or diabetes mellitus before inclusion, recruited from the third wave of the Nord-Trøndelag Health Study in Norway (17). Controls were matched 1:1 for age, sex, systolic blood pressure, and body mass index.

TREATMENT. Treatment details were obtained retrospectively from medical records, the clinical quality register for lymphomas at the Oslo University Hospital, and radiotherapy registries.

Use of anthracyclines (i.e., doxorubicin and daunorubicin), cyclophosphamide, cisplatinum, and bleomycin were registered and the total cumulative dose calculated for doxorubicin and cyclophosphamide. For daunorubicin, cumulative doses were converted to doxorubicin isotoxic doses using a conventional conversion factor of 0.83 (18). Conditioning regimens consisted of total body irradiation (TBI) and high-dose cyclophosphamide from 1987 to 1995, thereafter of chemotherapy only (carmustine, etoposide, cytarabine, and melphalan [BEAM]). We also

ABBREVIATIONS AND ACRONYMS

ACCT = anthracycline-containing chemotherapy

auto-HCT = autologous hematopoietic stem cell transplantation

cardiac-RT = radiation therapy involving the heart

HL = Hodgkin lymphoma

LS = lymphoma survivor(s)

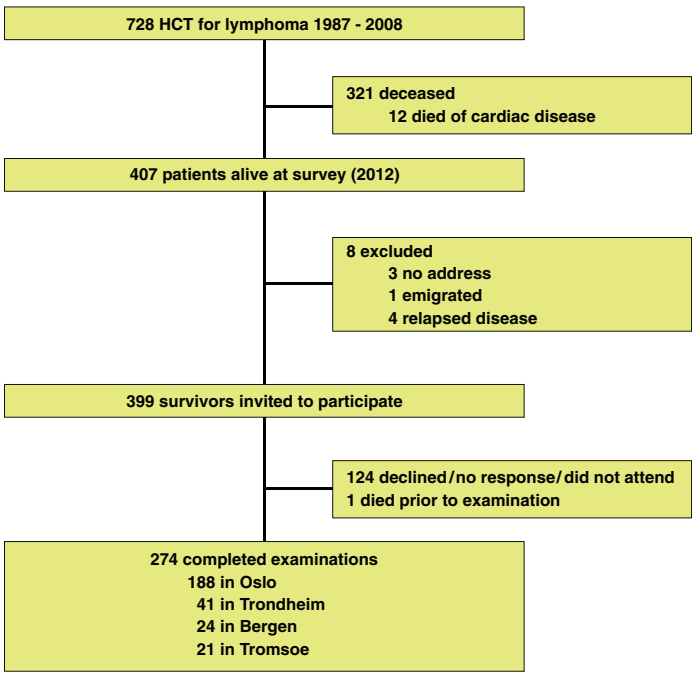
LV = left ventricle

OR = odds ratio

TBI = total body irradiation

VD = valvular dysfunction

FIGURE 1 Recruitment Strategy



Recruitment of eligible lymphoma survivors after autologous hematopoietic stem cell transplantation (auto-HCT) in Norway. All examinations were performed between March 2012 and March 2014.

registered the total number of treatment lines of chemotherapy (a defined and planned number of courses followed by response evaluation) for each participant before auto-HCT. Some received reduced-intensity allogeneic stem cell transplantation due to relapse after auto-HCT, and these were registered.

Subgroups received additional radiation therapy, and for the purpose of the present study, cardiac-RT was registered (mediastinal fields, mantle field radiation, and TBI). In TBI, 13 Gy was given in total, which is equivalent to a radiation dose of approximately 20 Gy to the heart. All mediastinal radiation fields were reevaluated to confirm cardiac involvement, and cumulative radiation dose involving the heart was calculated. Cutoff limit for high-dose cardiac-RT was defined as 30 Gy (19).

Finally, the survivors were categorized in 3 groups according to lymphoma treatment: 1) ACCT alone; 2) ACCT and low dose cardiac-RT (equivalent to ≤30 Gy); and 3) ACCT and high-dose cardiac-RT (>30 Gy).

ECHOCARDIOGRAPHY. The LS were examined in the left lateral decubitus position after a minimum of 5 minutes of rest using parasternal and apical projections (20). Ultrasound recordings were obtained using digital high-end echocardiographic scanners (Vivid 7 or Vivid E9, GE Vingmed Ultrasound, Horten, Norway). Valvular regurgitations were defined by visual assessment (21) in combination with 2-dimensional and Doppler echocardiography (22), and the magnitude of regurgitation graded according to a scale ranging from 0 to 3, with 0 denoting none, ≤1 mild, 1.5 to 2.0 moderate, and 2.5 to 3.0 as severe regurgitation. Valvular stenosis was evaluated after recommendations (23). VD was defined as either of regurgitations more than mild, any stenosis, or prior valve replacement. The presence of valvular degenerative changes (i.e., fibrosis and/or calcification) was registered in all valves. Conventional echocardiographic parameters were obtained and measured after recommendations (24) and left ventricle (LV) systolic function was assessed using traditional ejection fraction by Simpson's biplane method (24). One investigator (K.M.) conducted all assessments in patients ending in March 2014, blinded from patient treatment. All echocardiograms in the control subjects was performed with a Vivid 7 scanner (GE Vingmed), and valvular function was reassessed from the original recordings in May and June 2014 by the same investigator (K.M.).

CLINICAL ASSESSMENTS AND BLOOD SAMPLING. All participants underwent a medical examination and blood sampling at 8 AM after an overnight fast. The blood was analyzed for lipids, creatinine, glucose, glycated hemoglobin, and N-terminal pro-B-type natriuretic peptide. Experienced clinicians performed a standardized interview and registered comorbidities and present cardiovascular medication. This information was cross-checked against the questionnaires.

Blood pressure was measured ≥3 times and the average of the 3 most consistent measures was used for analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current treatment with antihypertensive agents.

Diabetes mellitus (type 1 or type 2) was defined as glycated hemoglobin ≥6.5% and/or current use of antidiabetics. Hypercholesterolemia was defined as low-density lipoprotein ≥4.1 mmol/l (160 mg/dl) or use of lipid-lowering agents without known cardiovascular disease. Thyroid disease was defined as abnormal thyroid function tests or the use of thyroid hormone replacement therapy.

STATISTICAL ANALYSIS. Data are presented as mean ± SD, median (ranges), or numbers (%). One-way analysis of variance and Student *t* tests were used to compare normally distributed continuous data. Mann-Whitney and Kruskal-Wallis tests were

TABLE 1 Patient Demographics and Clinical Data According to Treatment Groups at Time of Survey

	All (n = 274)	Anthracyclines (n = 177)	Anthracyclines and Cardiac-RT ≤30 Gy (n = 59)	Anthracyclines and Cardiac-RT >30 Gy (n = 38)	p Value
Age at diagnosis, yrs	42 ± 13	47 ± 13	35 ± 11	31 ± 10	<0.001
Observation from lymphoma diagnosis, yrs	13 ± 6	11 ± 5	18 ± 7	15 ± 5	<0.001
Time, diagnosis to HCT, yrs	1.3 (0.2–22.7)	1.2 (0.2–21.4)	1.2 (0.2–17.2)	1.7 (0.6–22.7)	0.02
Non-Hodgkin lymphoma	78	90	71	32	<0.001
Males	62	64	59	58	0.65
Body mass index, kg/m^2	26 ± 4	26 ± 4	26 ± 4	26 ± 5	0.92
Systolic blood pressure, mm Hg	131 ± 21	134 ± 21	129 ± 17	121 ± 20	0.003
Diastolic blood pressure, mm Hg	77 ± 10	78 ± 10	75 ± 9	74 ± 11	0.01
Smoking (current, ever, never)	18/40/42	18/41/41	19/44/37	16/32/53	0.65
Cancer treatment					
Doxorubicin, mg/m^2	300 (0–775)	300 (0–520)	300 (90–775)	400 (80–729)	0.07
Cyclophosphamide, g/m^2	4.5 (0–12.3)	4.5 (0–10.7)	5.8 (0–12.3)	3.0 (0–8.0)	0.002
Cardiac-RT, Gy	29.75 (19–67)	-	20 (19–30)	40 (31–67)	<0.001
No. of chemotherapy lines before auto-HCT (1/2/≥3)	30/56/14	33/54/13	36/52/12	5/69/26	0.005
Cisplatinum	4	5	3	3	0.82
Bleomycin	12	7	20	24	0.002
Allogeneic HCT after auto-HCT	7	9	2	3	0.08
Comorbidities					
Hypertension	35	36	39	21	0.15
Diabetes mellitus	10	9	19	5	0.05
Hypercholesterolemia	41	38	49	42	0.36
Thyroid disease	14	9	15	34	<0.001
Laboratory parameters					
Hemoglobin, g/dl	14.0 ± 1.3	13.9 ± 1.3	14.0 ± 1.3	14.1 ± 1.1	0.59
Creatinine, μmol/l	82 ± 22	83 ± 24	81 ± 18	79 ± 18	0.69
NT-pro-BNP, pmol/l	17 (1–538)	16 (1–538)	14 (2–321)	35 (2–379)	0.05
Glycated hemoglobin, %	5.8 ± 0.7	5.8 ± 0.6	6.0 ± 1.0	5.6 ± 0.5	0.04
Total cholesterol, mmol/l	5.4 ± 1.2	5.5 ± 1.2	5.4 ± 1.1	5.2 ± 1.2	0.36
LDL cholesterol, mmol/l	3.4 ± 1.1	3.4 ± 1.0	3.4 ± 1.1	3.3 ± 1.2	0.73
Current medication					
Cardioactive medication	17	14	29	11	0.02
Statin	14	10	24	18	0.02
Beta-blockers	8	9	7	5	0.75
ACEI/ARB	11	7	25	8	0.001
Calcium-channel blockers	4	3	10	0	0.02

Values are mean ± SD, median (range), or %.The p values are derived from 1-way analysis of variance for normally distributed data and Kruskal-Wallis for skewed data.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; auto-HCT = autologous hematopoietic stem cell transplantation; cardiac-RT = radiation therapy involving the heart; LDL = low-density lipoprotein; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.

used to compare skewed data, and chi-square tests were used for categorical data.

We used logistic regression analysis to estimate the odds ratio (OR) for VD in all LS compared with controls. Multivariable logistic regression analysis was used to estimate the OR for VD in the 3 treatment groups compared with the controls, adjusted for age and gender. Due to a possible selection bias with respect to controls, we also performed analysis after excluding LS already diagnosed with cardiovascular disease (i.e., heart failure [n = 10], valvular replacement [n = 2] or myocardial infarction [n = 9]), hypertension (n = 28), or diabetes mellitus (n = 17) at the time of survey in all regression analyses concerning comparisons with controls.

Simple and multivariable logistic regression analyses were used to identify variables significantly associated with VD (dependent variable) in the whole cohort of LS. In the simple analyses, we included a pre-defined set of variables including known risk factors for cardiovascular disease, treatment related determinants and patient characteristics. Only variables with a $p < 0.15$ in simple analyses were included in the multivariable regression analysis. Finally, we

performed a separate multivariable logistic regression analysis in the ACCT group only, to evaluate risk factors associated with VD and presence of aortic valve degeneration.

All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois), and $p \leq 0.05$ was considered significant.

RESULTS

In total, 274 LS (69% of the eligible patients) participated (Figure 1). Age at survey, sex, primary diagnosis (non-Hodgkin's lymphoma or HL), mean doxorubicin dose, proportions receiving cardiac-RT, and observation time from lymphoma diagnosis or auto-HCT did not differ from nonparticipants (data not shown). Among participants, the median age at survey was 56 years (range 25 to 77 years), mean cumulative doxorubicin dose was 316 ± 111 mg/m^2, and 95% of the LS received ≤450 mg/m^2 of doxorubicin. One LS had no doxorubicin exposure. In 38 of the LS (14%), TBI and high-dose cyclophosphamide were used as conditioning regimen. Smoking and hypertension was equally prevalent in LS and controls (18% vs. 14% and 35% vs. 31%, respectively; $p > 0.20$ for both). Patient characteristics are displayed in Table 1, and matching variables were highly congruent between patients and controls (sex, $p = 1.00$; age, $p = 1.00$; systolic blood pressure, $p = 0.80$; and body mass index, $p = 0.26$).

PREVALENCE AND RISK OF VD. Table 2 displays the VD characteristics in the LS and controls. We observed 82 dysfunctional valves in 61 LS (22.3%). of which 59 were left sided (72.0%) (Table 2). Valvular regurgitations constituted 86.6% of all VD. All treatment groups had a significantly increased risk for VD compared with controls, with higher cardiotoxic burden leading to increased VD risk (Figure 2). In the ACCT group, 16.9% had VD, corresponding with a 3-fold increased VD risk compared with controls (OR: 3.3; 95% confidence interval [CI]: 1.7 to 6.2; $p < 0.001$). The results were maintained when subsequent analysis was performed after excluding LS already diagnosed with cardiovascular disease, hypertension or diabetes mellitus (OR: 2.9; 95% CI: 1.5 to 5.8; $p = 0.002$) (Figure 2).

The prevalence of mitral regurgitation (MR) was comparable in the ACCT group and controls (5.1% vs.

TABLE 2 Echocardiographic Parameters and Valvular Characteristics in LS and Controls

	All LS (N = 274)	Controls (n = 274)	Anthracyclines (n = 177)	Anthracyclines and Cardiac-RT ≤30 Gy (n = 59)	Anthracyclines and Cardiac-RT >30 Gy (n = 38)
Echocardiographic parameters					
LV internal diameter index, cm/m^2	2.6 ± 0.3	2.6 ± 0.3	2.6 ± 0.3	2.6 ± 0.3	2.6 ± 0.3
LV EDV index, ml/m^2	66.4 ± 14.3	66.6 ± 11.5	65.9 ± 14.2	66.8 ± 15.6	67.8 ± 13.3
LV ESV index, ml/m^2	30.5 ± 9.8*	28.1 ± 6.0	29.8 ± 8.4	31.8 ± 12.2	33.5 ± 11.1
LV ejection fraction, %	54 ± 6*	58 ± 4	55 ± 5	53 ± 7	51 ± 8
LV mass index, g/m^2	80 ± 19*	93 ± 22	82 ± 19	83 ± 20	70 ± 16
RV basal diameter index, cm/m^2	2.0 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.3	2.0 ± 0.3
TAPSE, mm	22.8 ± 4.3*	27.2 ± 4.2	23.2 ± 4.2	22.3 ± 4.1	20.8 ± 4.4
LA volume index, ml/m^2	29 ± 10	29 ± 6	30 ± 10	29 ± 9	24 ± 6
Distribution of dysfunctional valves					
Aortic stenosis	10 (3.6)*	0	3 (1.7)	1 (1.7)	6 (15.8)*
Aortic regurgitation	24 (8.8)*	4 (1.5)	11 (6.2)	4 (6.8)	9 (23.7)*
Mitral regurgitation	24 (8.8)*	9 (3.3)	9 (5.1)	7 (11.9)	8 (21.1)*
Tricuspidal regurgitation	22 (8.0)*	3 (1.1)	11 (6.2)	6 (10.2)	5 (13.2)
Valvular degeneration					
Any valvular involvement	54 (19.7)*	13 (4.7)	25 (14.1)	12 (20.3)	17 (44.7)†
Aortic valve involvement	47 (17.2)*	8 (2.9)	23 (13.0)	11 (18.6)	13 (34.2)†
Mitral valve involvement	21 (7.7)*	5 (1.8)	7 (4.0)	2 (3.4)	12 (31.6)†
Valvular degeneration in dysfunctional valves					
Aortic regurgitation	16/24	2/4	6/11	2/4	8/9
Mitral regurgitation	9/24	4/9	2/9	2/7	5/8

Values are mean ± SD, n (%), or n/N. *$p < 0.01$. The p values for comparisons in echocardiographic parameters between the LS and controls are derived from independent Student *t* tests; comparisons between treatment subgroups not performed. The p values for other comparisons between the LS and controls derived from chi-square test. The p values for comparisons between treatment subgroups in distribution of dysfunctional valves and valvular degeneration by chi-square test (†$p < 0.05$ compared with both other groups).

EDV = end-diastolic volume; ESV = end-systolic volume; LA = left atrium; LS = lymphoma survivors; LV = left ventricle; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.

3.3%, respectively), whereas increased for aortic regurgitation and tricuspid regurgitation ($p < 0.001$ for both) (Table 2).

We observed 1 mitral stenosis (mild) and 1 moderate pulmonic regurgitation. Severe VD was found in 3.3% of the LS (7 aortic stenosis, i.e., valve area <1.0 cm^2, of whom 2 had valvular replacement after auto-HCT, 1 mitral regurgitation and 1 tricuspid regurgitation). In the LS with severe aortic stenosis, the median age at survey was 53 years (range 42 to 70 years), the median observation time since primary lymphoma diagnosis was 23 years (range 15 to 34 years), 6 received concomitant cardiac-RT (5 high dose and 1 low dose), whereas the last LS had diabetes mellitus and hypertension.

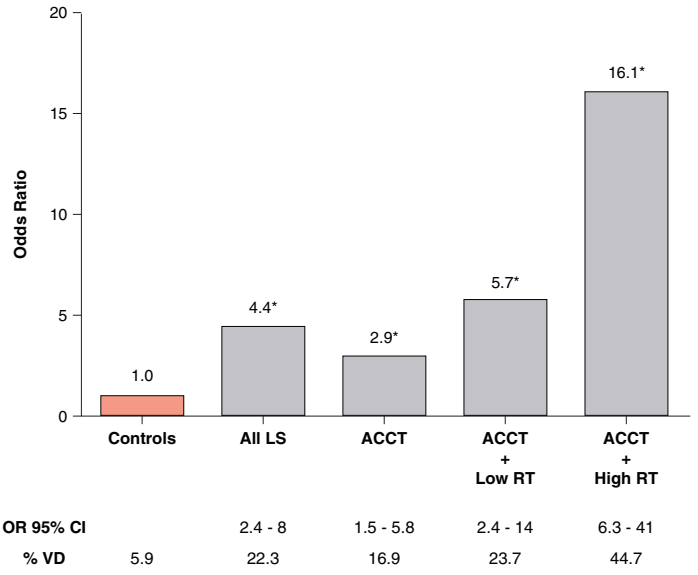
VALVULAR CHARACTERISTICS. Valvular characteristics in the LS and controls are displayed in Tables 2 and 3. Valvular degenerative changes were equally distributed between LS with no/low cardiac-RT, but significantly more common in the high dose cardiac-RT group compared with both other groups (Table 2). None had degenerative changes in the tricuspid valve. In patients, 2 VD-cases had bicuspid aortic valve (1 had degenerative changes), and 1 VD case had a dilated aortic root without degeneration.

Degenerative changes in the aortic valve were more prevalent in the ACCT group compared with controls (Table 2). We identified age at survey, creatinine, left ventricular ejection fraction and hypertension as significantly associated with degenerative changes in the aortic valve in the ACCT group in univariate analyses. When including these factors in a multivariable model, only age at survey (ß = 0.08 ± 0.03; p = 0.01) and left ventricular ejection fraction (ß = −0.14 ± 0.04; p = 0.001) remained associated.

RISK FACTORS OF VD IN ALL LS. Generally, VD cases were older at survey (Table 3). In the multivariable analysis, female gender (OR: 2.0; 95% CI: 1.1 to 3.9; p = 0.03), age ≥50 years at primary diagnosis (OR: 3.4; 95% CI: 1.5 to 7.9; p = 0.004), ≥3 lines of chemotherapy pre-HCT (OR: 2.9; 95% CI: 1.1 to 7.8; p = 0.04) and cardiac-RT > 30Gy (OR: 5.3 95% CI: 2.0 to 13.7; p = 0.001) were associated independently with VD in the LS (Table 4). After multivariable adjustments, we found no difference in risk of VD between LS treated with ACCT alone compared with additional low-dose cardiac-RT (Table 4).

RISK FACTORS OF VD IN LS WITHOUT CARDIAC RT. Multivariable logistic regression analysis for the ACCT group (n = 177) displayed that age ≥50 years at primary diagnosis (OR: 5.7; 95% CI: 1.8 to 17.8; p = 0.003) and ≥3 lines of chemotherapy before auto-HCT (OR: 4.4; 95% CI: 1.1 to 17.5; p = 0.03) were significantly associated with VD.

FIGURE 2 Estimated Risk of Valvular Dysfunction in Treatment Groups Compared With Controls



Odds ratios (ORs) for estimated risk of valvular dysfunction (VD) in treatment groups compared with controls. The ORs for VD are stratified according to cancer-related treatment groups. Controls are used as reference, and lymphoma survivors (LS) already diagnosed with cardiovascular disease (i.e., heart failure, myocardial infarction or valvular replacement), hypertension or diabetes mellitus at time of survey are excluded from the comparisons with controls. All comparisons are adjusted for sex and age. The presented prevalence of VD includes all the LS. Bars indicate OR. *p < 0.001 compared with controls. ACCT = anthracycline containing chemotherapy; high RT = radiation therapy involving the heart >30 Gy; low RT = radiotherapy involving the heart ≤30 Gy.

ECHOCARDIOGRAPHIC PARAMETERS OF CARDIAC FUNCTION AND DIMENSION. Echocardiographic measurements in the LS, treatment subgroups, and controls are displayed in Table 2, and concerning LS with/without VD in Table 3. In the LS, VD cases had impaired LV/right ventricle systolic function compared with non-VD cases, and accompanied by increased LV end-diastolic volume and end-systolic volume index and a borderline increased left atrial volume index and LV inner dimension index (Table 3).

DISCUSSION

In this national, cross-sectional study in LS, we identified an association between ACCT and VD also in the absence of cardiac-RT, with a 3-fold increased risk of VD and indications of increased aortic valve degeneration compared with controls. The whole cohort (including LS with cardiac-RT) had further

TABLE 3 A Selection of Patient Characteristics, Echocardiographic Parameters and Clinical Data in LS With and Without VD

	LS With VD (n = 61)	LS Without VD (n = 213)	p Value
Age at survey, yrs	58 ± 13	54 ± 12	0.03
Observation time from diagnosis, yrs	15 ± 7	12 ± 6	0.02
Body mass index, kg/m^2	26 ± 5	26 ± 4	0.92
Males	53	65	0.07
Smoking (current/ever/never)	15/32/53	18/43/39	0.17
Echocardiographic parameters			
LV internal diameter index, cm/m^2	2.7 ± 0.3	2.6 ± 0.3	0.09
IVSd, mm	8.8 ± 1.2	9.3 ± 1.5	0.02
LVPWd, mm	8.1 ± 1.3	8.2 ± 1.2	0.61
LV EDV index, ml/m^2	70 ± 17	65 ± 13	0.03
LV ESV index, ml/m^2	35 ± 13	29 ± 8	<0.001
LV ejection fraction, %	51 ± 8	56 ± 5	<0.001
LV mass index, g/m^2	82 ± 21	80 ± 18	0.21
RV basal diameter index, cm/m^2	2.0 ± 0.3	2.0 ± 0.2	0.24
TAPSE, mm	20.8 ± 5.0	23.3 ± 3.9	<0.001
LA volume index, ml/m^2	31 ± 13	28 ± 8	0.07
Valvular degeneration			
Any valvular involvement	34 (55.7)	20 (9.4)	<0.001
Aortic valve involvement	29 (47.5)	18 (8.5)	<0.001
Mitral valve involvement	16 (26.2)	5 (2.3)	<0.001
Comorbidities			
Hypertension	36	34	0.87
Diabetes mellitus	5	11	0.22
Hypercholesterolemia	51	39	0.09
Thyroid disease	17	13	0.44
Cancer treatment			
Lines of chemotherapy before auto-HCT (1/2/≥3)	22/49/29	32/58/10	0.001
Doxorubicin, mg/m^2	339 ± 126	309 ± 105	0.09
Cyclophosphamide dose, g/m^2	4.5 (0–11.7)	4.5 (0–12.3)	0.75
Cisplatinum	8	3	0.11
Bleomycin	12	13	0.89
Allogeneic HCT after auto-HCT	7	7	0.94
Cardiac-RT (0/≤30 Gy/>30 Gy)	49/23/28	69/21/10	0.001
Laboratory parameters			
Creatinine, μmol/l	87 ± 25	81 ± 21	0.08

Values are mean ± SD, %, n (%), or median (range). The p values derived from independent Student *t* test and chi-square test when appropriate.

Auto-HCT = autologous hematopoietic stem cell transplantation; cardiac-RT = radiation therapy involving the heart; IVSd = interventricular septum thickness in end-diastole; LVPWd = left ventricular posterior wall thickness in end-diastole; VD = valvular dysfunction; other abbreviations as in Table 2.

increased prevalence of VD, corresponding to a 4- to 5-fold increased VD risk in comparison with controls. The vast majority of dysfunctional valves were moderately diseased; severe VD was rare. Left-sided regurgitations were observed most frequently. Moreover, female sex, age ≥50 years at primary diagnosis, ≥3 lines of chemotherapy before auto-HCT, and cardiac-RT >30 Gy were identified as independent risk factors of VD in the LS. Importantly, low-dose cardiac-RT (≤30 Gy) added no significantly increased risk for VD compared with ACCT alone.

The association between ACCT and heart failure is well-documented, and the cumulative incidence of heart failure in female LS 15 years after HCT has been estimated to be as high as 15% (25). Any association between ACCT and VD is less well-studied. In HL survivors, there is conflicting evidence for the development of VD after ACCT combined with cardiac-RT. A report in 51 HL survivors observed no effect (13), whereas another large retrospective study of 1,474 HL survivors identified a >2-fold independently increased risk for VD after ACCT and cardiac-RT compared with cardiac-RT alone (14). Our findings suggest an ACCT-associated risk of VD, independent of treatment with cardiac-RT in LS.

The underlying mechanism for VD after ACCT has not been reported previously. In VD cases, we observed a modest increase in LV end-diastolic volume and reduced LV/right ventricle systolic function, whereas LV inner dimension was borderline increased compared with LS without VD. Furthermore, we noted that degenerative changes of dysfunctional valves in the ACCT group was infrequent with respect to the mitral (n = 2) and tricuspid valve (n = 0). In addition, we also identified number of lines of chemotherapy before auto-HCT as an independent risk factor for VD in the ACCT group. A previous study in HCT survivors reported a similar treatment-related variable as a risk factor for heart failure (26). Thus, it is conceivable that the most likely cause of VD (i.e., mitral regurgitation and tricuspid regurgitation) in the ACCT group was a combination of reduced LV/right ventricle systolic function and a mild left ventricular remodeling, a phenomenon previously observed in HL survivors after ACCT (13). We also found an increased prevalence of aortic regurgitation and degenerative changes in the aortic valve in the ACCT group compared with controls. There was, however, no difference between patients and controls with respect to general risk factors, such as smoking habits and hypertension, suggesting a relation between valve degeneration and ACCT in LS. This notion was further supported by a highly significant association between reduced LV systolic function (i.e., indicating anthracycline-related cardiac dysfunction) and degenerative changes in the aortic valve in the ACCT group.

Time is a pivotal factor for development of VD in HL survivors after cardiac-RT (10), as reported in a 13 years follow-up study where 1 of 3 moderate regurgitations evolved into severe regurgitation (13). In our study, no regurgitations observed in the ACCT group were graded as severe. However, one cannot directly extrapolate data obtained from HL survivors

treated with cardiac-RT into LS without cardiac-RT, due to possibly different pathophysiologic mechanisms for the VD. Consequently, further long-term observations are needed to clarify the clinical significance of this finding in LS treated with ACCT alone.

The reported cumulative incidence of VD after cardiac-RT in LS varies due to differences in study design, cardiotoxic treatment burden, classification of VD and observation time (10-12,14). In the subgroup of LS treated with high-dose cardiac-RT, we observed a VD-prevalence of 44.7% at a mean follow-up of 15 years. Lund et al. (12) reported a VD prevalence of 31% in HL survivors after high-dose cardiac-RT using a similar definition of VD as in the present study with a mean observation time of 9 years. Our observed prevalence is somewhat greater, most likely due to longer follow-up, a more comprehensive use of anthracyclines, and participants being nearly 10 years older at survey. Further, aortic stenosis was observed in 16% in this subgroup and highly comparable with previous findings (10).

Age is a determinant for valvular disease (27,28). In a large population-based study, there was a substantial increase in VD after the age of 65 years (28). We found that age ≥50 years at primary treatment, corresponding with a mean age at survey of 67 years, was an independent risk factor for VD in LS after auto-HCT. We think this reflects the observations from the normal population, even though the valvular ageing process is most likely accelerated because of cardiotoxic treatment in LS, as we observed in the aortic valve.

In the general population, there are no gender differences in the prevalence of VD (28). In contrast, we found that female LS had a 2-fold increased VD risk compared with males. Previously, a similar observation has been reported in irradiated HL survivors (12). Female gender has also been identified as a risk factor for heart failure in HCT survivors (25), hence a possible mechanism could be an increased risk of ventricular remodeling. This may imply a gender difference in tolerance for cardiotoxic treatment and subsequent risk of VD.

In HL survivors after cardiac-RT, former reports have advocated a threshold of approximately 30 Gy, both in children (29) and adults (10,30,31) to avoid subsequent VD. Our observations are in accordance with this threshold, further supported by the comparable degree of degenerative valvular changes after no/low-dose cardiac-RT over 18 years of follow-up, whereas significantly increased in the high dose cardiac-RT group compared with both other groups.

TABLE 4 ORs in Simple and Multivariable Logistic Regression Analyses for Identification of Risk Factors Associated With Valvular Dysfunction in Lymphoma Survivors

	Simple			Multivariable		
	ORs	95% CI	p Value	ORs	95% CI	p Value
Female (reference = male)	1.7	1.0-3.0	0.07	2.0	1.1-3.9	0.03
Hypertension (reference = no)	1.1	0.6-2.0	0.80			
Thyroid disease (reference = no)	1.5	0.7-3.3	0.29			
Hypercholesterolemia (reference = no)	1.8	1.0-3.2	0.05	1.4	0.7-2.7	0.30
Age, yrs, at lymphoma diagnosis (reference = 31-49)						
18-30	1.6	0.8-3.3	0.22	1.0	0.4-2.4	0.88
≥50	1.8	0.9-3.5	0.08	3.4	1.5-7.9	0.004
Observation time >15 yrs (reference = ≤15 yrs)	2.0	1.1-3.5	0.02	1.7	0.8-3.5	0.15
Cumulative doxorubicin dose, mg/m^2	1.0	1.00-1.01	0.07	1.0	0.99-1.01	0.25
Lines of chemotherapy pre auto-HCT (reference = 1)						
2	1.2	0.6-2.4	0.64	1.0	0.4-2.0	0.79
≥3	3.8	1.6-8.8	0.002	2.9	1.1-7.8	0.04
Cardiac-RT (reference = none)						
≤30 Gy	1.5	0.7-3.1	0.25	1.8	0.7-4.5	0.19
>30 Gy	4.0	1.9-8.4	<0.001	5.3	2.0-13.7	0.001

Auto-HCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; cardiac-RT = radiation therapy involving the heart; OR = odds ratio.

STUDY LIMITATIONS. This survey is cross-sectional and nationwide, and all eligible LS are accounted for. The participants did not differ from non-participants in important clinical and treatment characteristics, further strengthening the validity of the results. Additionally, we had a matched control group from the general Norwegian population assessed with echocardiography using the same equipment and technique for recording and analyses. The echocardiographic images were reanalyzed for VD, eliminating the possibility of interobserver variability. Comparisons with controls were performed first between all patients and their matched healthy counterparts, and subsequently after excluding patients with cardiovascular disease, hypertension, or diabetes at study start, thus overcoming a possible bias in the selection criteria. The consistently increased OR for VD in the patient group regardless of analysis strategy strengthened the validity of the observed differences in VD risk between LS and controls. Echocardiographic data from patients at the time of lymphoma diagnosis would have allowed us to evaluate any progression of VD after cardiotoxic exposure, but were not available for this study.

CONCLUSIONS

We observed a 3-fold increased risk for VD and evidence for direct valve damage in the ACCT group,

findings never reported previously. The majority of VD observed was moderate, and longer observation time is necessary for further clarification of the clinical significance of this findings. Overall, female sex, age ≥50 years at primary diagnosis, ≥3 lines of chemotherapy before auto-HCT, and cardiac-RT >30 Gy were identified as independent risk factors for VD, whereas lower dosed cardiac-RT added no significantly increased risk for VD. Our findings may help to identify LS at risk for VD after auto-HCT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prevalence and risk factors for VD in LS after auto-HCT are unknown. Anthracyclines are cardiotoxic and can induce heart failure, but any association between ACCT and VD is not well-defined.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Overall, VD was prevalent and increasing with total cardiotoxic treatment burden. In this cohort of LS after auto-HCT, ACCT was associated with a 3-fold increased risk of VD and increased aortic valve degeneration compared with controls. The vast majority of observed VD was of moderate severity. Female gender, older age at diagnosis, higher doses of cardiac-RT and more lines of chemotherapy before HCT were identified as independent risk factors for VD.

TRANSLATIONAL OUTLOOK: An association between ACCT and both VD and valve degeneration has not previously been reported in the absence of cardiac-RT. Overall, moderate VD was prevalent in the LS. Other independent studies are needed to further substantiate these observations and longer follow-up would clarify the long term clinical significance of the observed VD.

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