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Serum ALT elevations in survivors of childhood cancer. A report from the St. Jude Lifetime Cohort Study

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Abstract

Background and Rationale for Study: To define the prevalence of and risk factors for elevated serum alanine aminotransferase (ALT) level among adult childhood cancer survivors (CCS).

Patients and Methods: 2751 CCS from the St. Jude Lifetime Cohort Study (>10 years post-diagnosis, age 18 years). Serum ALT level graded using the Common Terminology Criteria for

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Adverse Events v 4.03. Modified Poisson regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI) for the association between demographic and clinical factors and grades 1 - 4 ALT on the selected models.

Main Results: 1339 (48.7%) of CCS were female; 2271 (82.6%) were non-Hispanic white. Median age at evaluation was 31.4 years (Interquartile Range (IQR) = 25.8 - 37.8); median elapsed time from diagnosis to evaluation was 23.2 years (IQR = 17.6 - 29.7). 1137 (41.3%) had ALT > Upper Limit of Normal [Common Terminology Criteria for Adverse Events v 4.03 - Grade 1 - 1058 (38.5%); Grade 2 - 56 (2.0%); Grade 3 - 23 (0.8%); Grade 4 - none]. Multivariable models demonstrated non-Hispanic white race/ethnicity, age at evaluation in years, being overweight or obese, presence of the metabolic syndrome, current treatment with atorvastatin or rosuvastatin or simvastatin, hepatitis C virus infection, prior treatment with busulfan or thioguanine, history of hepatic surgery, and the percentage of liver treated with 10 Gray, 15 Gray, or 20 Gray were associated with elevated ALT.

Conclusion: Grade 3 or 4 hepatic injury is infrequent in CCS. Mild hepatic injury in this group may be amenable to lifestyle modifications.

Keywords

hepatitis C; drug induced liver injury; radiation injury; statin; busulfan

Five-year survival rates following a diagnosis of childhood cancer have improved dramatically with more than 80% now expected to reach this milestone (1). As a result, over 420,000 survivors of childhood cancer were estimated to be living in the United States in 2013 with anticipated growth of this population to 500,000 by 2020 (2). This progress has largely resulted from improvements in treatment regimens, some of which may cause hepatic injury. Abdominal irradiation can cause acute and/or chronic hepatic injury (3, 4) that may be potentiated by treatment with dactinomycin (4) or doxorubicin (5), which modify the dose at which repair of sublethal radiation damage ceases. Several chemotherapeutic agents, including carmustine (6), busulfan (7, 8), melphalan (9), conventional (10) and high-dose (11) methotrexate, mercaptopurine (12), and asparaginase, used alone (13) or in combination (14), can produce acute liver injury. Elevations of aspartate aminotransferase and/or alanine aminotransferase (ALT) may occur after major hepatic resections (15), but prolonged liver dysfunction has not been reported. In addition, survivors may experience liver injury related to hepatitis virus infection (16), iron overload (17), and/or lifestyle factors, such as excessive alcohol use (18) or obesity (19).

The true prevalence of hepatic injury in long-term adult childhood cancer survivors (CCS) has not been well defined. Generalizability of outcomes reported in previous studies has been limited by the clinical heterogeneity of the cohorts studied and variable methods used to define hepatotoxicity. While some studies have exclusively reported outcomes of survivors with chronic hepatitis (16) or treated with hematopoietic stem cell transplantation (8), others have excluded these high risk populations (20). Definitions of hepatotoxicity have ranged from elevations of transaminases (e.g., ALT, aspartate aminotransferase), to abnormal liver synthetic function (prothrombin time, albumin) and pathological liver histology. Assessment of factors contributing to persistent treatment-related liver dysfunction has been

limited by small cohort size and/or lack of detailed treatment information (cumulative chemotherapy dose and hepatic radiation dosimetry). Moreover, the prevalence of clinically significant liver dysfunction in aging survivors and the potential impact of lifestyle factors and medication use on survivors' liver health are unknown.

Data regarding the prevalence of and risk factors for hepatic injury in CCS could inform both the initial treatment of future patients and the follow-up and management of current survivors. Thus, we undertook the present study to determine the prevalence of elevated ALT, a marker of hepatic injury, in a clinically assessed cohort of CCS whose prior chemotherapy and radiation therapy exposures, as well as current pharmaceutical use and lifestyle, were well characterized.

Patients and Methods

The current analysis uses the St. Jude Lifetime Cohort Study (SJLIFE). Eligibility for SJLIFE included: 1) diagnosis of childhood malignancy treated at St. Jude Children's Research Hospital; 2) survival 10 years from diagnosis; and 3) current age 18 years. All patients included in the current analysis returned to the St. Jude Children's Research Hospital campus for a multiple day evaluation during which they underwent anthropometric measurements, measurement of markers of liver function and injury, dual energy x-ray absorptiometry, and other risk-based evaluations as indicated by previous treatment exposures. The detailed methods for ascertainment, recruitment, and evaluation of the members of this cohort have been reported previously (21, 22). This investigation was approved by the Institutional Review Board at St. Jude Children's Research Hospital in accord with an assurance filed with and approved by the Department of Health and Human Services. All participants or their guardians provided written informed consent.

Laboratory Measurements

All participants had the serum level of ALT measured at St. Jude Children's Research Hospital using the alanine aminotransferase according to International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Committee on Reference Systems of Enzymes without pyridoxal phosphate (ALTL) (Roche Diagnostics, Indianapolis, Indiana) reagents on the Roche Cobas 6000 analyzer. Results were interpreted as a multiple of the sex-specific upper limit of normal (ULN) (ULN = 30 U/L for males and ULN = 19 U/L for females) (23, 24) and of the institutional ULN (ULN = 40 for males and females) using the Common Terminology Criteria for Adverse Events version 4.03 (Grade 0 ULN; Grade 1 - > ULN to $3 \times$ ULN; Grade 2 - > $3 \times$ ULN to $5 \times$ ULN; Grade 3 - > $5 \times$ ULN - $20 \times$ ULN; grade 4 - > $20 \times$ ULN) (25). Alkaline phosphatase was measured using the Cobas C system alkaline phosphatase according to International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Committee on Reference Systems of Enzymes IFCC Generation 2 (ALP2) (Roche Diagnostics, Indianapolis, Indiana) reagents on the Roche Cobas 6000 analyzer. The ULN was < 131 U/L for females > 15 years of age and males > 19 years of age, and < 261 U/L for males 18 and < 19 years of age. HDL-cholesterol was measured using the Cobas C system HDL-Cholesterol plus 3rd generation (HDL-C3) (Roche Diagnostics, Indianapolis, Indiana). Triglycerides were measured using

the Cobas C system triglycerides (TRIGL) (Roche Diagnostics, Indianapolis, Indiana), and blood glucose was measured using the Cobas C system Glucose HK (GLUC3) (Roche Diagnostics, Indianapolis, Indiana). Serum albumin was measured using the Cobas C system Albumin Gen.2 (ALB2) (Roche Diagnostics, Indianapolis, Indiana) (Normal 3.8 g/dL). Serum total bilirubin was measured using the Bilirubin Total Gen.3 (BILT3) (Roche Diagnostics, Indianapolis, Indiana) (Normal < 1.1 mg/dL). All assays were performed using the Cobas C501 system (Roche Diagnostics, Indianapolis, Indiana).

Screening for hepatitis B virus infection and immunity included measurement of anti-hepatitis B surface antigen antibody (Bio-Rad MONOLISA™ Anti-HBs EIA, Bio-Rad, Hercules, California), total anti-hepatitis B core antigen IgG/IgM antibodies (MONOLISA™ Anti-HBc EIA, Bio-Rad, Hercules, California) and hepatitis B surface antigen (Bio-Rad Genetic Systems™ HBsAg EIA, Bio-Rad, Hercules, California). Screening for hepatitis C virus infection included measurement of anti-hepatitis C virus encoded antigen antibody (ORTHO® HCV Version 3.0 ELISA Test System, Ortho-Clinical Diagnostics, Raritan, New Jersey). All assays were performed using the Bio-Rad EVOLIS™ Automated EIA Processor (Bio-Rad, Hercules, California).

Anthropometric Body Composition Measurements

Anthropometric and body composition measurements were performed as previously described (26). Height (in centimeters), weight (in kilograms), and waist circumference (in centimeters) at the narrowest point between the anterior superior iliac crest and the lowest rib were measured. Waist circumference was dichotomized for males (< 102 cm versus > 102 cm) and females (< 88 cm versus > 88 cm) (26). Body mass index was calculated as the weight (kg)/height (m)². Individuals were classified as overweight if their body mass index was ≥ 25 kg/m² to < 30 kg/m² and as obese if their body mass index was ≥ 30 kg/m². Body weight was adjusted for those with amputated extremities (27).

Metabolic syndrome was defined by the presence of three or more of: 1) abdominal obesity (waist circumference of > 102 cm in males and > 88 cm in females); 2) fasting triglycerides ≥ 150 mg/dL; 3) fasting high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL in females; 4) hypertension (systolic pressure ≥ 130 mm Hg or diastolic pressure ≥ 85 mm Hg) or current treatment with a pharmaceutical to lower blood pressure; and 5) fasting plasma glucose ≥ 100 mg/dL or current treatment with a pharmaceutical to lower blood sugar (28).

Dual energy x-ray absorptiometry and height were used to determine relative appendicular lean muscle mass, summing lean mass in arms and legs, and dividing by height in meters squared. Those with relative mass 1.5 standard deviations below age-, sex-, and race-specific values from the National Health and Nutrition Examination Study were classified as low lean muscle mass (26).

Exposure Definitions

Hepatotoxic therapy included the following surgical procedures: right hepatic lobectomy, extended right hepatic lobectomy, right hepatic trisegmentectomy, left hepatic lobectomy,

extended left hepatic lobectomy, left hepatic trisegmentectomy, left lateral segmentectomy, and central hepatectomy. Hepatotoxic chemotherapy included methotrexate, mercaptopurine, thioguanine, asparaginase, carmustine, busulfan, dactinomycin, and doxorubicin. The definition of hepatotoxic radiation therapy was based on the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer (29).

Exposure Quantification

The cumulative doses for 32 specific chemotherapeutic agents (5-azacytidine, bleomycin, busulfan, carboplatin, carmustine, cisplatin, cyclophosphamide (intravenous or oral), cytarabine (intravenous, intramuscular, intrathecal or subcutaneous), dacarbazine, dactinomycin, daunorubicin, dexamethasone, doxorubicin, etoposide (intravenous or oral), fludarabine, 5-fluorouracil, hydroxyurea, idarubicin, ifosfamide, asparaginase, lomustine, melphalan, methotrexate (intravenous, intramuscular, intrathecal or oral), nitrogen mustard, prednisone, procarbazine, teniposide, thioguanine, thiotepa, tretinoin, vinblastine, vincristine), surgical procedures, and radiation treatment (fields, dose, and energy source) were abstracted from the medical records according to a protocol similar to that utilized in the Childhood Cancer Survivor Study (30). High-dose methotrexate was defined as any single dose $\geq 1000 \text{ mg/m}^2$ (29).

Radiation fields potentially involving the liver included the following: hepatic, renal, right or left upper quadrant, partial or entire spleen, paraaortic, right or left flank/hemiabdomen, whole abdomen, extended mantle, inverted Y, total lymphoid irradiation, subtotal lymphoid irradiation, and total body irradiation. Additional treatment volumes not included in the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer were evaluated including spinal treatment volumes that included the lower thoracic and/or upper lumbar vertebral bodies. Hepatic radiotherapy dose was quantified by reconstructing each patient's individual radiation treatment on a computed-tomography based phantom with an organ library for calculation of normal organ radiation doses. For each patient's reconstructed radiation treatment plan, the volumetric dose to the liver was calculated by recreating the treatment ports and actual beam energies in a modern radiation therapy planning software system (Eclipse, Varian Medical Systems, Milpitas, California). The volumes of liver receiving 10 Gray (Gy) (V10), 15 Gy (V15), and 20 Gy (V20) were used in our analysis as both dichotomous (yes/no) and continuous (per 10% of liver volume) variables.

Risky drinking was defined in the National Institute for Alcohol Abuse and Alcoholism physicians' guidelines as drinking for women that exceeds three drinks per day or seven drinks per week, and for men as more than four drinks per day or 14 drinks per week (31, 32). Heavy drinking was defined as five or more drinks per day for women and six or more drinks per day for men at least once a month in the past year (33, 34).

Hepatotoxic pharmaceuticals were defined as those pharmaceuticals which produced drug-induced liver injury in $\geq 1\%$ of reported patients who survived without liver transplantation six months after the acute drug-induced liver injury with evidence of either chronic or no

chronic liver injury (35). Current use of atorvastatin, rosuvastatin, simvastatin, duloxetine, amoxicillin, amoxicillin with clavulanic acid, azithromycin, ciprofloxacin, levofloxacin, minocycline, nitrofurantoin, sulfamethoxazole with trimethoprim, terbinafine, isoniazid, lamotrigine, phenytoin, or diclofenac was abstracted from the SJLIFE Clinic Note. Current use of over the counter medications or herbal preparations was not included because such use could not be documented reliably.

Statistical Analysis

Descriptive statistics were used to summarize demographic and treatment variables for participants and non-participants. The Chi-squared test was used to compare categorical variables and the T-test was used to compare continuous variables between these two groups.

Given little *a priori* justification for including a particular set of covariates in the model, to adjust for confounding bias, Elastic Net was applied to all demographic, lifestyle, and treatment variables to perform model selection for elevated ALT using the GLMNET in R 3.2.2 (36, 37). Models with the smallest Akaike Information Criterion were selected as the final models.

Modified Poisson regression models (Poisson regression with a robust error variance) (38, 39) were used to identify risk factors for elevated ALT on models selected by using Elastic Net. This approach produces unbiased parameter estimates and improves the prediction of error. Results for ALT were presented as relative risks (RR) with 95% confidence intervals (CI). These analyses were conducted using Statistical Analysis System software (SAS 9.4, Cary North Carolina).

Results

Among 4421 eligible individuals, 2751 participants (62.3%) diagnosed between April 1962 and November 2000 had an evaluable ALT as part of their clinical assessment at St. Jude Children's Research Hospital (Figure 1). The evaluable cohort included 48.7% female, and 82.6% non-Hispanic white participants. The 1668 non-participants were more likely to be male and non-Hispanic black. Fewer non-participants were diagnosed with acute lymphoblastic leukemia, and fewer had been treated with Erwinia or Escherichia coli l-asparaginase, high-dose methotrexate, or mercaptopurine (Tables 1 and 2). The median age of the participants at diagnosis was 7.4 years, the median age at evaluation was 31.4 years, and the median elapsed time from diagnosis to evaluation was 23.2 years (Table 1). Table 3 summarizes additional characteristics of the cohort.

Use of hepatotoxic pharmaceuticals is detailed in Table 4. Among the potentially hepatotoxic medications analyzed, liver injury was associated with use of several 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors ("statins"), phenytoin, and lamotrigine, whether evaluated using the sex-specific definitions of the ULN (Table 4) or the institutional ULN (Supplementary Table 1). Among patients who received hepatic irradiation, the median percentage of the liver that received 10 Gy was 51.4%, among those who received 15 Gy was 34.6%, and among those who received 20 Gy was 25.3% (Table 5).

Participants were considered at risk for hepatitis B if they were diagnosed prior to 1972, and at risk for hepatitis C if they were diagnosed prior 1993. Fourteen of 1592 at risk have not been screened for hepatitis C. Of the 1578 who were screened, 98 (6.2%) were seropositive. Twenty of 93 at risk were not screened for hepatitis B. Of the 73 who were screened, 7 (9.6%) were seropositive.

ALT > ULN, using the sex-specific ULN values, was identified in 1137 (41.3%) survivors. Five hundred eighty-one were male and 556 were female. Among males, 541 (38.3 %) had grade 1, 27 (1.9%) had grade 2, 13 (0.9%) had grade 3, and none had grade 4 ALT. Among females, 517 (38.6 %) had grade 1, 29 (2.2%) had grade 2, 10 (0.8%) had grade 3, and none had grade 4 ALT. The prevalence of ALT > ULN was 15.2% (419) when the data were analyzed using the institutional ULN. The distributions of CTCAE grade for ALT versus normal or abnormal albumin, total bilirubin and alkaline phosphatase are shown in Supplementary Table 2.

In multivariable models non-Hispanic, white race/ethnicity, age at evaluation in years, body mass index $\geq 25 \text{ kg/m}^2$, metabolic syndrome, current treatment with atorvastatin or rosuvastatin or simvastatin, hepatitis C virus infection, prior treatment with busulfan or thioguanine, and history of hepatic surgery were all significant risk factors for elevated ALT. Radiation therapy dosimetric variables V10, V15 and V20 (by 10% volume increment) achieved statistical significance in the multivariable models (Table 6).

Multivariable models using both the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer definitions for hepatic irradiation, and an expanded definition that included T11 through L3 spinal irradiation volumes provided comparable results (Supplementary Table 3). The results of the Standardized Pearson Test for Goodness of Fit demonstrate that the models developed fit the available data well (Supplementary Table 4).

Cause of Death

The causes of death among 1225 deceased individuals eligible for SJLIFE were reviewed. For 17 of these (1.4%), liver disease was a significant factor contributing to death. The details regarding these 17 individuals are shown in Supplementary Table 5.

Discussion

Acute hepatic injury is frequently observed during treatment of childhood cancer, but its persistence and impact on liver health during adulthood have not been well studied. With more precise assessment of hepatotoxic chemotherapy and radiation exposures, we have characterized liver injury related to lifestyle factors and medication use in adults followed for more than 20 years after childhood cancer diagnosis. The prevalence of liver injury in our cohort as measured by elevated ALT was 41.3% using sex-specific values for ULN, and was substantially higher than either 15.2% using our institutional unisex ULN or 5.8% among a younger group of Dutch CCS with shorter follow-up (20). ALT elevations were generally low grade in severity, which may be related to progress in pediatric cancer

therapeutic strategies and advances in supportive care. We identify several novel treatment and post-treatment factors that increase the risk for liver injury during adulthood.

Radiation therapy doses to the liver have been intentionally minimized to the lowest, effective dose and smallest volume to reduce injury. No prior study has evaluated the dose or volume relationships between prior hepatic irradiation and evidence of liver injury among aging survivors of childhood cancer. The current study identified a significant association between the percentage of the liver treated with 10 Gy, 15 Gy, or 20 Gy and elevated ALT. This excess risk for liver injury was also observed in individuals who received spinal radiation at the level of T11-L3, a field not previously identified as one that exposes the liver. Future updates to screening guidelines should consider including T11-L3 spinal irradiation.

Aging survivors develop chronic health conditions at higher rates compared to those of non-cancer control populations, some of which require management with potentially hepatotoxic medications (21, 40). A novel finding in the present study was the association of current treatment with one of three commonly prescribed “statins” with an increased risk for liver injury among SJLIFE participants. In the general population, elevations of serum levels of ALT are reported in < 1% of patients receiving “statins” with the exception of atorvastatin, where a frequency of 2% to 3% has been reported among patients treated with 80 mg/day (41, 42). In our cohort, almost one in two survivors taking a statin had ALT elevations. These data suggest that survivors may be more vulnerable to statin-related liver injury, possibly related to prior, treatment-related hepatic injury.

Prior treatment with busulfan, a frequent component of hematopoietic stem cell transplantation conditioning regimens, and thioguanine, were independently associated with an increased risk for grades 1 - 4 ALT. Hematopoietic stem cell transplantation complications, such as sinusoidal obstruction syndrome/veno-occlusive disease and graft-versus-host disease, may also produce liver injury (43, 44). This group of survivors, excluded from prior large studies of hepatic injury among CCS, warrant particularly careful evaluation and follow-up.

Metabolic syndrome is defined by a composite of modifiable health and lifestyle factors. Larger waist circumference and overweight/obesity are associated with an increased risk of elevated ALT (19). The prevalence of non-alcoholic fatty liver disease among participants in the National Health and Nutrition Examination Study III, defined by the presence of moderate to severe hepatic steatosis with normal ALT and aspartate aminotransferase, was 16.4% (45). These data suggest that interpretation of the results of the current study must be cautious, because the known higher prevalence of overweight/obesity (46, 47) and visceral adiposity (48) among CCS may be associated with the presence of non-alcoholic fatty liver disease with a normal ALT. Evaluation using ultrasound (45), or other non-invasive methods for categorizing hepatic steatosis may provide a more definitive picture of the prevalence of liver injury among childhood cancer survivors.

Heavy drinking was not identified as an independent risk factor for liver injury in our cohort when the data were analyzed using sex-specific values for ULN. A previous report showed

that consumption of more than 14 units/week was associated with an Odds Ratio = 2.53 (95% CI, 1.04, 6.18) for elevated ALT (20). This level of alcohol consumption was endorsed by 5.9% of the Dutch cohort and by 21.5% of the SJLIFE cohort. In another study, 24.0% of those who drank more than two drinks/day had an elevated ALT, but a dose-response relationship could not be demonstrated³⁸. Survivors should be counseled about the potential for alcohol to exacerbate their underlying liver injury from complications associated with cancer treatment. CCS with chronic hepatitis B or C infection, most of whom were treated prior to routine testing of blood products for these viruses (16, 49), represent a group that is particularly vulnerable to additional hepatotoxic insults as they age. In the SJLIFE cohort, prior infection with hepatitis C virus was associated with an almost two fold increased risk of elevated ALT. Non-Hispanic, white race/ethnicity was associated with an increased risk for elevated ALT compared to non-Hispanic, black race/ethnicity, a finding previously noted during treatment for acute lymphoblastic leukemia (50).

A potential limitation of this study is that 38% of the eligible survivors did not have an ALT value and non-participants did differ from participants on some demographic characteristics and cancer diagnoses. Thus, the potential exists that the rate of elevated ALT could be different among non-participants. In addition, this is a retrospective cohort study in which data for some variables, such as HBV and HCV status, fasting blood sugar, HDL and triglycerides were incomplete. We do not have liver imaging to identify findings consistent with hepatic steatosis, cirrhosis, or portal hypertension. However, this study has several important strengths, including large size, prolonged follow-up (median - 23.2 years), detailed exposure data including radiation dosimetry and prescription pharmaceutical use, and comprehensive clinical assessment including measurement of body composition.

In summary, a significant minority of adults treated for cancer during childhood have an elevated ALT, a marker of liver injury, related to specific cancer treatments, treatment complications, medications, and health and lifestyle factors. While contemporary treatment strategies aim to limit hepatotoxic therapy, CCS should be counseled about the risk of additional insults to liver health as they age. Future research should define the prevalence of non-alcoholic steatosis and steatohepatitis in CCS, which may interact with both prior therapeutic exposures and current pharmaceutical use and lifestyle choices, to produce liver injury not associated with elevations of ALT, and which may be amenable to intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of Abbreviations

ALT	alanine aminotransferase
CCS	childhood cancer survivors

SJLIFE	St. Jude Lifetime Cohort Study
ULN	upper limit of normal
Gy	Gray
V10	percentage of the liver treated with 10 Gy or more
V15	percentage of the liver treated with 15 Gy or more
V20	percentage of the liver treated with 20 Gy or more
RR	relative risk
CI	Confidence interval

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Figure 1.
– Flow diagram for SJLIFE cohort included in hepatic injury analysis

Table 1

– Demographic and disease characteristics of participants and non-participants

Variable	Category	SJLIFE participants (N = 2751)		SJLIFE non-participants (N = 1668)		p-value
		Frequency	Percent	Frequency	Percent	
Gender		N	%	N	%	
	Female	1339	48.7	672	40.3	<0.001
Race/Ethnicity	Male	1412	51.3	996	59.7	
	Non-Hispanic White	2271	82.6	1337	80.2	0.028
	Non-Hispanic Black	383	13.9	258	15.5	
	Hispanic	49	1.8	25	1.5	
	Other	48	1.7	48	2.9	
Age at Diagnosis (years)	0 to 4	1024	37.2	615	36.9	0.613
	5 to 9	647	23.5	412	24.7	
	10 to 14	641	23.3	359	21.5	
	15 to 20	429	15.6	276	16.6	
	21	10	0.4	6	0.4	
	Mean $\pm$ SD	8.3 $\pm$ 5.6		8.4 $\pm$ 5.6		
Educational level	Median (IQR)	7.4 (3.3,13.2)		7.4 (3.4,13.1)		
	Not reported	103	3.7			
	No HS or GED	249	9.1			
	HS or GED	623	22.7			
	Some college and no bachelor's degree	865	31.4			
	Bachelor's degree or higher	911	33.1			
Age at Evaluation (years)	18 to 25	715	26.0			
	26 to 35	1169	42.5			
	36 to 45	679	24.7			
	46 to 55	171	6.2			
	> 55	17	0.6			
	Mean $\pm$ SD	32.4 $\pm$ 8.3				

Variable	Category	SJLIFE participants (N = 2751)		SJLIFE non-participants (N = 1668)		p-value
		Frequency	Percent	Frequency	Percent	
		N	%	N	%	
	Median (IQR)	31.4 (25.8,37.8)				
Elapsed time from diagnosis to evaluation						
	Mean $\pm$ SD	24.1 $\pm$ 8.1				
	Median (IQR)	23.2 (17.6, 29.7)				
Diagnosis	Acute lymphoblastic leukemia	934	34.0	487	29.2	<0.001
	Acute myeloid leukemia	85	3.1	64	3.8	
	Central Nervous System (CNS)	259	9.4	165	9.9	
	Ewing sarcoma family of tumors	88	3.2	39	2.3	
	Hodgkin lymphoma	339	12.3	174	10.4	
	Neuroblastoma	121	4.4	78	4.7	
	Non-Hodgkin lymphoma	200	7.3	162	9.7	
	Osteosarcoma	108	3.9	53	3.2	
	Rhabdomyosarcoma	91	3.3	64	3.8	
	Wilms tumor	178	6.5	117	7.0	
	Other	348	12.7	265	15.9	

HS – High school; GED – General Educational Development certificate; SD – standard deviation, IQR – interquartile range

Table 2

– Treatment exposures of participants and non-participants

Variable	Category	SJLIFE participants		SJLIFE non-participants		p-value
		Frequency	Percent	Frequency	Percent	
Busulfan	No	2728	99.2	1648	98.8	0.233
	Yes	23	0.8	20	1.2	
Carmustine	No	2739	99.6	1662	99.6	0.699
	Yes	12	0.4	6	0.4	
Melfalan	No	2746	99.8	1661	99.6	0.231 *
	Yes	5	0.2	7	0.4	
Dactinomycin	No	2351	85.5	1435	86.0	0.599
	Yes	400	14.5	233	14.0	
Erwinia Asparaginase or Escherichia coli L-Asparaginase	No	1833	66.6	1185	71.0	0.002
	Yes	918	33.4	483	29.0	
High Dose Methotrexate ^a	No	2004	72.9	1267	76.0	0.022
	Yes	747	27.2	401	24.0	
	Mean ± SD (mg/m ²)	21369.8 ± 28695.9		22228.2 ± 28900.5		0.636 **
	Median (IQR) (mg/m ²)	15212.9 (4064.5, 21697.3)		15222.6 (5124.1, 21846.4)		
Mercaptopurine	No	1679	61.0	1091	65.4	0.004
	Yes	1072	39.0	577	35.0	
Methotrexate	No	1423	51.7	901	54.0	0.139
	Yes	1328	48.3	767	46.0	
PEG-Asparaginase	No	2734	99.4	1655	99.2	0.526
	Yes	17	0.6	13	0.8	
Thioguanine	No	2725	99.1	1645	98.6	0.182
	Yes	26	0.9	23	1.4	
Hepatic Surgery	No	2727	99.1	1643	98.5	0.054
	Yes	24	0.9	25	1.5	
Hepatic Irradiation	No	2383	86.6	1473	88.3	0.103

Variable	Category	SJLIFE participants		SJLIFE non-participants		p-value
		Frequency	Percent	Frequency	Percent	
Total Body Irradiation	Yes	368	13.4	195	11.7	
	No	2682	97.5	1617	96.9	0.276
	Yes	69	2.5	51	3.1	
Hematopoietic Stem Cell Transplant (HSCT)	None	2675	97.2	1618	97.1	0.691 *
	Autologous HSCT	29	1.1	21	1.3	
	Allogeneic HSCT	45	1.6	26	1.6	
Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease	Autologous and allogeneic HSCT	2	0.1	3	0.2	
	No	2739	99.6	1664	99.8	0.292
	Yes	12	0.4	4	0.2	

^a – high-dose methotrexate = individual dose 1000 mg/m²; SD – standard deviation, IQR – interquartile range

* - Exact Chi-Square Test

** - T-Test

Table 3

– Lifestyle characteristics of SJLIFE participants

Variable	Category	Frequency	Percent
Body Mass Index (kg/m ²)	Missing	45	1.6
	13 to <25	984	35.8
	25 to <30	763	27.7
	30 to <35	503	18.3
	35 to <40	247	9.0
	40	209	7.6
Risky drinking	Missing	112	4.1
	No	2048	74.5
	Yes	591	21.5
Heavy drinking	Missing	112	4.1
	No	2179	79.2
	Yes	460	16.7
Waist circumference (cm)	Missing	50	1.8
	Male 102, Female 88	1850	67.3
	Male>102, Female>88	851	30.9
	Mean $\pm$ SD	89.7 $\pm$ 17.0	
	Median (IQR)	87.5 (77.0,100.4)	
Fasting glucose	Missing	175	6.4
	<100 mg/dL	1874	68.1
	100 mg/dL	702	25.5
Blood pressure	Missing	45	1.6
	Systolic pressure < 130 mm Hg and diastolic pressure < 85 mm Hg	1477	53.7
	Systolic pressure $\geq$ 130 mm Hg or diastolic pressure $\geq$ 85 mm Hg	1229	44.7
Fasting triglycerides	Missing	238	8.7
	< 150 mg/dL	2091	76.0
	150 mg/dL	422	15.3
Fasting high-density lipoprotein cholesterol	Missing	310	11.3
	40 mg/dL in males and 50 mg/dL in females	1823	66.3
	< 40 mg/dL in males and <50 mg/dL in females	618	22.5
Metabolic syndrome	Missing	225	8.2
	No	1980	72.0
	Yes	546	19.9
Lean muscle mass decreased	Missing	32	1.2
	No	1932	70.2
	Yes	787	28.6
Hepatitis B	Grade<1	2739	99.6
	Grade $\geq$ 1	12	0.4

Variable	Category	Frequency	Percent
Hepatitis C	Grade<1	2626	95.5
	Grade 1	125	4.5

SD – standard deviation; IQR – Interquartile range

Table 4

– Pharmaceutical use by SJLIFE participants and sex-specific ALT > ULN

Variable	Category	Frequency ^a	Percent	ALT	
				< ULN	ULN
Atorvastatin	No	2721	98.9	1600 (58.8)	1121 (41.2)
	Yes	30	1.1	14 (46.7)	16 (53.3)
Rosuvastatin	No	2726	99.1	1609 (59.0)	1117 (41.0)
	Yes	25	0.9	5 (20.0)	20 (80.0)
Simvastatin	No	2687	97.7	1592 (59.2)	1095 (40.8)
	Yes	64	2.3	22 (34.4)	42 (65.6)
Duloxetine	Missing	2	0.1	2 (100.0)	0 (0.0)
	No	2730	99.2	1603 (58.7)	1127 (41.3)
	Yes	19	0.7	9 (47.4)	10 (52.6)
Phenytoin	No	2739	99.6	1608 (58.7)	1131 (41.3)
	Yes	12	0.4	6 (50.0)	6 (50.0)
Lamotrigine	Missing	1	0.0	1 (100.0)	0 (0.0)
	No	2722	99.0	1599 (58.7)	1123 (41.3)
	Yes	28	1.0	14 (50.0)	14 (50.0)
Diclofenac	No	2750	100.0		
	Yes	1	0.0		
Antibiotic [*]	Missing	1	0.0	0 (0.0)	1 (100.0)
	No	2739	99.6	1605 (58.6)	1134 (41.4)
	Yes	11	0.4	9 (81.8)	2 (18.20.0)
Amoxicillin	Missing	1	0.0		
	No	2750	100.0		
	Yes	0	0.0		
Ciprofloxacin	No	2749	99.9		
	Yes	2	0.1		
Nitrofurantoin	No	2747	99.9		

Variable	Category	Frequency ^a	Percent	ALT	
				< ULN	ULN
	Yes	4	0.1		
Amoxicillin/clavulanic acid	No	2751	100.0		
	Yes	0	0.0		
Trimethoprim/sulfamethoxazole	No	2749	99.9		
	Yes	2	0.1		
Minocycline	No	2750	100.0		
	Yes	1	0.0		
Azithromycin	No	2749	99.9		
	Yes	2	0.1		
Terbinafine	No	2751	100.0		
	Yes	0	0.0		

* - ciprofloxacin and/or nitrofurantoin and/or trimethoprim/sulfamethoxazole and/or minocycline and/or azithromycin; ALT – alanine aminotransferase; ULN – Upper Limit of Normal (Males – 30; Females – 19); N – Number of patients

^a - Cells with fewer than ten patients were not further evaluated.

Table 5

– Radiation therapy dosimetry of SJLIFE participants

Variable	Category	Frequency	Percent
V10 ^a	Missing	64	2.3
	No	2171	78.9
	Yes	516	18.8
	Median (IQR)	32.4 (23.1, 95.7)	
V10 ^b	Missing	64	2.3
	No	2327	84.6
	Yes	360	13.1
	Median (IQR)	48.8 (24.6, 100.0)	
V15 ^a	Missing	64	2.3
	No	2306	83.8
	Yes	381	13.9
	Median (IQR)	25.6 (13.8, 35.0)	
V15 ^b	Missing	64	2.3
	No	2440	88.7
	Yes	247	9.0
	Median (IQR)	26.6 (15.5, 68.4)	
V20 ^a	Missing	64	2.3
	No	2357	85.7
	Yes	330	12.0
	Median (IQR)	17.8 (5.2, 32.0)	
V20 ^b	Missing	64	2.3
	No	2469	89.8
	Yes	218	7.9
	Median (IQR)	20.7 (7.0, 44.4)	

Gy – Gray; V10 – Percentage of the liver treated to 10 Gy; V15 – Percentage of the liver treated to 15 Gy; V20 – Percentage of the liver treated to 20 Gy

^a – Radiation therapy including volumes defined by COG Guidelines and additional volumes treating T11 to L3

^b – Radiation therapy including only volumes included in the COG Guidelines; IQR – Interquartile range

– Elastic Net multivariable analysis for Sex-Specific ALT > Upper Limit of Normal using COG Guideline definition of hepatotoxic radiation therapy and metabolic syndrome

Table 6

Variable	Category	V10			V15			V20		
		RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
Race/Ethnicity	Non-Hispanic white vs non-Hispanic black, other	1.38	1.19 - 1.59	<0.001	1.37	1.18 - 1.58	<0.001	1.36	1.18 - 1.57	<0.001
Age at evaluation in years	Per year	1.01	1.00 - 1.01	0.003	1.01	1.00 - 1.01	0.011	1.01	1.00 - 1.01	0.008
Body Mass Index (kg/m ²)	25 vs < 25	1.64	1.45 - 1.85	<0.001	1.60	1.42 - 1.81	<0.001	1.59	1.41 - 1.80	<0.001
Metabolic syndrome	Yes vs No	1.36	1.23 - 1.51	<0.001	1.40	1.26 - 1.55	<0.001	0.72	0.65 - 0.79	<0.001
Atorvastatin or rosuvastatin or simvastatin	Yes vs No	1.20	1.02 - 1.42	0.032	1.20	1.02 - 1.42	0.032	1.21	1.02 - 1.43	0.030
Hepatitis C	Grade 1 vs Grade <1	1.77	1.54 - 2.04	<0.001	1.76	1.52 - 2.02	<0.001	1.75	1.52 - 2.01	<0.001
Busulfan	Yes vs No	1.42	0.95 - 2.13	0.086	1.54	1.02 - 2.33	0.038	1.56	1.03 - 2.38	0.036
Thioguanine	Yes vs No	1.32	0.98 - 1.77	0.070	1.38	1.02 - 1.85	0.034	1.37	1.01 - 1.84	0.040
Hepatic surgery	Yes vs No	1.96	1.50 - 2.55	<0.001	1.90	1.45 - 2.49	<0.001	1.94	1.52 - 2.49	<0.001
V10	Per 10%	1.05	1.04 - 1.07	<0.001						
V15	Per 10%				1.06	1.03 - 1.08	<0.001			
V20	Per 10%							1.06	1.03 - 1.09	<0.001

ALT – alanine aminotransferase; Upper Limit of Normal = 30 U/L for males and = 19 U/L for females; RR – Relative risk; CI – Confidence interval; Gy – Gray; V10 – Percentage of the liver treated to 10 Gy; V15 – Percentage of the liver treated to 15 Gy; V20 – Percentage of the liver treated to 20 Gy