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Suicide in European Hodgkin Lymphoma Patients

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Abstract

The purpose of this study was to determine whether there is an increased risk of suicide in European Hodgkin Lymphoma (HL) patients compared to the general European population.

European HL patients enrolled in the German Hodgkin Study Group (GHSG) HD7 through HD15 studies were analyzed and standardized mortality ratio (SMR) was calculated using suicide mortality rates for the general European population. Case-control analysis was performed to identify characteristics associated with risk of death by suicide. Among 12,202 European HL patients observed for 94,972 person-years, 19 suicides (17 males and 2 females) were identified resulting in a SMR 1.63 (95% CI: 1.01–2.50, p = 0.046). The only characteristic associated with a statistically significant increased risk of suicide was male sex with an odds ratio (OR) 8.42 (95% CI = 1.04–67.85; p = 0.046) on multivariate analysis. These findings were confirmed in an independently analyzed Surveillance, Epidemiology, and End Results Program (SEER) validation dataset. European HL patients have a significantly increased incidence of suicide compared to the general European population. Male HL patients have a greater than 8-fold increased risk of suicide compared to female HL patients. Further study of social risk factors associated with an increased risk of suicide in HL patients is needed.

Keywords: European, German Hodgkin Study Group, Hodgkin lymphoma, Male, Suicide

Introduction

A retrospective population study in the United States using the Surveillance, Epidemiology, and End Results Program (SEER) database compared suicide rates by anatomic cancer site and found a statistically significant standardized mortality ratio (SMR) of 2.07 in Hodgkin Lymphoma (HL) patients compared to the general US population.[1] This study was not specific to HL, nor did it look at clinical information related to HL. The largest clinical trials in HL have been performed in Europe, and suicide has not been studied in this population. To determine if there is an increase in suicide incidence in European HL patients compared to the general European population, we analyzed data from several randomized European HL clinical trials. We sought to identify demographic, disease, and treatment-specific characteristics in HL patients associated with an increased risk of suicide. We also attempted to validate our findings by an independent review of SEER registry data for HL patients and suicide.

Results

Nineteen patients (17 males and 2 females) died by suicide in the GHSG HD7-HD15 studies. Demographic, disease, and treatment information of the entire cohort and the 19 patients with death by suicide is included in Table 1. Suicide was the seventh most common cause of death, making up 1.6% of all deaths, in the analyzed cohort of HL patients (Fig. 1). Median follow-up time was 85 months, total observation time was 94,972 person-years, and the crude suicide rate of HL patients was 20.01/100,000 person-years. The corresponding expected suicide rate in the general European population was 12.29/100,000 person-years (Eurostat).[16] SMR for the entire HL cohort was 1.63 (95% CI: 1.01–2.50) that was significantly elevated ($p < 0.05$) with $p = 0.046$. The crude suicide rate of male HL patients was 32.29/100,000 person-years, and the corresponding expected suicide rate in the general male European population was 19.85/100,000 person-years with a SMR of 1.63 (95% CI: 0.98–2.55) that was

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Table 1

Patient characteristics

	Death by suicide *N*=19; (n (%))	Total study cohort *N*=12,202; (n (%))
Median age at diagnosis (years)	38 (range 19–59)	36 (range 16–75)
Median time to suicide (months)	42 (range 1–142)	N/A
Median age at suicide (years)	46 (range 22–59)	N/A
Study generation, Time of initial diagnosis		
HD7–9, 02/1993–03/1998	4 (21%)	2887 (24%)
HD10–12, 05/1998–01/2003	7 (37%)	4159 (34%)
HD13–15, 01/2003–09/2009	8 (42%)	5156 (42%)
Sex		
Male	17 (89%)	6899 (57%)
Female	2 (11%)	5303 (43%)
Stage of Disease		
Early stage favorable	6 (32%)	3319 (27%)
Early stage unfavorable	5 (26%)	3987 (33%)
Advanced Stage	8 (42%)	4896 (40%)
Histological subtype		
Nodular sclerosis	11 (58%)	5968 (49%)
Mixed cellularity	5 (26%)	2753 (23%)
Other Classical HL	1 (5%)	840 (7%)
NLPHL	0	461 (4%)
Not Available	2 (11%)	2180 (18%)
Chemotherapy Regimen		
ABVD-based	12 (63%)	5801 (48%)
BEACOPP-based	7 (37%)	6090 (50%)
Radiotherapy alone	0	311 (3%)
Secondary Malignancy		
Solid Tumor	1 (5%)	488 (4%)
NHL	0	180 (1%)
Leukemia/MDS	0	108 (1%)
Radiation Therapy + Median Dose	12 (63%) + 30 Gy	8952 (73%) + 30 Gy
Relapsed Disease	2 (11%)	1256 (10%)

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine, BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, Gy = Gray, MDS = Myelodysplastic Syndrome, NHL = non-Hodgkin Lymphoma, NLPHL = Nodular Lymphocyte Predominant Hodgkin Lymphoma.

*German Hodgkin Study Group (GHSG) risk classification: -Early stage favorable = Stage IA, IIA, IIA, or IIB cHL, without risk factors: large mediastinal mass, extranodal disease, three or more involved lymph node areas, or elevated ESR ($\geq$ 50 for stages IA and IIA and $\geq$ 30 for stages IB and IIB): -Early stage unfavorable = Stage IA, IB, or IIA with one or more above risk factors. Stage IIB only if risk factors of elevated ESR and/or involvement of 3 or more lymph node areas are present -Advanced stage = Stage IIB with risk factors of extranodal involvement and/or large mediastinal mass. Stage IIIA, IIIB, IVA, or IVB.

not significantly different from 1 likely due to a smaller sample size ($p=0.059$). Female HL patients did not have an increased suicide rate compared to the general female European population (SMR 0.95, 95%-CI: 0.16–3.13, $p=0.940$). We confirmed these findings in the independent SEER dataset, with 105 suicides in a total observation time of 483,264 person-years. The crude incidence in the SEER data was 21.73/100,000 person-years. The corresponding expected suicide rate in the U.S. population was 13.46/100,000 person-years, resulting in a SMR of 1.56 (95% CI: 1.29–1.89) that was significantly different from 1 ($p<0.001$) and remarkably similar to the SMR obtained in the European population. We also confirmed the elevated suicide rate in male HL patients (SMR: 1.57, 95%-CI: 1.27–1.92, $p<0.001$) and the non-elevated suicide rate in female HL patients (SMR: 1.15, 95%-CI: 0.66–1.89, $p=0.58$) in the SEER validation dataset.

Suicide risk over time

The highest risk of suicide was during the first year after diagnosis of HL (Fig. 2). Median time to suicide of patients diagnosed with HL between ages 15–49 was 56 months (95% CI: 36–91), and only 13 months (95% CI: 1–34) for patients diagnosed between ages 50–59 (Fig. 3). The highest risk of suicide in both male and female HL patients was between ages 50–59. Male HL patients of most age groups had increased suicide risk, reaching statistical significance in the group of 40–49-year-olds. In females, risk of suicide was only increased in those aged 50–59 years (Table 2). These findings were confirmed in the independent SEER dataset. The median time to suicide of patients ages 15–49 was 98 months (95% CI: 72–122) and 49 months (95% CI: 6–93) for patients ages 50–59 and thus similarly shorter. Patients between ages 50–59 and male HL patients age 40–49 in the validation cohort had SMRs of 1.63 (95%-CI: 0.83–2.91, $p=0.14$) and 1.63 (95%-CI: 0.93–2.68, $p=0.08$), respectively.

Case-control analysis

Nineteen patients with death by suicide (cases) were matched with 57 controls. The results of the univariate analysis are summarized in Table 3. Male sex was the only variable associated with a statistically significant increased risk of suicide, odds ratio (OR) 9.37 (95% CI: 1.12–75.2; $p=0.035$). Male sex remained statistically significant on multivariable conditional logistic regression adjusting for stage (stage IV vs stage I-III) and presence of large mediastinal mass, OR 8.49 (95% CI: 1.06–68.22; $p=0.044$). We validated this finding in the SEER dataset with a multivariable conditional logistic regression controlling for stage (data on mediastinal mass is not available as part of the

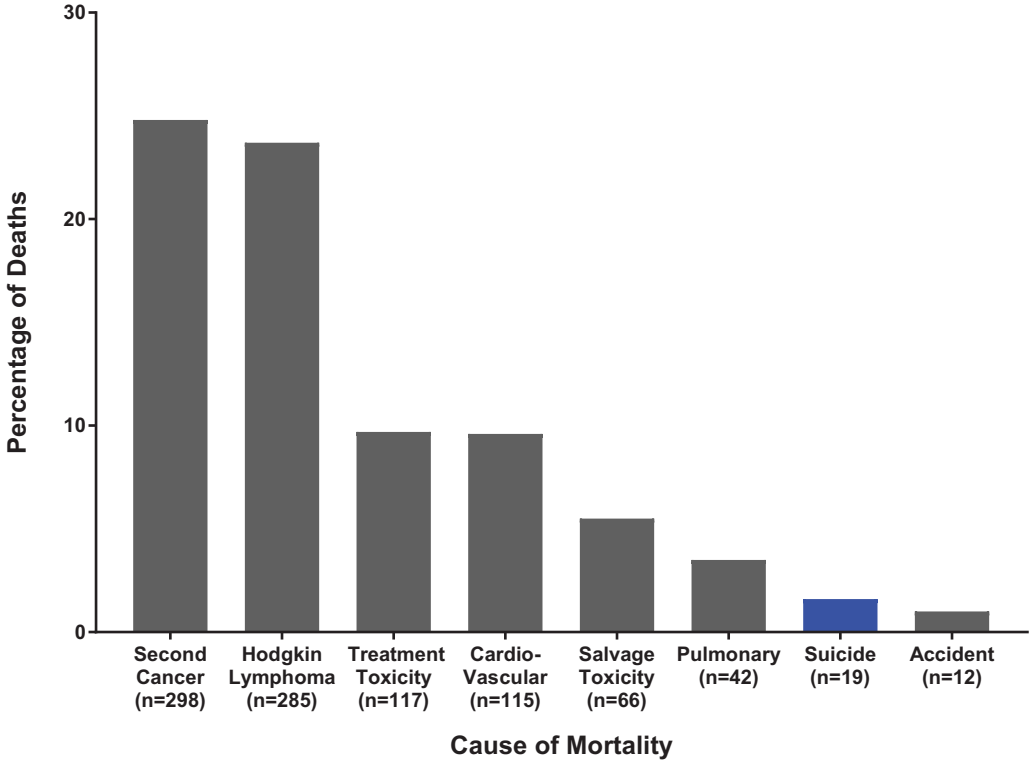

Figure 1. **Cause of Mortality in HD7-HD15 studies.**

SEER data) and confirmed the increased suicide risk for male compared to female HL patients OR 5.86 (95%-CI: 2.62–13.10, $p < 0.001$).

Discussion

European HL patients from the GHSG HD7-HD15 clinical trials had a significantly increased risk of suicide, SMR 1.63, compared to the general European population. The only variable found on both univariate and multivariate analysis to be associated with a statistically significant increased risk of suicide in HL patients was male sex. We did not find an increased risk of suicide in HL patients with relapsed disease, more intensive treatment regimens, or development of secondary malignancy. Male sex was found to confer a greater than 8-time risk of suicide in our study of HL patients by multivariate analysis. In the general population, males are nearly 3 to 4 times more likely than females to commit suicide, although females are twice as likely as men to experience major depression during their lifetime.[18] This increased risk of suicide, especially in male HL patients, was confirmed in an independent validated SEER dataset of HL patients from the United States.

Our data suggest that the highest risk of suicide for HL patients is within the first 3 months and the first year after diagnosis of HL. This is consistent with the study by Fang et al,[19] who

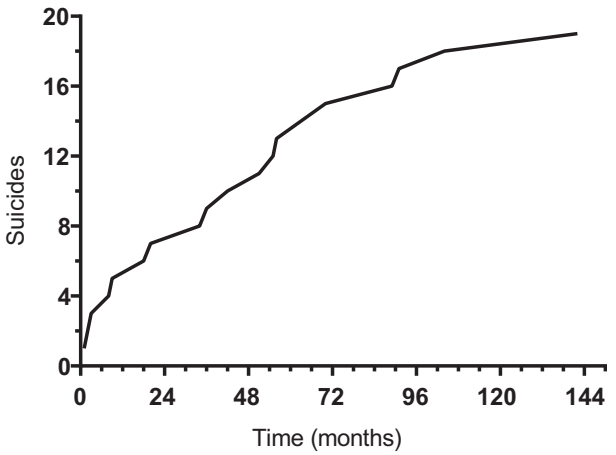

Figure 2. **Cumulative incidence and time to suicide (months) following diagnosis of HL in HD7-HD15**.

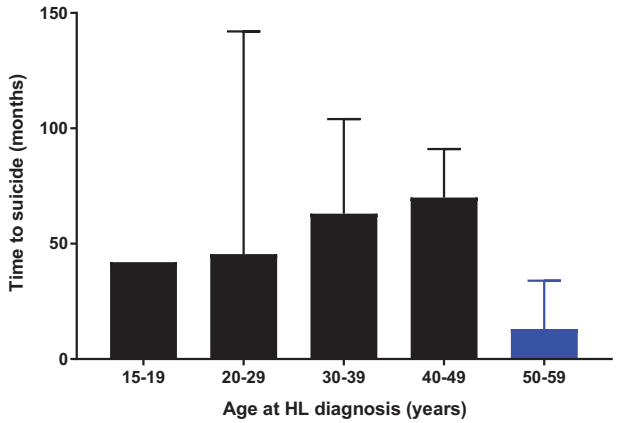

Figure 3. **Median time to suicide stratified by age at time of HL diagnosis, including 95% confidence intervals**.

Table 2

Standardized mortality ratio (SMR) stratified by age and sex in German Hodgkin Study Group (GHSG) cohort

	Overall (male and female)				Male patients				Female Patients			
Age (years)	Observed No. of Suicides	Expected No. of Suicides	SMR	95% CI	Observed No. of Suicides	Expected No. of Suicides	SMR	95% CI	Observed No. of Suicides	Expected No. of Suicides	SMR	95% CI
20–29	4	1.77	2.26	0.72–5.45	4	1.40	2.86	0.91–6.89	0	0.33	0	N/A
30–39	1	2.91	0.34	0.02–1.70	1	2.54	0.39	0.02–1.94	0	0.51	0	N/A
40–49	7	3.22	2.17	0.95–4.30	7	3.01	2.33	1.02–4.60	0	0.55	0	N/A
50–59	7	2.20	3.18	1.39–6.29	5	2.10	2.38	0.87–5.28	2	0.39	5.13	0.86–16.94
Total	19	11.67	1.63	1.01–2.50	17	10.45	1.63	0.98–2.55	2	2.11	0.95	0.16–3.13

reported in a Swedish population study that the relative risk (RR) of suicide in the first 3 months after a cancer diagnosis was 4.8 (95% CI: 4.0–5.8) and 3.1 (95% CI: 2.7–3.5) in the first year after a cancer diagnosis. Kwak et al reported the highest levels of distress in adolescent and young adult survivors of cancer to be at time of diagnosis and at 12 months, considered to be the time of transition to survivorship.[20]

To our knowledge, this is the first study looking specifically at Hodgkin Lymphoma patients and the risk of suicide. Our study analyzed HL clinical trial patients, and thus we were able to evaluate the effects of demographic, disease, treatment, and treatment complication information on the risk of suicide in HL patients. The suicides were distributed nearly exactly among the different study generations as the total cohort of HL patients (Table 1). Thus, the suicide rates in the different trial generations were very similar and stable over time. Stable suicide rates were also seen over time in the SEER validation cohort. The major strength of our study is the large cohort of over 12,000 European HL patients with long term median follow-up of over 7 years and nearly 95,000 person-years of observation time. Due to the long follow-up and observation time, the frequency of deaths from suicide was reliably able to be compared to other more well-established and well-studied causes of death in HL patients.

The limitations to our study include the retrospective design and the clinical trial data focusing on HL-specific outcome measures that did not allow for the investigation of relevant comorbidities such as depression and other psychiatric illnesses such as alcohol or drug-related disorders. Aside from age and gender, demographic information such as marital status, race, and employment status, all relevant risk factors for suicide, were not available. Suicides were recorded only if the patient's treating physician in charge of follow up reported suicide as the cause of death, so there is the possibility of an underestimation of deaths due to suicide but unlikely to be an overestimation. These results are limited to European HL patients ages 16 to 75 at time of first HL diagnosis and would need to be validated and reproduced in other parts of the world.

In conclusion, our study shows an increased risk of suicide in European HL patients compared to the general European population. The only risk factor associated with an increased risk of suicide in European HL patients was male sex that conferred a greater than 8 times the risk of suicide. These findings were confirmed in an independent validated SEER dataset. Of note, the only death reported in the recent CALGB 50604 trials of risk-adapted treatment of nonbulky early-stage HL was by suicide in an interim PET positive patient.[21] Further studies of social risk factors are needed in addition to the disease, treatment, and treatment complication factors analyzed here to obtain a better understanding of suicide in HL patients. In the meantime, an understanding by clinicians that male HL patients have a significantly higher risk of suicide compared to the general population may allow these patients to obtain earlier and increased access to emotional and social support systems. This understanding, considering the high-risk window of 12 months from diagnosis, may also help to inform that the optimal timing to assess for depression and suicidality may be during and immediately after the end of treatment.

Materials and methods

This study was approved by the University of Massachusetts Medical School institutional review board (Certificate of Exemption No. H00011362) and included 12,202 patients between the ages of 16 to 75 enrolled in the German Hodgkin

Table 3

Univariate analyses of characteristics associated with suicide in HL patients

Characteristic	Frequency among suicide cases, *N*=19 (*N* (%))	Frequency among controls, *N*=57 (*N* (%))	OR	95% CI	p
Sex (Male vs Female)	17 (89%)	34 (60%)	9.37	1.12–75.20	0.04
B symptoms	5 (26%)	21 (37%)	0.47	0.11–2.01	0.31
Elevated ESR	8 (42%)	22 (39%)	1.20	0.36–3.99	0.76
Large Mediastinal Mass	1 (5%)	9 (16%)	0.32	0.04–2.58	0.28
≥ 3 Nodal Areas	9 (47%)	31 (54%)	0.65	0.19–2.30	0.51
Stage IV vs Stage I-III	5 (26%)	8 (14%)	4.38	0.50–38.04	0.18
Radiation Therapy	12 (63%)	39 (68%)	0.39	0.04–4.39	0.45
BEACOPP vs ABVD Chemotherapy	7 (37%)	28/56 (50%)*	0.63	0.22–1.84	0.40
Secondary Malignancy	1 (5%)	2 (4%)	1.35	0.18–10.10	0.77
Relapsed Disease	2 (11%)	8 (14%)	0.78	0.18–3.36	0.74

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine, BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, ESR = erythrocyte sedimentation rate.
* 1 control from HD7 arm A (received RT only) excluded in this analysis.

Study Group (GHSG) HD7 through HD15 studies. The GHSG HD7-HD15 studies accrued patients from Germany, Switzerland, the Netherlands, the Czech Republic, and Austria between 1993 and 2009 and were analyzed to identify those patients with Hodgkin Lymphoma whose cause of death was suicide. All causes of death in the HD7-HD15 studies were reported to the GHSG by the patients' treating physician. Death by suicide was documented when the treating physician reported suicide as the cause of death. The present study includes the final analyses of all 9 trials and the 10 and 15-year follow-up analyses of the GHSG HD7-HD12 studies. We restricted the single-patient analysis to include only suicides and survival data published in manuscript or abstract form.[2–14] All 9 GHSG HD7-HD15 trials were approved by respective local institutional review boards. Our validation cohort included all SEER patients with available survival data diagnosed with HL between 1973 and 2013 (n = 52,115).[15] This registry does not contain the same in-depth clinical information as the GHSG data, but does contain age, date of diagnosis, stage, survival data, and cause of death.

Cohort analysis

Primary endpoints of this analysis were the crude death rate and SMR of death from suicide. SMR was obtained by calculating the ratio of observed number of suicides in the GHSG HL cohort to the expected number of suicides in the general European standardized population for 2014 taken from the statistical office of the European Union, Eurostat.[16] Eurostat includes data from 28 European countries (EU-28) to generate overall and sex-specific mortality rates for all causes of death. Eurostat cause of death data is derived from death certificates from all member states that are coded based on ICD10 (International Statistical Classification of Diseases and Related Health Problems). ICD10 codes X60-X84 were included in the analysis for suicide (intentional self-harm). To account for the age distribution of the GHSG HL cohort, the sum of the observed person-years within each age group (ages 15–19, 20–24, 25–29 . . . ., ≥85) was used to calculate the expected number of suicides within each age group, referencing the 2014 EU-28 crude suicide rates of each age group. The SEER validation data was analyzed in the same manner; however, the U.S. population was the reference for which age- and sex-specific suicide data was obtained from the Center for Disease Control and Prevention (CDC).[17]

Variables

Variables extracted from the GHSG HD7-HD15 trials included sex and age at time of diagnosis and suicide, B symptoms, elevated ESR, bulky mediastinal disease, ≥ 3 nodal areas, relapsed disease, stage, radiation therapy, ABVD or BEACOPP-based chemotherapy, and development of secondary malignancies.

Case-control and statistical analyses

For each case of suicide, 3 controls matched for exact age were selected from the same GHSG trial. Thus, the 5-year time range at enrollment (1993–1998, 1998–2003, or 2003–2008) and GHSG HL risk stratification group (early stage favorable, early stage unfavorable, and advanced stage) were also matched. Case-control approach was used to identify the variables above associated with risk of death by suicide. The SEER validation data was similarly analyzed, though only 1 control for each case of suicide was matched for exact age and year of diagnosis, as 3 controls were not available for all cases.

Univariate and multivariate conditional logistic regression analyses were performed to generate odds ratios (OR) and their 95% confidence intervals (CI) for each of the variables listed to identify factors associated with an increased risk of death by suicide. Male sex, the presence of large mediastinal mass, and stage (stage IV vs stage I-III) were selected for a multivariate analysis as they were the variables in the univariate analyses with OR furthest from 1. Other variables in the univariate analyses were omitted from the multivariate analyses as there were not enough cases of suicide to support their inclusion. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC). All p values are 2-sided with type I error rate fixed at 0.05.

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