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**Short and long-term mental and functional disorders in young adult Hodgkin lymphoma survivors**

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**Running heads:** Mental & Functional disorders in HL Survivors

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**Data-sharing statement:** Data were retrieved from the longitudinal database of Maccabi Healthcare Services, the second largest integrated Health Maintenance Organization in Israel. The MHS ecosystem is organized into validated, thematic clinical registries, including pharmacy (drug), cardiovascular, endocrine (NIDDM), and mental health registries, which aggregate comprehensive, real-world patient data. For this study, patient-level variables were extracted and linked across these relevant registries to construct a dedicated, multi-dimensional dataset for the primary analysis.

**Trial registration:** This research has approval from Maccabi Healthcare Service' Institutional Review Board (IRB), MHS-0075-23. Title of research: Long-term effects and comorbidities among survivors of lymphoproliferative diseases

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## Abstract

Hodgkin lymphoma (HL) is a curable malignancy with excellent long-term survival, shifting the focus of care toward survivorship challenges, including mental and functional health. This population-based retrospective cohort study evaluated the incidence, timing, and risk factors for mental and functional disorders (including fibromyalgia, irritable bowel syndrome, insomnia and related conditions) among young adult HL survivors in Israel compared with age- and sex-matched controls. Data was retrieved from the electronic medical database of Maccabi Healthcare Services, encompassing 1007 young (18-50 years) HL patients, diagnosed between 1995 and 2021, and 20140 controls, with a median follow-up of 12 years.

Prior to HL diagnosis, mental or functional disorders were more prevalent among patients than controls (15.3% vs. 10.2%, $p<0.001$). Among HL survivors, 53% developed new-onset mental or functional complications during follow-up, compared with 33% of controls ($p<0.001$). Early-onset disorders (within 6 months of diagnosis) occurred 12-fold more frequently in HL survivors, most commonly anxiety, depression, opioid use, and fibromyalgia. Late-onset disorders (>6 months) were also significantly higher in HL survivors.

Multivariate analyses identified Jewish ethnicity (HR=2.24; 95% CI, 1.06 - 4.77; $p=0.036$) and cardiovascular comorbidity (HR=7; 95% CI, 1.67 - 29.6; $p=0.008$) as independent risk factors for developing mental and/or functional disorder. These findings, in a relatively large cohort, highlight a substantial and sustained risk of mental and functional health complications among HL survivors and underscore the need for systematic psychosocial screening and tailored interventions within survivorship programs to optimize long-term well-being**.**

## Introduction

Hodgkin lymphoma (HL) is a curable malignancy, with excellent long-term survival rates. Advances in risk stratification, chemotherapy regimens, radiation techniques and targeted treatments have significantly improved outcomes, making long-term survivorship a central focus in HL patient care. As survivorship rates increase, attention has turned toward long-term effects of therapy, including psychosocial sequelae, which can affect long-term quality of life and well-being.

Survivors of HL are at increased risk for various mental health challenges. Studies report that up to 30% of HL survivors experience psychological distress[1,2], which may include anxiety, depression, and post-traumatic stress disorder (PTSD)[3,4]. These may emerge during or post-treatment.

Mental health complications have a profound impact on the overall quality of life for HL survivors[2,5]. Moreover, these individuals seem to be at increased risk for financial difficulties and social challenges[6]. Depression and anxiety are associated with decreased adherence to follow-up care[7], which may impair early detection of relapses or secondary malignancies. Furthermore, growing evidence suggest that psychological stress may influence immune function[8], thus, theoretically, affecting long-term survival.

Several risk factors predispose HL survivors to mental health complications, including gender, higher intensity of treatment (e.g. combined chemotherapy and radiotherapy), prior history of mental illness and low education level[9].

Survivorship programs for HL patients, including routine screening for mental health issues, using validated tools like the Hospital Anxiety and Depression Scale (HADS) or Patient Health Questionnaire (PHQ-9), are highly recommended[7,10], but, unfortunately, rarely performed on routine basis. Psychological interventions, including cognitive behavioral therapy (CBT) and mindfulness-based approaches have shown efficacy in alleviating anxiety and depression in cancer survivors[11]. These findings underscore the importance of recognizing and addressing both the short- and long-term psychological complications faced by HL survivors.

Fibromyalgia, irritable bowel syndrome (IBS), insomnia, conversion disorder, somatization, and unexplained persistent pain, are often referred to as Functional Somatic Syndrome. As they share common underlying pathophysiologies, including central sensitization, stress-system loop (Hypothalamus-Pituitary-Adrenal axis) dysregulation, accompanied by somatic amplification and hypervigilance[12,13] - they were grouped here under the term "functional disorders".

In the current study, we evaluated the incidence of short and long-term mental/functional disorders in a large ethnically and socioeconomically heterogeneous population of young Israeli HL survivors, as compared with age and sex matched controls. We assessed the timing of mental/functional disorder onset in relation to HL diagnosis, and identified specific risk factors for these complications.

## Methods

### Data source

This retrospective, observational cohort study utilized anonymized longitudinal electronic medical record data from Maccabi Healthcare Services (MHS), a nationwide

health provider covering approximately 25% of the Israeli population (2.8 million individuals). The MHS database provides extensive longitudinal data on a stable population, including medical conditions such as body mass index (BMI), smoking status, and various comorbidities (cardiovascular diseases, diabetes, hypertension, and malignancies), alongside a comprehensive pharmaceutical registry for prescriptions and purchases. The study was approved by the institutional and MHS ethics committees (MHS-0075-23).

**Study design and population**

The study cohort included all consecutive patients diagnosed with HL between ages 18–50, from January 1995 to November 2021. Inclusion required at least 12 months of continuous MHS registration both before and after the index date (diagnosis), alongside documented medication purchase records. To isolate the clinical impact of HL, patients with prior or concomitant malignancies (excluding non-melanoma skin cancer) were excluded. Healthy controls were matched by sex and birth year using propensity score (PS) nearest neighbor matching. While an initial matching ratio of 1:25 was employed, this was subsequently refined to a 1:20 ratio following the application of identical exclusion criteria to the control group. Standardized mean differences were utilized to verify the balance of covariates between the matched groups. Mental/functional disorders were documented across three distinct phases—prior to diagnosis, during therapy, and throughout follow-up. We distinguished between "early onset" disorders, occurring within 6 months from diagnosis of HL, and "late onset" disorders, identified beyond 6 months from diagnosis. The 6-month threshold for distinguishing "early" and "late" onset mental/functional disorders was selected to correspond with the standard duration of primary systemic frontline therapy. As these regimens often span up to 6 months, this cutoff effectively differentiates between disorders emerging during active exposure to frontline cytostatic treatment, and those developing as late-onset survivorship sequelae.

**Disorder Definitions**

Mental disorders included anxiety, depression, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), PTSD, obsessive-compulsive disorder (OCD) and substance/opioid abuse. Functional disorders included fibromyalgia, IBS, insomnia, conversion and somatization, and unexplained persistent pain. The diagnoses composing "functional disorders" were analyzed as a unified composite endpoint due to their shared pathophysiology and to maintain adequate statistical power (given the relative rarity of individual chronic somatic events in this young survivor population). Yet, their individual frequencies were separately analyzed as well.

Mental/functional disorders were identified based on ICD-9 codes accompanied by purchasing of relevant medications (detailed below). In part of the patients with mental disorders, diagnosis was based on **continuous** purchasing of these medications without an official documentation of mental diagnosis in the medical records. This required reported purchasing of relevant medications for at least 3 months. For patients defined with "early onset" mental disorders, inclusion based on "continuous purchasing of relevant medications" required purchasing of the relevant drugs, starting during therapy (months 0-6) and lasting for at least 3 additional months beyond the 6-month period.

Conversely, functional disorders were identified based solely on ICD-9 diagnostic codes.

Specifically, relevant medications identifying anxiety and depression were selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, or benzodiazepines; ADD/ADHD- by amphetamine salts and opioid use by consumption records. Insomnia was identified through sleep aids, including benzodiazepines, non-benzodiazepine hypnotics, melatonin receptor agonists, and orexin receptor antagonists.

### Variables and Statistical Analysis

Baseline characteristics included socioeconomic status (Israel Central Bureau of Statistics index), BMI, and comorbidities such as hypertension, cardiovascular disease (ischemic heart disease, valvular disorders, congestive heart failure), and diabetes. Mental and functional conditions were tracked before diagnosis, during treatment, and throughout the follow-up period.

Statistical analyses employed descriptive statistics (medians with IQRs for continuous variables; proportions for categorical). Cumulative incidence was estimated using the Kaplan-Meier method, and univariate/multivariate Cox proportional hazards regression models calculated hazard ratios (HRs) comparing HL survivors to controls. Comparative tests included Pearson's Chi-squared, Fisher's exact, and Wilcoxon rank sum tests as appropriate. For each time-to-event of specific disorder onset, the proportional-hazards assumption was tested using scaled Schoenfeld residuals FDR correction was used to address multiple comparisons. All tests were two-tailed (alpha = 0.05). Analyses were conducted using R version 4.5.2 and R Studio version 2024.03.0.

## Results

### Cohort characteristics at index day

One thousand and seven newly diagnosed HL patients were recorded in MHS database during the study period. Twenty thousand one hundred and forty individuals with no prior history of HL, matched by age, sex and index year, served as controls. The median follow-up period was 144 months (range 13-287) for HL patients and 145 months (range 12-288) for the control cohort.

The median age at index day, of both HL and control patients, was 26 years (range: 18-≤50 years for both groups). There were no statistically significant differences between the HL patients and their matched control counterparts in terms of socioeconomic status (high vs. standard or low), ethnicity and BMI on index day.

There was a higher percentage of past or current smokers ($p<0.001$), cardiovascular disorders ($p<0.001$) and hypertension ($p=0.002$) among HL patients, prior to diagnosis, compared to their matched controls (**Table 1**).

### Incidence of mental/ functional disorders prior to diagnosis of HL

One hundred and fifty-five of 1007 HL patients were diagnosed with mental/ functional disorder prior to being diagnosed with HL (15.3%), compared to 2055 of 20140 (10.2%) in the control cohort ($p<0.001$). Specifically, prior to the index day, anxiety and depression [7.2% (N=73) vs. 4.8% (N=974), $p<0.001$], fibromyalgia [3.8% N=38) vs. 2.2% (N=441), $p<0.001$], ADD and ADHD (7% (N=70) vs. 4.8% (N=976), $p=0.003$], chronic pain syndrome [1.3% (N=13) vs. 0.5% (N=91), $p=0.001$] and opioid

use [2.3% (N=23) vs. 1.2% (N=242), p=0.003] were more frequent among HL patients compared to the control cohort, respectively.

In terms of age and sex, there were no significant differences in the characteristics of HL patients with mental/functional disorders diagnosed prior to the diagnosis of HL and their matched controls. However, HL patients had higher rates of prior cardiovascular diseases compared to their matched controls [7.1% (N=11/155) vs. 1.7% (N=35/2055), respectively, p<0.001].

**Incidence of new onset mental/ functional disorders post-diagnosis of HL**

Among 852 patients with no previous history of mental/functional disorders, 53.2% (453/852) were diagnosed with new onset mental/functional disorders since the index day and during the follow-up period, compared to 33% (5978/18,085) in the control group (p<0.001).

Of these, newly diagnosed mental disorders were recorded in 40.9% (349/852) of HL patients, compared with 26.4% (4788/18,085) in the control group (p<0.0001), while newly diagnosed functional disorders were recorded in 25.3% (216/852) of HL patients compared with 16.8% (3045/18,085) among controls (p<0.0001).

A total of 111 HL patients (13%) experienced both mental and functional disorders, compared to 1855 in the control group (10.2%, p=0.01).

An official diagnosis in patient records was the first acknowledgment of a mental/functional disorder in 12% of HL patients with newly diagnosed conditions. In the remaining HL patients with new onset mental/functional disorders, prescription and consumption of relevant medications were recorded prior to an official documentation of these disorders in the patient's medical record or that such a diagnosis was not officially documented at all.

As mental disorders were diagnosed based on documented ICD-9 diagnosis or prescription and consumption of relevant medications ("functional disorders" diagnosis was restricted to documented ICD-9 diagnosis), we performed a subgroup analysis, comparing the incidence of mental disorders between HL patients and controls, restricted to cases identified via documented ICD-9 diagnoses. This analysis as well demonstrated increased incidence of mental disorders within the HL cohort, across various diagnostic subtypes.

**Incidence and characteristics of early-onset mental/functional disorders (within the first 6 months post diagnosis of HL)**

The incidence of new, early onset mental/functional disorder, occurring within 6 months from the index day, was 12.5 times higher in the HL cohort compared with the control cohort (13.7% vs. 1.1%, p<0.001) (**Figure 1 and Table 2** present the incidence of the various types of mental/functional disorders reported within the first 6 months from the index day).

Anxiety and depression were the most common mental/functional disorders reported in HL patients within the first 6 months, documented in 8.4% (vs. 0.5% in the control group, p<0.001), followed by opioid use, fibromyalgia and insomnia, all more frequent among HL patients (reported in 5.3% vs. 0.13%, p<0.001; 3.8% vs. 0.2%, p<0.001 and 0.8% vs. <0.1%, p<0.001, in HL patients compared to controls, respectively). Median time from diagnosis of HL to the emergence of early onset mental/functional complications was 2 months (range 1-6 months).

There were no significant differences in the characteristics of HL patients diagnosed with early onset mental/functional disorders and their matched controls, in terms of age, sex demographics and prior comorbidities.

**Incidence and characteristics of late-onset mental/functional disorders, diagnosed beyond the first 6 months post index day**

Out of 735 HL patients who were not diagnosed with mental/functional disorders at an earlier time point, 337 (46%) were diagnosed with late onset mental/ functional disorders, first recorded >6 months from index day, compared to 5779 of 17886 (32%) subjects in the control cohort ($p<0.001$).

The most common late onset mental/functional disorders documented in this group of HL survivors were anxiety and depression, with an incidence of 31.4% compared to 20.5% in the control group ($p<0.001$). Late onset fibromyalgia, pain syndromes, ADD and ADHD, opioid use, and insomnia were all significantly more common in HL patients, compared with their control counterparts (**Figure 2, Table 3**).

Interestingly, the highest risk of developing late onset mental/functional disorders occurred in the 12-18 months post-diagnosis period (HR-1.93; 95%CI, 0.86-4.3). The risk decreased over time but remained significantly elevated, compared to the control group, throughout the follow-up period [HR- 1.62 and 1.41 at 18-24 and 24-30 months post diagnosis, respectively (data presented in **Table 1s, Supplementary file**)].

**Risk factors for developing mental/functional disorders in HL survivors**

Univariate analysis showed that smoking (compared to patients who never smoked), cardiovascular disease and modern orthodox Jewish affiliation were all associated with increased risk for developing mental/functional disorders among patients treated for HL (see **Table 2s, supplementary file**). As smoking may simultaneously predispose to pre-diagnostic functional disorders, cardiovascular complications, and HL per se[14,15], it represents a profound confounding element that limits our capacity to isolate independent causal paths.

Multivariate analysis identified Jewish ethnicity as a risk factor to develop mental/functional disorders among HL patients (HR=2.24; 95%CI, 1.06-4.77; p=0.036), with orthodox Jew patients at the highest risk among the various Israeli demographic groups (HR=4.42; 95% CI, 1.63-12; p=0.004), as well as cardiovascular disease (HR=7; 95% CI, 1.67-29.6; p=0.008, **Table 4**).

When risk factors for developing either mental or functional disorders were separately analyzed, univariate analysis found that patients of low socioeconomic status (HR=1.24; 95% CI, 1.00-1.54; p=0.047), modern orthodox Jewish affiliation (HR=3.18; 95%CI, 1.30-7.76; p=0.011), immigrants from former Soviet Union (HR=2.17; 95%CI, 1.11-4.27; p=0.024) and patients with cardiovascular diseases (HR=3.32; 95% CI, 1.76-6.27; p<0.001) were all at increased risk to develop mental disorders, while cardiovascular disease (HR=3.14; 95% CI, 1.28-7.71; p=0.012) and diabetes (HR=3.63; 95% CI, 1.49-8.86; p=0.005) were associated with increased risk to develop functional disorders.

Multivariate analysis demonstrated that patients of low socioeconomic status (HR=1.72; 95% CI 1.03 - 2.86; p=0.039), those of Jewish ethnicity—particularly orthodox Jews (HR=6.23; 95% CI 1.89-20.6; p=0.003) and patients with cardiovascular disease (HR=10.4; 95% CI 2.06-51.5; p=0.004) were at increased risk to develop mental disorders, while only modern orthodox Jewish affiliation was associated with

an increased risk to develop functional disorders among HL survivors (HR=5.68; 95% CI 0.95-33.9; p=0.057).

## Discussion

This study demonstrates the frequent occurrence of both early and late mental/functional disorders among young HL survivors, in a large heterogeneous Israeli cohort, thus contributing to further understanding the substantial long-term implications of HL and its treatments in this population.

Previous studies have shown that lymphoma survivors, specifically HL survivors, experience higher rates of mental and functional disorders, particularly anxiety, depression and cognitive impairments, compared to normative controls[1,9,16]. We found that a substantial percentage (53.2%) of young HL patients with no previous history of mental/functional disorders were identified with mental/functional disorders in the period from the diagnosis of HL and during follow-up. These high rates along with wide use of psychotropic drugs among HL patients, coincide with previous reports indicating that the prevalence of anxiety and depression among HL survivors reach 24% and 18%, respectively[9], and that a large proportion of HL patients are prescribed with anti-depressant (16.3%) and anxiolytic (23.9%) medications[1].

We recorded the incidence of mental/functional disorders at different time points, in an attempt to pinpoint their emergence, relatively to the diagnosis and treatment of HL. Interestingly, anxiety and depression, fibromyalgia, chronic pain syndrome, ADHD and opioid use were all more frequent among HL patients prior to the diagnosis of HL, compared to their matched controls. This is in agreement with previous data where higher cumulative incidence of psychotropic drug usage was already detected 2 years prior to the index day among HL patients, compared to the background population[1], as were impaired cognitive functions [17]. However, paraneoplastic and constitutional symptoms can precede a formal HL diagnosis, causing significant secondary psychological distress, which may contribute to the higher baseline incidence observed in our HL cohort. Regrettably, we cannot extract the exact *date of symptom onset* or the precise chronological initiation for these baseline mental/functional disorders.

After excluding patients diagnosed with mental/functional problems prior to diagnosis of lymphoma, HL survivors were still at higher risk to develop both early and late onset mental/functional complications, compared to their matched counterparts. **Early-onset** mental/functional disorders, diagnosed within the first six months post-diagnosis of HL, were about 12.5-fold more frequent in HL patients, compared to the controls, emphasizing the emotional and psychological challenges faced by these patients.

Approximately 46% of HL survivors experienced **late onset** mental/functional health complications. Previous studies reported high rates of mental disorders among HL survivors, with even higher rates reported at 7-10 years compared to those reported at 3-4 years from diagnosis[9,18], thus underscoring the need for continuous psychological monitoring and support in HL survivors.

Previous studies showed that younger age, lower socioeconomic status and lower education are associated with higher incidence of mental complications among HL patients[1,9]. Risk factors for developing mental/functional complications identified in our study included low socioeconomic status, ethnicity (Jewish, in particular orthodox Jewish affiliation), and prior cardiovascular disease. However, wide confidence

intervals in certain subgroup analyses, likely reflecting small event counts, suggest that these hazards ratios should be interpreted with caution.

We also found that in most cases, patients were prescribed or consumed medications relevant to mental/functional disorders prior to an official documentation of such disorders in their medical records. Considering that our study population was composed of young patients, this, perhaps, rises from patients' preference to avoid an official diagnosis of mental disorder, or from their difficulties in addressing mental issues, at young age. This is supported by a large Japanese study, where a substantial proportion of cancer patients reported of "barriers to emotional disclosure" when consulting with their physicians (including negative attitude, fear of negative impact)[19].

Thus, by integrating routine mental health screenings, normalizing using validated tools such as the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire (PHQ-9) in survivorship programs, we can help reduce stigma[7,20] and ensure that patients receive the necessary care.

Current modern regimens, incorporating brentuximab vedotin (BV) and checkpoint inhibitors (CPIs) into 1$^{st}$ line regimens, reduced the risk of primary treatment failure. BrECADD regimen has a shorter treatment timeline, which may protect long-term mental health, yet, BV is associated with high rates of peripheral neuropathy. CPIs may inflict immune related adverse events, including lifelong, manageable endocrine autoimmunity. Hence, the net effect of modern regimens on the incidence of mental/functional disorders is yet to be determined.

Our study has some limitations. First, the retrospective nature of our analysis relies on the accuracy and completeness of the electronic medical records, which may be biased due to documentation practices. Moreover, the MHS records do not contain data regarding specific treatment regimens, therefore, the effects of different regimens, modalities and treatment intensity on mental issues could not be reliably evaluated.

Additionally, in part of our patients the diagnosis of mental disorders was based on continuous purchasing of relevant medications. Reliance on medication prescriptions as a proxy for mental/functional health diagnoses, though established in large-scale cancer survivorship registries [1], may introduce a risk of misclassification. This risk was mitigated by using a strict 90-day persistent consumption threshold, with longer consumption period required during the early period of treatment. We also acknowledge the inherent challenge in definitively distinguishing true mental/functional disorders from acute treatment-related toxicities, especially in the "early onset" setting. While our methodology sought to minimize over-reporting by requiring both an official ICD-9 medical diagnosis and documented medication consumption in all patients with functional- and most patients with mental disorders, direct side effects of treatment, appearing within the first 6 months, may still be misinterpreted as chronic disorders.

Furthermore, since HL survivors undergo intensive surveillance during the early post-treatment years, the higher frequency of healthcare interactions naturally increases the detection and documentation of mental/functional complaints, thus, may partially account for the elevated early-onset rates.

In conclusion, our findings advocate for the integration of comprehensive psychosocial care in the management of HL. By addressing mental health concerns, as part of routine oncology care, we can improve both quality of life and health outcomes for HL

survivors. Further research is necessary to explore effective interventions that can mitigate the risks of mental/functional health complications.

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**Table 1**: **Characteristics of Hodgkin lymphoma patients and controls**

| | **HL patients** (N = 1,007) | **Control** (N = 20,140) | **p-value** | **q-value (FDR)** |
|---|---|---|---|---|
| Age ,years Median (range) | 26 (18 - 50) | 26 (18 - 50) | 0.6 | >0.9 |
| Sex , Male | 452 (45%) | 9,040 (45%) | >0.9 | >0.9 |
| **Socio Economic Status** | | | 0.6 | >0.9 |
| High | 528 (53%) | 10,682 (54%) | | |
| Standard-Low | 459 (47%) | 9,013 (46%) | | |
| **Demographic Sector** | | | 0.9 | >0.9 |
| Arabic | 71 (7.1%) | 1,362 (6.8%) | | |
| Former Soviet Union | 42 (4.2%) | 979 (4.9%) | | |
| Jewish | 769 (76%) | 15,230 (76%) | | |
| Jewish, modern orthodox | 40 (4.0%) | 783 (3.9%) | | |
| Jewish, orthodox | 85 (8.4%) | 1,786 (8.9%) | | |
| Past/present smoker ** | 24/159 (18.2%) | 327/2502 (14%) | <0.001 | 0.005 |
| BMI (median) | 23.3 | 23.1 | 0.6 | >0.9 |
| Cardiovascular disease | 30 (3.0%) | 181 (0.9%) | <0.001 | <0.001 |
| NIDDM | 11 (1.1%) | 215 (1.1%) | >0.9 | >0.9 |
| Hypertension | 32 (3.2%) | 362 (1.8%) | 0.002 | 0.007 |
| Follow-up period, (months) Median (range) | 144 (13 - 287) | 145 (12 - 288) | 0.7 | >0.9 |

*Patients with prior mental or functional disorders were excluded

****** Percentage shows total smokers

BMI – body mass index; NIDDM- non-insulin dependent diabetes mellitus

**Table 2: Early onset of mental and functional disorders (within 0-6m from index day)***

| | **HL patients** N = *852 | **Control** N = *18,085 | **p-value** | **q-value (FDR)** |
|---|---|---|---|---|
| Months to Diagnosis, Median (range) | 2.00 (1.0-6.0) | 4.00 (1.0-6.0) | <0.001 | 0.002 |
| Any Functional/Mental Diagnosis | 117 (13.7%) | 199 (1.1%) | <0.001 | <0.001 |
| Mental Diagnosis | 73 (8.6%) | 158 (0.9%) | <0.001 | <0.001 |
| Functional Diagnosis | 37 (4.3%) | 58 (0.3%) | <0.001 | <0.001 |
| ADD and ADHD | 1 (0.1%) | 62 (0.3%) | 0.5 | 0.65 |
| Insomnia | 7 (0.8%) | 12 (<0.1%) | <0.001 | <0.001 |
| Anxiety and Depression | 72 (8.4%) | 91 (0.5%) | <0.001 | <0.001 |
| Opioid Use | 46 (5.3%) | 24 (0.13%) | <0.001 | <0.001 |
| Substance Abuse | 0 (0%) | 2 (<0.1%) | >0.9 | >0.9 |
| PTSD | 0 (0%) | 6 (<0.1%) | 0.6 | 0.71 |
| Conversion and Somatization Disorders | 0 (0%) | 1 (<0.1%) | >0.9 | >0.9 |
| Pain Syndromes | 2 (0.2%) | 14 (<0.1%) | 0.2 | 0.29 |
| Fibromyalgia | 32 (3.8%) | 42 (0.2%) | <0.001 | <0.001 |
| # Fatigue Syndromes | 0 | 0 | - | |
| # IBS | 0 | 0 | - | |

*Excluding patients with prior Mental/Functional disorders

# Not reported during this period

ADD- attention-deficit disorder; ADHD- attention-deficit/hyperactivity disorder; PTSD- post traumatic stress disorder

**Table 3: Late onset mental and functional disorders (beyond 6m from index day)***

| Characteristic | HL patients N = *735 | Control N = *17886 | p-value | q-value (FDR) |
|---|---|---|---|---|
| Months to Diagnosis, Median (range) | 78 (7 - 280) | 93 (7 - 291) | <0.001 | 0.002 |
| Functional or Mental Disorder | 337 (46%) | 5,779 (32%) | <0.001 | <0.001 |
| Mental Disorder | 276 (37.5%) | 4,630 (26%) | <0.001 | <0.001 |
| Functional Diagnosis | 179 (24%) | 2,987 (17%) | <0.001 | <0.001 |
| ADD and ADHD | 87 (12%) | 1,475 (8.1%) | 0.033 | 0.055 |
| Insomnia | 53 (7.2%) | 980 (5.4%) | 0.044 | 0.066 |
| Anxiety and Depression | 231 (31.4%) | 3,669 (20.5%) | <0.001 | <0.001 |
| PTSD | 11 (1.5%) | 254 (1.4%) | 0.86 | >0.9 |
| Substance Abuse | 1 (0.1%) | 72 (0.4%) | 0.3 | 0.38 |
| Opioid Use Diagnosis | 87 (11.8%) | 1,283 (7.17%) | <0.001 | <0.001 |
| Conversion and Somatization Disorders | 2 (0.3%) | 28 (0.15%) | 0.4 | 0.46 |
| Pain Syndromes | 48 (6.5%) | 787 (4.4%) | 0.0063 | 0.012 |
| Fibromyalgia | 155 (21%) | 2,219 (12.4%) | <0.001 | <0.001 |
| Fatigue Syndromes | 2 (0.3%) | 23 (0.1%) | 0.3 | 0.38 |
| IBS | 0 (0%) | 7 (<0.1%) | >0.9 | >0.9 |

*Excluding patients with prior Mental/Functional disorders

ADD - attention-deficit disorder; ADHD - attention-deficit/hyperactivity disorder; IBS - irritable bowel syndrome; PTSD - post-traumatic stress disorder

**Table 4: Multivariate analysis for factors associated with increased risk to develop mental or functional disorder**

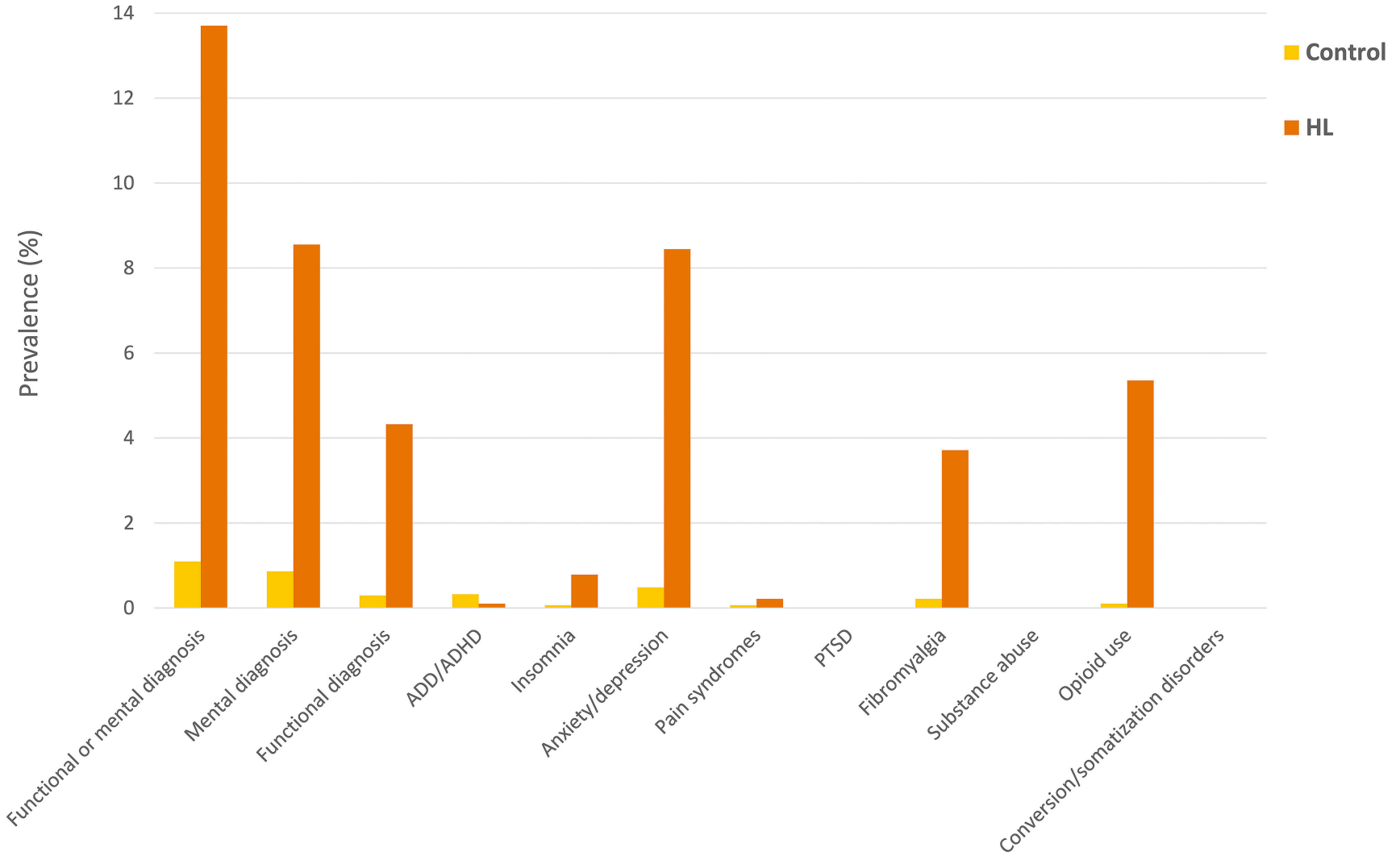
| Characteristic | HR | 95% CI | p-value | q-value (FDR) |
|---|---|---|---|---|
| Sex, Female (vs. male) | 1.43 | 0.91 - 2.24 | 0.12 | 0.34 |
| Socio-economic, Standard-Low (vs. high) | 1.21 | 0.77 - 1.91 | 0.4 | 0.62 |
| **Demographic sector** | | | | |
| Arabic | — | — | | |
| Former soviet union immigrant | 1.32 | 0.24 - 7.37 | 0.8 | 0.86 |
| Jewish | 2.24 | 1.06 - 4.77 | 0.036 | 0.17 |
| Modern orthodox Jewish | 3.62 | 1.00 - 13.1 | 0.049 | 0.17 |
| Orthodox Jewish | 4.42 | 1.63 - 12.0 | 0.004 | 0.056 |
| Smoking, Never smoked (vs. current/previous) | 1.37 | 0.57 - 3.33 | 0.5 | 0.70 |
| **BMI** | | | | |
| ≤18.4 | — | — | | |
| 18.5-24.9 | 1.34 | 0.78 - 2.31 | 0.3 | 0.60 |
| 25-29.9 | 0.70 | 0.07 - 7.30 | 0.8 | 0.86 |
| 30-34.9 | 0.88 | 0.40 - 1.90 | 0.7 | 0.86 |
| ≥35 | 3.07 | 0.57 - 16.6 | 0.2 | 0.47 |
| Cardiovascular disease, Yes (vs. No) | 7.0 | 1.67 - 29.6 | 0.008 | 0.056 |
| Diabetes, Yes (vs. No) | 0.84 | 0.09 - 7.44 | 0.9 | 0.90 |
| Hypertension, Yes (vs. No) | 0.61 | 0.18 - 2.04 | 0.4 | 0.62 |

BMI – body mass index

## Figure legends:

**Figure 1. Early (0–6 months) prevalence of mental and functional disorders in HL patients versus controls.**
Bar chart showing the proportion of individuals diagnosed with specific mental and functional disorders within the first 6 months following the index date (date of HL diagnosis for patients and assigned reference date for controls). Only individuals without prior mental/functional disorders were included in this analysis. HL – Hodgkin lymphoma; ADD – attention-deficit disorder; ADHD – attention-deficit/hyperactivity disorder; PTSD – post-traumatic stress disorder.

**Figure 2. Late (>6 months) prevalence of mental and functional disorders in HL patients versus controls.**
Bar chart showing the proportion of individuals diagnosed with specific mental and functional disorders more than 6 months after the index date, excluding patients with prior or early-onset diagnoses. HL survivors demonstrated a higher prevalence of most disorders compared with controls, with anxiety/depression, fibromyalgia, opioid use, and attention-related disorders being the most prominent. Higher prevalence compared to early-onset analysis reflects the longer follow-up period and cumulative incidence over time HL – Hodgkin lymphoma; ADD – attention-deficit disorder; ADHD – attention-deficit/hyperactivity disorder; PTSD – post-traumatic stress disorder; IBS - irritable bowel syndrome.


Prevalence (%)
14
12
10
8
6
4
2
0
Control
HL
Functional or mental diagnosis
Mental diagnosis
Functional diagnosis
ADD/ADHD
Insomnia
Anxiety/depression
Pain syndromes
PTSD
Fibromyalgia
Substance abuse
Opioid use
Conversion/somatization disorders

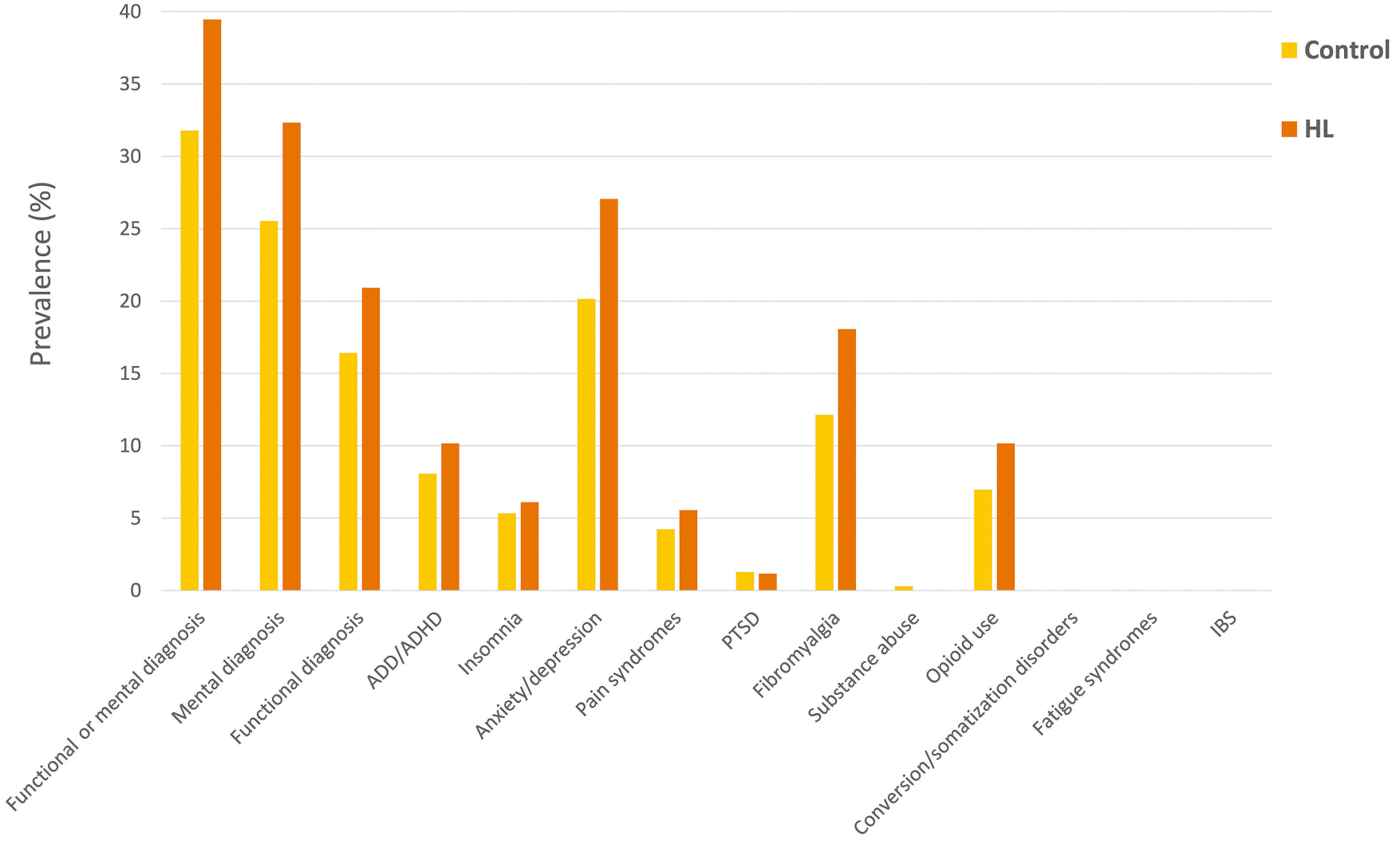

Prevalence (%)
40
35
30
25
20
15
10
5
0
Control
HL
Functional or mental diagnosis
Mental diagnosis
Functional diagnosis
ADD/ADHD
Insomnia
Anxiety/depression
Pain syndromes
PTSD
Fibromyalgia
Substance abuse
Opioid use
Conversion/somatization disorders
Fatigue syndromes
IBS

**Table 1s.** Period-specific risk for mental and function disorders*

| Period (months) | Hodgkin lymphoma survivors | | Matched controls | |
|---|---|---|---|---|
| | Risk, % (95% CI) | RR (95% CI) | Risk, % (95% CI) | RR (95% CI) |
| 0–6 | 0.97 (0.51–1.83) | 1.00 (reference) | 0.62 (0.52–0.75) | 1.00 (reference) |
| 6–12 | 0.98 (0.51–1.84) | 1.01 (0.40–2.53) | 0.56 (0.47–0.68) | 0.91 (0.70–1.17) |
| 12–18 | 1.86 (1.16–2.96) | 1.93 (0.86–4.30) | 0.58 (0.48–0.70) | 0.94 (0.72–1.21) |
| 18–24 | 1.56 (0.93–2.60) | 1.62 (0.70–3.72) | 0.58 (0.48–0.70) | 0.93 (0.72–1.21) |
| 24–30 | 1.36 (0.78–2.36) | 1.41 (0.60–3.32) | 0.57 (0.47–0.69) | 0.91 (0.70–1.18) |

*Relative risks with the 0–6 month period as the reference

**Table 2s.** Univariate analysis for factors associated with increased risk to develop mental or functional disorder

| | HR | 95% CI | p-value |
|---|---|---|---|
| Sex: F/M | 1.03 | 0.85 - 1.23 | 0.7 |
| Socioeconomic status: low | 1.19 | 0.98 - 1.44 | 0.079 |
| Demographic sector; Modern orthodox Jewish | 2.93 | 1.4 - 6.13 | 0.004 |
| Smoking: Never smoked | 0.5 | 0.25 - 1.01 | 0.05 |
| BMI >30-34.9 | 1.67 | 0.92 - 3. 03 | 0.094 |
| Cardiovascular | 2.64 | 1.4 - 4.98 | 0.003 |
| Diabetes | 1.63 | 0.67 - 3.95 | 0.3 |
| Hypertension | 1.44 | 0.83 - 2.51 | 0.2 |

BMI – body mass index