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ORIGINAL ARTICLE

Individual differences in physical symptom burden and psychological responses in individuals with chronic lymphocytic leukemia

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Abstract Chronic lymphocytic leukemia (CLL) is an incurable illness, with some patients requiring no treatment until disease progression. Burden from physical symptoms has been associated with depression, anxiety, and stress in cancer patients. Additionally, patient factors, i.e., individual differences, have been associated with worse psychological outcomes. There are few psychological studies of CLL, with no examination of individual differences. A cross-sectional design studied the covariation of symptom burden with depressive and anxiety symptoms and cancer-specific stress, and tested patients' individual differences as predictors and as moderators. CLL patients ($N = 112$) receiving active surveillance participated. They were Caucasian (100 %) and predominately male (55 %) with a mean age of 61; most (62.5 %) had stage 0 disease. A composite measure of physical symptom burden (CLL symptoms, fatigue, pain, impaired functional status) was tested as a predictor of psychological responses. Individual differences in psychiatric history and social support were tested as moderators. Using multiple linear regression, greater symptom burden covaried with higher levels of depressive and anxiety symptoms and cancer stress ($ps < .05$). Those with a psychiatric history, low social support, and low relationship satisfaction with one's partner reported greater symptom burden and more psychological symptoms and stress ($ps < .05$). Findings suggest that CLL patients in surveillance with a psychiatric history and/or low social support are at risk for greater distress when coping with high symptom burden. These new data clarify the experience of CLL surveillance and identify characteristics of patients with heightened risk for symptom burden, stress, and anxiety or depressive symptoms.

Keywords Chronic lymphocytic leukemia · Active surveillance · Physical symptom burden · Psychological responses · Individual differences

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Introduction

Chronic lymphocytic leukemia (CLL) is incurable. When diagnosed in the early stages, symptoms may be vague or non-specific. The disease course is variable, depending on the presence of clinical, biological, and molecular risk factors [1]. Progression of disease is marked by emerging and/or worsening signs and symptoms (e.g., bone marrow failure, enlarged spleen, and/or lymph nodes) [2]. Currently, treatment is not offered for early-stage CLL as it provides no survival advantage [3]. Instead, patients are monitored, with active surveillance through regular appointments to assess changes in physical signs/symptoms and biological markers.

In contrast to research on psychological variables and quality of life (QoL) for solid tumor cancer patients, the literature for CLL is limited and comes from treatment trials rather than studies with a QoL focus. Thus far, QoL differences between surveillance and previously treated patients have not been found [1]. The limited

QoL data in CLL makes it challenging to offer recommendations to oncology providers caring for patients with poor quality of life, particularly when the contributing factors are unknown. One study by Levin et al. [4] does provide some information about untreated and treated patients regarding psychiatric symptoms. They reported that 25 % of surveillance patients compared to 15 % of patients undergoing treatment reported the use of psychotropic medications for anxiety or depression. The difference between groups was not statistically significant, but both estimates suggest that psychological symptoms, and those significant enough to merit treatment, may be present in CLL patients.

Despite having indolent disease, surveillance patients are symptomatic. In studies of solid tumor cancer patients, physical symptom burden is associated with greater severity of depressive and anxiety symptoms [5–7] and cancer-specific stress [8–12]. In CLL, physical symptom burden for patients undergoing treatment is linked with reduced QoL [1, 13], though its relationship to stress and psychological symptoms is unknown. Common cancer-related symptoms such as fatigue [7, 14–16] and pain [7, 14, 17], as well as poor functional status [18], also covary with psychological outcomes. Functional status captures overall physical well-being, including that associated with comorbid illnesses/conditions.

Psychological responses to cancer are not uniform, and studies of solid tumor patients have identified individual differences which place some patients at risk for heightened psychological symptoms. A positive psychiatric history, for example, is predictive of later psychological distress [19–22]. Social support is also relevant. Being unpartnered, or the perception that one's social support is inadequate, is associated with distress, reduced mental QoL, and increased risk of cancer death [23, 24].

To address the gap in psychosocial knowledge of the CLL surveillance experience, a cross-sectional design was used to study patients in surveillance returning to a comprehensive cancer center for routine follow-up. The study had two aims. The first determined the association between physical symptom burden and psychological responses (cancer-specific stress and symptoms of depression and generalized anxiety). We anticipated that greater physical symptom burden would covary with greater severity of stress and psychological symptoms. The secondary aim was exploratory, examining individual differences (psychiatric history, social support) in psychological responses and symptom burden. Considering the research reviewed above, we anticipated that psychiatric history and low social support would be associated with more negative psychological responses; however, we were most interested in their role as moderators of the relationship between symptoms and psychological responses.

Methods

Participants

Patients ($N = 112$) had Rai stage [25] 0 disease (0: 62.5 %, I: 32.1 %, II: 4.5 %), with a mean time since diagnosis of 4.6 years (range 0–16 years). They were non-Hispanic Caucasians (100 %) with a mean age of 61 (range 37–76 years); 55 % were male (ratio 1.2). Most (63.1 %) completed a college degree or above and were either employed full-time (46.7 %) or retired (37.1 %). Nearly half (48.5 %) reported a household income of ≥$100 K/year. The majority of participants were married/partnered (87.7 %). Based on household zip codes, 75 % resided within state of the cancer center.

Procedures

This study was approved by an institutional ethics review board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Patients returning for follow-up at a hematologic oncology clinic at a National Cancer Institute-designated comprehensive cancer center were approached. Inclusion criteria were the following: CLL diagnosis (0-II), no history of cancer treatment, time since diagnosis greater than 3 months, between the ages of 20 and 80 (inclusive), and ability to provide written consent. Informed consent was obtained from all patients for being included in the study.

One hundred thirty-nine (139) patients were eligible; 126 provided consent (91 % accrual). Medical chart review obtained disease-specific information (date of diagnosis, stage of disease, treatment history). Three individuals were found to be ineligible (1: stage IV disease; 2: history of radiation treatment); 11 did not complete the assessment due to loss of interest. The remaining participants ($N = 112$) completed a 45-minute telephone assessment of interviewer-rated and self-report measures of sociodemographic information, physical symptoms, and psychological responses.

Measures

Physical symptom burden

Symptom burden was operationalized using a composite of physical and functional variables, as has been done previously [26, 27]. This methodology mapped on to our model of symptom burden and offered statistical simplicity [28]. Four measures contributed to the composite. (1) Frequency and severity of CLL symptoms were assessed using a symptom list generated by our physician investigators, consistent with CLL

symptom descriptions from national sources [29]. Nine symptoms/signs were assessed: tiredness, enlarged lymph nodes, infections, night sweats, excessive bleeding/bruising, weakness, shortness of breath, unintentional weight loss, and fever. The frequency of each symptom/sign was rated from 0 (none in the past month) to 3 (more than three times a week); total scores range from 0 to 27. (2) Pain is not a typical symptom/sign of CLL but is a common cancer-related symptom and was therefore examined. Pain interference was assessed using the Brief Pain Inventory (BPI) [30]. Seven items were rated on a scale ranging from 0 (none) to 10 (completely), assessing interference with general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. Total scores range from 0 to 70. (3) The seven-item Total Disruption Index of the Fatigue Symptom Inventory (FSI) assessed fatigue interference with daily life in the following domains: general level of activity, bathing/dressing self, normal work activity, concentration, relations with others, enjoyment of life, and mood [31, 32]. Items were scored from 0 (no interference) to 10 (extreme interference) with a total score ranging from 0 to 70. (4) Functional status was measured using the single-item interviewer-rated Karnofsky Performance Status Scale (KPS) [33] with ten-point intervals ranging from 0 (dead) to 100 (normal).

Pearson intercorrelations between the CLL symptoms/signs and the pain, fatigue, and performance measures supported the calculation of a composite score. To eliminate redundancy with fatigue interference, the tiredness item on the CLL symptom scale was omitted. Inspection of the intercorrelations found that all were significant (rs = .30 to .86, ps < .01), excepting that for the correlation between pain and CLL symptoms (r = .24, p = .17). To calculate the composite, scores for functional status were reversed for ease of interpretation. Next, standardized z-scores for the four measures were calculated and summed for the composite. To assess the veracity of the composite, four modified versions (e.g., one omitted CLL symptoms only; another omitted fatigue only; and so on) were tested. The four analyses showed high correlations (rs = .94 to .99, ps < .01) between the composite score and the variations.

Psychological responses

Depressive symptoms The Center for Epidemiological Studies Depression Scale (CES-D) [34] is a 20-item measure of depressive symptoms. Unlike other depressive symptom measures, the CES-D includes no physical symptom items and as such, it is commonly used with medical patients [35]. Item scores range from 0 (rarely/none of the time) to 3 (most/all of the time). Total scores range from 0 to 60. A score ≥16 is the recommended cutoff indicative of clinically relevant symptomatology. Cronbach's alpha was 0.90.

Anxiety symptoms The Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV) [36] consists of nine items to assess symptoms of generalized anxiety disorder. Eight of the nine items are quantitative, scored either dichotomously (0 for absence; 1 for presence) or on a nine-point scale (0, none, to 8, very severe). The one qualitative item was not used here. Total scores range from 0 to 27. A score ≥5.7 is the recommended cutoff indicative of clinically relevant symptomatology [36, 37]. Cronbach's alpha was 0.78.

Stress The Impact of Events Scale-Revised (IES-R) [38] is a 22-item measure that assesses intrusive thoughts, physiological arousal, and hypervigilance. Items were worded with regard to having CLL. Item scores range from 0 (not at all) to 4 (extremely). Total scores range from 0 to 88. A score ≥37 is the recommended cutoff for clinically relevant symptomatology [39]. Cronbach's alpha was 0.91.

Individual differences

Psychiatric history was assessed with three self-reported questions: receipt of psychiatric diagnosis in one's lifetime (diagnosis); receipt of medications to manage mood, anxiety, or sleep (pharmacotherapy); and prior therapy/counseling for emotional/psychological problems (psychotherapy). Each item was scored 0 for absence, 1 for presence. Items were summed with a total score ranging from 0 to 3.

Social support was assessed with measures of perceived support for all patients and relationship satisfaction for partnered individuals. The Interpersonal Support Evaluations List (ISEL) [40] is composed of 40 statements assessing perceived availability of social support. Items were scored as 1 (probably false) or 2 (probably true), with total scores ranging from 40 to 80. Cronbach's alpha was 0.86. For partnered participants (87.7 % of the sample), the satisfaction item of the Dyadic Adjustment Scale (DAS) [41], a common approach for assessing relationship satisfaction [42], was used and rated on a seven-point scale ranging from 1 (extremely unhappy) to 7 (perfect).

Analytic strategy

Based on an alpha of 0.05 and the estimation of a medium to large effect size for multiple linear regression (using SPSS, v. 21.0) [43] between physical symptom burden and psychological response variables, power exceeded 0.995. Descriptive statistics and correlations were conducted. For the regression analyses, demographic (age, gender, education, employment, household income) and disease relevant variables (stage of disease, time since diagnosis) were considered as potential controls.

Multiple linear regressions tested the covariation between physical symptom burden and psychological response, controlling for the appropriate covariates. First,

three independent models tested the covariation of physical symptom burden and the following: (a) depressive symptoms, (b) generalized anxiety symptoms, and (c) cancer-specific stress. Second, individual differences were tested as predictors of psychological responses, but of greater interest was to test their role as moderators between the physical symptom burden and the psychological response variables. For this, the individual difference variables were standardized; psychiatric history was coded as a dichotomous variable (0 = absence vs. ≥1 = presence), and for perceived social support and relationship satisfaction (both continuous variables), z-scores were used. For these regressions, variable entry was as follows: (1) control variable(s), (2) physical symptom burden, (3) individual difference (psychiatric history or perceived social support or relationship satisfaction), and (d) interaction term (physical symptom burden × individual difference).

Results

Descriptive

Summary statistics for physical symptom reports and psychological response variables are provided (see Table 1). Regarding CLL symptoms, 80.4 % of patients reported at least one symptom; the mean score reported was 5.6 (SD = 4.8; observed range 0–22; possible range 0–27). Of the CLL symptoms, tiredness (fatigue) was most commonly endorsed (57.9 %). Patients reported a mean fatigue interference score of 11.4 (SD = 13.1; observed range 0–54, possible range 0–70). Nearly one third of the sample (32.7 %) endorsed pain unrelated to CLL. The mean score for pain interference was 13.7 (SD = 13.1; observed range 0–50; possible range 0–70). These data are consistent with the high median score found for functional status (KPS), with 90 defined as "able to carry on normal activity, minor signs/symptoms of disease."

Comparison is made with data from other samples. For the item "fatigue interference with general level of activity" [31], the score found here (mn = 2.4, SD = 2.5) is comparable to that reported by breast cancer patients in treatment (mn = 2.3) and posttreatment (mn = 2.1), though higher than reports from healthy controls (mn = 1.3) [31]. Pain was endorsed by 32.7 %. For those with pain, the mean interference score (mn = 13.7, SD = 13.1) was higher than that found with primary care patients with non-malignant chronic pain (mn = 7.6, SD = 2.0) [44]. In general, however, this was a sample with high functional status (KPS; mn= 88.7) and few symptoms, consistent with their early-stage diagnosis and surveillance status.

For the psychological response measures, cutoffs for clinically significant symptoms were considered. Few (6.3 %) reported stress specific to CLL (IES-R) being at clinically significant levels. However, 20.5 % met the CES-D criterion (≥16) for significant depressive symptoms and 20.5 % met the GAD-Q-IV criterion significant generalized anxiety symptoms (≥5.7). Of these patients, 11.6 % had depressive and anxiety symptom comorbidity.

Table 1 Prevalence rates for CLL symptoms and mean scores on self-report measures of physical symptoms and psychological responses in surveillance patients ($N = 112$)

Variable	
CLL symptoms[a]	Prevalence
Tiredness	57.9 %
Enlarged lymph nodes	38.3 %
Infections	37.4 %
Night sweats	27.4 %
Excessive bleeding/bruising	21.5 %
Weakness	15.9 %
Shortness of breath	15.9 %
Fever	3.7 %
Unintentional weight loss	3.7 %
None	19.6 %
Self-report measures	Mean (SD)
Fatigue (FSI)	11.4 (13.1)
Pain (BPI)	13.7 (13.1)
Functional status (KPS)	88.7 (10.7)
Depressive Symptoms (CES-D)	10.2 (8.1)
Generalized anxiety symptoms (GAD-Q-IV)	3.8 (6.5)
Cancer-specific stress (IES-R)	13.7 (12.4)

FSI Fatigue Symptom Inventory, *BPI* Brief Pain Inventory, *KPS* Karnofsky Performance Status Scale, *CES-D* Center for Epidemiology Studies Depression Scale, *GAD-Q-IV* Generalized Anxiety Disorder Questionnaire, *IES-R* Impact of Events Scales-Revised

[a] Percent endorsing the presence of the symptom in the last month; coded 0 = none, 1 = some

Comparison of the psychological data to that from other cancer groups and community samples is relevant. The mean for CLL-specific stress (IES-R) was 13.7, roughly half that found in cancer patients with a recent initial (mn = 25.8) or recurrence (mn = 23.4) diagnosis, but comparable to those on follow-up and remaining disease free (mn = 12.4) [45]. Mean scores from healthy individuals in the community are lower (mn = 1.8) [46]. Mean score for depressive symptoms on the CES-D was 10.2, higher in comparison to that of a healthy community sample of comparably aged adults (mn = 8.3; mean age 63.9) [47]. Mean score for generalized anxiety symptoms using the GAD-Q-IV (mn = 3.8, SD = 6.5) was lower than that reported in a clinical sample of individuals with clinically diagnosed GAD (mn = 10.5, SD = 1.9) but also lower than for individuals in the same study without GAD (mn = 7.6, SD = 4.0) [48].

Regarding psychiatric individual differences, a positive history was reported by two thirds (66 %) of the sample.

Thirty-two percent (32.1 %) reported "yes" to having received a psychiatric diagnosis in their lifetime. Of them, the most prevalent self-reported diagnoses were mood [27.2 %, major depressive disorder (MDD); 3.2 %, bipolar disorder] and anxiety/stress disorders [8.7 %, generalized anxiety disorder (GAD); 2.9 %, posttraumatic stress disorder]; 5.4 % reported MDD/GAD comorbidity. Fifty-five percent (55.7 %) responded yes to current or past pharmacotherapy use, with commonly reported medications being antidepressants (29.5 %), anxiolytics (19.6 %), and over-the-counter or prescribed sleep aids (15.7 %). Forty six percent (45.6 %) reported yes to having sought psychotherapy for emotional/psychological problems; treatment was sought from psychologists (68.8 %), psychiatrists (29.5 %), and family counselors (23.8 %).

Regarding the social support variables, the mean score for perceived social support was high at 74.7 (median = 77.0, SD = 5.3; observed range 55–80; possible range 40–80). Those who were married/partnered (87.7 %) reported 5.1 as the mean rating for relationship satisfaction (median = 5.0; SD = 1.1; observed range 2–7; possible range 1–7).

Analyses

Preliminary Correlations testing for potential covariates found age to be negatively correlated with depressive symptoms ($r = -.20$, $p = .00$) and stress ($r = -.26$, $p = .00$), and stage of disease negatively correlated with generalized anxiety ($r = -.20$, $p = .04$). Therefore, age was included in the CES-D and IES-R analyses, and stage was included in the GAD-Q-IV analyses.

Regression analyses As predicted, analyses showed that greater physical symptom burden covaried with greater depressive symptoms (CES-D) [$\beta = 0.44$; 95 % confidence interval (CI) = 0.84, 1.96; $p = .00$] and cancer-specific stress (IES-R) [$\beta = 0.20$; 95 % CI = 0.05, 1.85; $p = .04$], controlling for age, and greater generalized anxiety symptoms (GAD-Q-IV) [$\beta = 0.37$; 95 % CI = 0.52, 1.46; $p = .00$], controlling for stage of disease.

Test of individual differences Entry of psychiatric history yielded significant results. When controlling for age, those with a psychiatric history reported greater depressive symptoms [$\beta = 0.26$; 95 % CI = 1.41, 7.23; $p = .00$], and as seen in Fig. 1, psychiatric history was also a significant moderator. When physical symptom burden was high, those with a psychiatric history reported even higher levels of depressive symptoms than those without a history [$\beta = 0.41$; 95 % CI = 0.10, 2.87; $p = .04$]. When controlling for stage of disease and age, respectively, psychiatric history was not significantly associated with generalized anxiety ($p = .08$) or cancer-specific stress ($p = .75$). Also, psychiatric history did not moderate the relationship between physical symptom burden and generalized anxiety ($p = .12$) or physical symptom burden and cancer-specific stress ($p = .18$).

Regarding individual differences in social variables, entry of perceived social support (ISEL) was significant. When controlling for age, lower social support was related to higher levels of depressive symptoms [$\beta = -0.43$; 95 % CI = −4.76, −2.27; $p = .00$], and social support was a significant moderator. When physical symptom burden was high, those reporting low support reported significantly higher levels of depressive symptoms [$\beta = -0.17$; 95 % CI = −1.06, −0.07; $p = .03$]. When controlling for stage of disease, perceived support was not significantly associated with generalized anxiety ($p = .41$) nor was it a significant moderator ($p = .67$). Controlling for age, perceived social support was not significantly associated with cancer-specific stress ($p = .79$); however, it was a significant moderator. When symptom burden was high, those reporting low support had significantly higher cancer-specific stress than those with high social support [$\beta = -0.21$; 95 % CI = −1.94, −0.10; $p = .03$].

Additional analyses were conducted with the sample of patients with partners ($n = 98$ of 112). Controlling for age, low relationship satisfaction (DAS) was significantly associated with higher levels of depressive symptoms [$\beta = -0.33$; 95 % CI = −3.43, −1.14; $p = .00$] but was not a significant moderator ($p = .11$). Controlling for stage of disease, relationship satisfaction was not associated with generalized anxiety symptoms ($p = .36$); however, it was a significant moderator (Fig. 2). When symptom burden was high, those reporting low relationship satisfaction reported significantly higher levels of generalized anxiety than those with high relationship satisfaction [$\beta = -0.21$; 95 % CI = −0.86, −0.06; $p = .02$]. Controlling for age, relationship satisfaction was not associated with cancer-specific stress ($p = .81$) but was again a significant moderator. When symptom burden was high, those with lower relationship satisfaction reported higher cancer-specific stress [$\beta = -0.24$; 95 % CI = −1.82, −0.18; $p = .02$].

Discussion

New data on the patient experience of CLL surveillance finds that patients reporting greater burden from their physical symptoms also reported higher levels of cancer-specific stress and symptoms of depression and anxiety; circumstances worsened for those with prior psychiatric histories and/or lower social support. The present study expands the psychosocial literature in CLL by identifying the relationship between physical symptom burden and psychological responses in a sample of early-stage CLL patients receiving active surveillance. Despite CLL being indolent, the majority of active surveillance patients (80.4 %) reported physical symptoms. More notable is that 20.5 % reported current, clinically

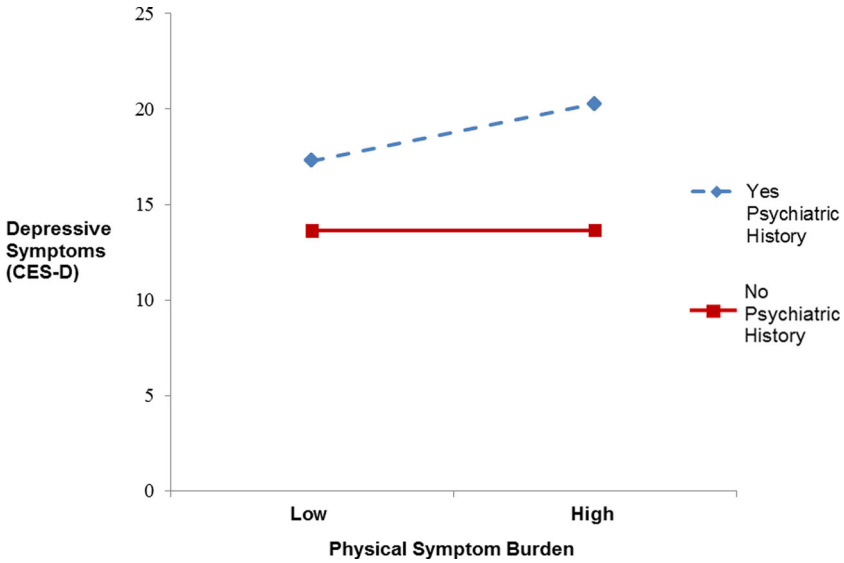

Fig. 1 Moderation effect of psychiatric history is shown. When physical symptom burden is high, those with a psychiatric history report higher levels of depressive symptoms

significant levels of depressive and generalized anxiety symptoms, with 11.6 % having comorbidity. For many, depressive and anxiety disorders remit, only to be followed with a later reemergence of symptoms. Thus, the reports of current symptom levels are consistent with patients' reports of positive psychiatric histories, i.e., 32.1 % acknowledged having received a prior diagnosis, with treatments of pharmacotherapy (55.7 %) and/or psychotherapy (45.6 %) received. As has been found, reports of a positive psychiatric history [19–22] or that one's social support or relationship satisfaction [23, 24, 49] is "low" impose risk for depressive symptoms, though not necessarily anxiety-related symptoms. However, these data suggest that the *interaction* of higher levels of CLL symptoms (burden) with specific individual differences (psychiatric history, low social support) conspire to further worsen the depression/anxiety symptom picture. As discussed below, oncology providers caring for surveillance patients might consider these data to tailor their follow-up care.

The correlations between CLL symptoms, fatigue, pain interference, and functional status (ranging from 0.30 to 0.86) supported the use of a composite measure. This enabled a clearer test of the role of physical symptom burden in relationship to psychological responses, with the findings that increasing symptom burden was associated with increases in depression (CES-D) and anxiety (GAD-Q-IV) symptoms, and cancer-specific stress (IES-R); a finding consistent with prior studies [5–12].

Comparison of mean scores of physical symptom burden and psychological symptoms suggests that patients in this study reported symptoms comparable to other cancer patients and higher than healthy controls. However, more important than overall mean scores is consideration of percentages of CLL patients exceeding clinical cutoffs and their (lifetime) history of psychiatric diagnoses and treatments. For comparison, incidence rates from the National Comorbidity Survey Replication (NCS-R) study ($N = 9090$) were considered [50, 51]. The latter provides nationally representative US data on prevalence of diagnoses confirmed by structured psychiatric interviews. Using self-report measure cutoffs to establish diagnosis estimates does, in general, overestimate

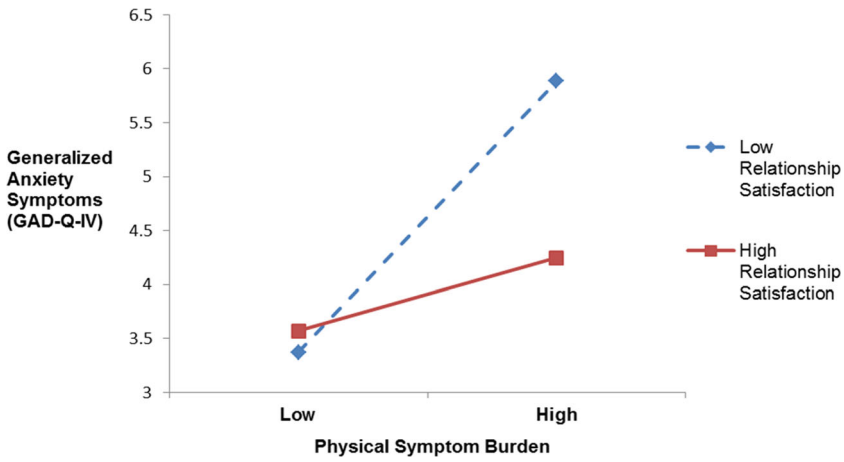

Fig. 2 Moderation effect of relationship satisfaction is shown. When physical symptom burden is high, those with low relationship satisfaction report higher levels of generalized anxiety symptoms

the numbers of "true" diagnoses that would be found by interview. Even acknowledging this, the CES-D/GAD-Q-IV estimates (both 20.5 %) are two to three times higher than the rates found in NCS-R. For MDD, the NCS-R 12-month total sample prevalence estimate is 6.6, with an odds ratio of 1.2 for adults ranging in age from 45–59. For GAD, 12-month total sample prevalence estimate is 3.1. In the CLL sample, MDD/GAD comorbidity was 5.4 %, significantly lower than the estimate of 67.8 in the NCS-R. The discrepancies between CLL patient reports and the NCS-R data on lifetime prevalence are smaller, but they are still in the direction of higher incidence reports from the CLL sample. CLL patient reports of lifetime diagnoses were 27.2 % for MDD and 8.7 % for GAD. By comparison, NCS-R reported the MDD lifetime prevalence to be 16.6 and 18.8 for the 45–59 age range. For GAD, NCS-R reported the lifetime prevalence was 5.7, with a 7.7 prevalence for the 45–59 age range. Thirty-two (32.1 %) percent of our patients reported having received a prior diagnoses, with higher numbers (45.6–55.7 %) receiving pharmaco- or psychotherapy. The only other CLL data come from Levin and colleagues [4] who reported that 25 % of the surveillance patients studied ($N = 57$) reported current pharmacotherapy use.

Demonstrating that higher levels of CLL symptoms/signs covary with psychological symptoms, and depressive symptoms in particular, is important. The data also show that in the context of "high" disease sign/symptom levels—even in this sample whose overall symptom/signs were, on average, objectively low—those with a psychiatric history reported even higher levels of depressive symptoms (see Fig. 1). A similar effect was observed for those perceiving their social support to be low. That is, with high symptom/sign burden, those reporting "low support" also reported even higher levels of depressive symptoms and cancer stress. Lastly, stress/anxiety responses, not depressive symptoms, were moderated by relationship satisfaction. There, the interaction of high disease sign/symptoms and low satisfaction was related to heightened generalized anxiety symptoms (see Fig. 2) and cancer-specific stress.

Coincident with monitoring CLL disease progression, oncology providers could implement the assessment of depressive and anxiety symptoms using measures validated for use in cancer patients and shown to be feasible in busy clinical settings [52]. Doing so would comply with the Commission on Cancer mandates. One example of the importance of ongoing assessment comes from a population-based cohort study of a mixed sample of 100 cancer patients showing that 26 % endorsed depressive symptoms across three assessments in 6 years [54]. The American Society of Clinical Oncology (ASCO) guidelines call for regular assessment of depression and anxiety symptoms [52]. The recommended measures in the ASCO guidelines include the Patient Health Questionnaire (PHQ-9) [53] and the Generalized Anxiety Questionnaire based on the DSM-IV (GAD-Q-IV) [35], chosen based on their wide use, particularly in primary care, their impressive reliability and validity data, and their assessment of psychological symptoms, not physical ones. Data from measures such as these would assist oncology providers in optimizing their CLL care. Significant anxiety or depressive symptoms would be found as they arise and then timely referral could occur for further psychological evaluation and possible treatment, as is reflected in the ASCO care pathways. For surveillance patients with later disease progression, the prospective psychiatric data would facilitate tailored treatment, anticipating the new stressors of disease progression.

Social support variables were also significant individual differences, consistent with solid tumor research [23, 24]. While the relationship between low social support and worse physical and psychological well-being is generally expected in cancer populations, it is of particular interest here as it might be assumed that patients under active surveillance do not require the same types of social support needed by patients coping with advanced disease and receiving treatment. But, active surveillance patients, like other individuals, are vulnerable to the adverse health consequences that co-occur with low social support and/or poor intimate relationship satisfaction [49]. Our data show that low perceived support and low relationship satisfaction were both associated with more depressive symptoms and conversely, higher relationship satisfaction appeared to have a protective ("buffering") effect in the face of higher symptom burden.

Methodological characteristics of the study are noted. The study was adequately powered to show direct effects as well as interaction effects. As the incidence of CLL is low, patients are often treated at regional centers, and in this study, 25 % of the sample came from out-of-state. The sample was similar to those in collaborative CLL trials [55], which tend to be younger. While age differences may be important for gauging CLL treatments, age effects in CLL QoL research are generally not found [1, 56–59]. When age effects are detected, they are as reported here, with "younger" patients reporting significantly higher levels of emotional disruption or depressive or anxious symptoms [4, 56, 60]. In CLL, there is an increased male-to-female ratio [61] with estimates in the range of 1.4 [62]; the ratio for this study was 1.2. We found that gender did not covary with psychological outcomes, consistent with other studies [4, 56–58, 63]. Regardless, future studies should test whether variables such as age, gender, marital status, and others covary with outcomes. This is the only CLL study providing both psychiatric history and symptom assessments of anxiety and depression, with the need for future studies to consider diagnostic interviews and treatment trials for a large minority (20 %) of patients having significant psychological symptoms.

Study findings highlight the covariation between physical symptom burden and psychological responses in early-stage, untreated CLL, an understudied patient group. Patients'

reports of current, clinically significant symptoms (20 %) and that upward of 30 % reported a positive psychiatric history are estimates higher than the national (NCS-R) data. This would suggest that the diagnosis—including its non-progressive chronicity and regularity of follow-up—exacts a tangible psychological toll. However, the toll could likely be interrupted and mitigated with routine assessments of psychological symptoms followed by referral for further evaluation and possible treatment. Doing so would directly lessen psychological symptom burden for those individuals with CLL in active surveillance.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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