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APPROVAL SHEET

PHYSICAL ACTIVITY'S IMPACT IN LYMPHOMA PATIENT'S OUTCOMES

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ABSTRACT COVER PAGE

PHYSICAL ACTIVITY'S IMPACT IN LYMPHOMA PATIENT'S OUTCOMES

By Andrew Ip, MD

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ABSTRACT

PHYSICAL ACTIVITY'S IMPACT IN LYMPHOMA PATIENT'S OUTCOMES

By Andrew Ip

PURPOSE: The impact of physical activity (PA) on survival in lymphoma patients is not known. We evaluated the association of PA and change in PA with overall (OS), lymphoma-specific (LSS) and event-free (EFS) survival in a prospective cohort of newly diagnosed lymphoma patients enrolled 2002-2012. As a follow up, we performed a feasibility study of a prospective PA intervention in lymphoma patients undergoing autologous stem cell transplant at Emory.

METHODS: Leisure Score Index (mLSI) was calculated from self-reported level of usual adult PA at enrollment (baseline) and at 3-years post-diagnosis (FU3), grouping patients by active versus insufficiently active by national PA guidelines. Associations of PA with survival were assessed using hazard ratios (HRs) and 95% confidence intervals (CI) from Cox models stratified by lymphoma subtype and adjusted for age, sex, baseline BMI and comorbidity score; change scores were adjusted for baseline PA.

A feasibility single-arm study was performed at Emory. Patients performed 150 minutes of PA per week on a stationary bicycle or by walking. PA was self-recorded and validated by an Apple Watch. Data was collected from date of hospitalization to discharge. Feasibility, the primary outcome, was assessed by average weekly minutes of PA performed by self-report. Validation of moderate intensity PA was shown by heart rate (HR) monitoring (goal 40% of HR reserve).

RESULTS: 3,060 participants were evaluable at baseline and 1,371 at FU3. Active patients had superior survival from baseline [HR (CI): OS 0.82 (0.72-0.94); LSS 0.74 (0.61-0.90); EFS 0.92 (0.82-1.02)] and FU3 [HR (CI): OS 0.64 (0.46-0.88); LSS 0.32 (CI 0.18-0.59); EFS 0.82 (0.61-1.10)] compared to insufficiently active. An increase in mLSI from baseline to FU3 (versus stable mLSI) was associated with superior OS (HR=0.70, CI 0.49-1.00) and LSS (HR=0.49, CI 0.26-0.94). These results were consistent across subgroups. Our feasibility study in 10 patients showed a 60% adherence rate by self-report, with 75% of PA validated by HR.

CONCLUSIONS: Higher PA among newly diagnosed lymphoma patients and 3-year survivors is associated with OS, LSS and EFS. An increase in PA after diagnosis is associated with improved survival outcomes. Prospective PA interventions are feasible but need further study.

COVER PAGE

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INTRODUCTION

Physical activity has been shown in various solid tumors to improve survival and health-related quality of life (1-4). However, very little is known about the impact of physical activity on survival in lymphoma patients (5). This led us to investigate the association of physical activity, as measured at baseline and 3 years post-diagnosis, with overall survival and lymphoma-specific survival.

For lymphoma patients, over 70% are expected to live at least five years (6). Many will relapse and will need to receive a bone marrow transplant (7). Few studies have specifically looked at the role of exercise in this lymphoma population. As a follow-up aim, we also investigated the feasibility of a physical activity intervention in the lymphoma subpopulation of patients undergoing bone marrow transplant.

To address whether survival in lymphoma patients is associated with physical activity, we performed a large prospective cohort analysis in collaboration with Mayo Clinic. From 2002-2012, over 3000 patients reported their physical activity data as a part of the Molecular Epidemiology Resource cohort at the Mayo Clinic at different time points allowing us to report on the impact of change in physical activity. We did adjust for age, sex, baseline BMI and comorbidities. We also looked at landmark analyses at 3 year follow-up and analyzed survival outcomes by change in physical activity from baseline to 3-year follow-up.

Following the prospective cohort analyses, we desired to answer the question “is a physical activity intervention feasible in lymphoma patients undergoing bone marrow transplantation?” We prescribed an inpatient exercise intervention while hospitalized, with a primary outcome of adherence by self-report. To validate patient’s heart rate

during exercise, we asked patients to wear Apple Watches as a novel method to study and deliver unsupervised physical activity interventions. We sought to determine whether wearable technology can improve efficient health care delivery and this study will address if these personal health devices can measure lymphoma patients' physical activity.

BACKGROUND

Physical Activity and Lymphoma*:* It is estimated, as of January 1, 2016, there were 219,570 Hodgkin lymphoma (HL) and 686,370 non-Hodgkin lymphoma (NHL) survivors in the United States (6). This number will continue to grow (6). In large retrospective cohorts, physical activity (PA) improves health-related quality of life (QOL) and survival in a multiple cancer types, including lymphoma, breast, and colorectal cancer (1-4). Increasing PA may not just increase overall survival (OS) but also decrease risk of cancer progression or relapse in patients with cancers of the breast, prostate and colon (8-12). Pre-diagnosis PA in diffuse large B-cell lymphoma (DLBCL) has been associated with improved survival outcomes (13). It is known from population-based studies that pre-diagnosis smoking, alcohol use, vitamin D, and obesity adversely affect lymphoma outcomes (14, 15). However, it is not known whether changes in PA after diagnosis can change lymphoma-specific outcomes in survivors (16). Furthermore, the effect of PA in lymphoma patients undergoing autologous stem cell transplantation (ASCT) is not well studied and typically investigated in a supervised setting (17).

Physical activity (PA) is recommended for all cancer patient survivors, including lymphoma patients (18). As it stands, only 30-50% of patients perform adequate amounts of PA per week (150 minutes of moderate PA, or 75 minutes of vigorous PA), as prescribed by national guidelines (19-21).

Physical Activity in Patients Undergoing Autologous Stem Cell Transplantation:

In general, PA across a spectrum of hematologic malignancies appears to improve physical function, fatigue, and depression (17). QOL benefits of PA remain robust but there remains significant questions given heterogeneity of studies and timing or type of

PA (22). There is a paucity of data investigating PA's effect on lymphoma patients undergoing ASCT. A randomized-control trial was recently reported in a more homogenous population of NHL and multiple myeloma patients that performed PA after their ASCT. This study did show some improvement in physical function and QOL, and questions arose on the optimal timing of PA for ASCT patients (23). There is evidence to suggest PA during, rather than before or after, ASCT has a larger treatment effect on QOL (22).

Physical Activity during Cancer Treatment with Digital Health Technology*:* Most prospective PA studies are supervised and conducted after traditional chemotherapy treatments are completed, and thus strategies to integrate PA into routine cancer care are needed (17). Only a few studies outside the U.S. have studied aerobic PA in patients during ASCT, focusing solely on QOL outcomes (23, 24). As the first 100 days are particularly distressing to ASCT patients, research is needed to bring structured PA interventions to this population in the U.S (24). Digital health technology is a novel, pragmatic method to implement and study PA in cancer patients, including those undergoing ASCT (25, 26). Use of mobile health devices such as an Apple Watch® can help motivate behavioral change by initiating, sustaining, and monitoring PA in an unsupervised setting (27).

Physical Activity's Effects on Survival – Potential Biologic Mechanisms*:* The mechanism by which PA affects cancer biology is likely multifactorial and not well understood. Explanations might include changes in metabolism, sex hormones, vitamin D, angiogenesis, and immune function (28-32). The immune response pathway in patients completing autologous stem cell transplant (ASCT) may be affected by PA,

potentially through an influence on post-ASCT natural killer cell, lymphocyte, or monocyte reconstitution (33-36). There is also evidence that tumor angiogenesis affects both lymphoma and myeloma outcomes, with measurement of increased endothelial progenitor cells (EPCs) as a surrogate (37-39). PA has been shown in non-cancer patients to increase circulating EPCs even with mild PA regimens such as walking (40).

METHODS

Hypotheses and Aims: We hypothesized that i) adults who are more physically active prior to and after lymphoma diagnosis have better lymphoma-related outcomes, ii) increasing the level of PA after lymphoma diagnosis is associated with improved survival, and iii) adherence to an unsupervised physical activity regimen while hospitalized will be a feasible intervention in lymphoma or myeloma patients undergoing ASCT. In order to appropriately investigate these hypotheses, the following aims were developed:

Aim 1: To investigate in a prospective cohort of newly diagnosed lymphoma patients in the Molecular Epidemiology Resource the association of self-reported PA and survival outcomes, including overall and lymphoma-specific survival.

Aim 2: Characterize the feasibility of a physical activity intervention for lymphoma or myeloma patients undergoing ASCT.

2a. Characterize the feasibility of a digital health tracker to validate by heart rate physical activity for lymphoma or myeloma patients undergoing ASCT.

Methods (Aim 1): This is a prospective cohort study with a primary objective to analyze survival outcomes associated with physical activity at different time points.

Study Population: Full details of the Lymphoma SPORE Molecular Epidemiology Resource (MER), a prospective cohort study of newly diagnosed lymphoma patients aged 18 years and older, have been previously described (41). This analysis includes participants from the Mayo Clinic in Rochester, Minnesota, from 2002 until 2012.

Measurements: At enrollment, participants completed a baseline health and a self-administered risk factor questionnaire (RFQ). The RFQ included self-reported items on usual adult exercise, smoking, alcohol use and diet prior to the diagnosis of lymphoma. Pathology was reviewed by a hematopathologist and classified based on the WHO criteria (42, 43). Study personnel abstracted baseline clinical data and initial course of therapy. Responses from the MER cohort baseline questionnaire were used to calculate a baseline co-morbidity score, assigning 1 point each for the following self-reported conditions: other cancer diagnosis within 3 years of lymphoma diagnosis (except non-melanoma skin cancer), coronary artery disease, congestive heart failure, diabetes, hip fracture, hepatitis, autoimmune disease, and elevated creatinine.

Data Collection: All participants were contacted every 6 months for the first 3 years after diagnosis, and then annually thereafter to update health status. Disease recurrence or progression, new therapies, and new cancers were validated against medical records. For decedents, death certificates and medical records were reviewed by study physicians to assign cause of death. At 3 years after diagnosis, a survivorship questionnaire (FU3) that included items on PA, smoking, alcohol, and diet was sent to all participants. This was an observational study and patients received care at provider discretion with no specific PA intervention.

Patient Eligibility: Patient inclusion criteria included age 18 years and older, no history of HIV infection, diagnosis of lymphoma within prior 9 months, English speaking and able to provide written consent. Patients had to be a resident of Minnesota, Iowa, or Wisconsin at time of diagnosis (41).

Participants were considered evaluable at baseline if they had completed baseline RFQ, including questions on usual adult PA. They were considered evaluable at FU3 if they had been evaluable at baseline and completed the FU3 questionnaire, including the Godin Leisure Time Exercise Questionnaire (Godin) (44). In order to minimize the effect of occult lymphoma recurrences on PA levels, patients who had events (disease recurrence, re-treatment or death) 6 months before or after FU3 were excluded from the FU3 and PA change analysis (CONSORT diagram Figure 1).

Assessment of physical activity: On the baseline RFQ, participants were asked "During most of your adult life, how often did you do strenuous/moderate/light exercise?" The questions listed examples of exercise by intensity and asked patients to exclude walking outside the home and PA associated with jobs. Participants answered on a 6-point frequency scale ranging from "rarely or never" to "5 or more days per week". At FU3, participants completed the Godin, a validated tool for measuring PA in oncology patients (44). At FU3, participants also reported their perceived change in level of PA since lymphoma diagnosis by answering "How has your level of PA changed since your diagnosis of lymphoma?" as no change, decreased or increased level of activity.

Statistical Analyses: We used PA data from the questionnaires to calculate a score corresponding to the Godin Leisure Score Index (LSI), which is a weighted summary measure of the frequency of self-reported weekly leisure-time exercise (times/week) calculated as (9 x strenuous activity) + (6 x moderate activity) + (3 x light activity) expressed in arbitrary units (44). On the Godin, a moderate-to-strenuous LSI of $\geq$24 is used to classify cancer survivors into active and insufficiently active categories as per the American Cancer Society guidelines ($\geq$ 150 minutes of moderate to vigorous physical activity per week) (45) . Although the RFQ did not have the specific Godin questions, we used the data on frequency, duration and intensity of PA to derive a modified LSI (mLSI). mLSI was modeled as a continuous score (per 10-point change) and by tertile for sensitivity analyses. mLSI change was calculated as baseline mLSI subtracted from FU3 LSI. Survival was measured as time from diagnosis (for baseline PA) and time from FU3

(for FU3 PA and PA change from baseline to FU3 PA) until death due to any cause and due to lymphoma. For event analysis beyond FU3, participants who had an event prior to FU3 were excluded. We evaluated the association of PA with outcomes using Kaplan-Meier curves as well as hazard ratios (HRs) and 95% confidence intervals (CI) from Cox models stratified by lymphoma subtype. All Cox models were adjusted for age, sex, baseline BMI and comorbidity score. Our stratified cox model $H(t) = H_{0g}(t) \exp(\beta_1 PA + \beta_2 Age + \beta_3 sex + \beta_4 BMI + \beta_5 Comorb + \beta_6 PA*Age + \beta_7 PA*sex + \beta_8 PA*BMI + \beta_9 PA*Comorb)$, where g=0 for aggressive lymphoma, g=1 for indolent lymphoma. Our cox model modeling survival function is $S(t) = S_{0g}(t)^{\exp(\beta 1PA + \beta 2Age + \beta 3sex + \beta 4BMI + \beta 5Comorb + \beta 6PA*Age + \beta 7PA*sex + \beta 8PA*BMI + \beta 9PA*Comorb)}$

The PA change models were also adjusted for baseline PA. Subset analyses stratified on age, body mass index (BMI), histological subtype, event free survival at 36 months (EFS36, defined as any lymphoma recurrence, complication due to lymphoma, or death due to lymphoma) and treatment status were also assessed. A complete case analysis was performed in event of missing data. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Methods (Aim 2):

Study Population/Patient Eligibility: Patient inclusion criteria included age 18 years and older, confirmed diagnosis at Emory of NHL or multiple myeloma, planned ASCT within 30 days of enrollment, an ECOG performance status of 0-2, and ability to complete 6 minute walk test. Key exclusion criteria include inability to consent and Hodgkin lymphoma.

Study Design: This is a feasibility single-arm study at Emory University. After enrollment and baseline assessment, the intervention will consist of an unsupervised exercise prescription using a stationary bicycle or walking for 30 minutes 5 times a week as recommended by national guidelines (18). Study staff will check in at least 2 times a week to ensure patients are motivated to continue to adhere to their prescribed PA. HR

and activity will also be monitored via a wearable digital health apparatus (Apple Watch®). Equipment will be returned once patient has engrafted a neutrophil count of ≥500 cells/µcl and is discharged home from hospital, at or before day 30.

Measurements:

Participants self-reported physical activity on a standard diary packet that allowed marking of 15 or 30 minute intervals of physical activity daily. Adherence was defined as 150 minutes of self-reported PA per week while hospitalized.

Validation of moderate intensity PA was shown by heart rate (HR) monitoring (goal 40% of HR reserve) by Apple Watches.

Patients also completed assessments at time of enrollment and at first post-discharge outpatient visit, around day +30 of ASCT. Instruments included: the Functional Assessment of Cancer Therapy (FACT) -lymphoma and FACT-myeloma validated QOL surveys and the validated Six minute walk test (6MWT) of exercise capacity (46, 47). We will also report time to neutrophil engraftment, defined as time in days from first day of chemotherapy for ASCT to first day of neutrophil count of ≥500 cells/µcl.

Sample Size and power calculation: According to an analysis of data by the CDC (48), about 40% of patients adhere to physical activity guidelines for aerobic exercise. Per a review of physical activity trials in bone marrow transplant patients (either before, during, or after treatment, and either at home, out-patient, or in-patient intervention), the range of feasibility is between 66-85% (49). For our study, the difference in proportion estimated will be around 35%. This is based on an average completion rate of 75% for patients on protocol compared to a control completion rate of 40%. With 16 patients, we

can detect an absolute difference in proportion of 35% (75% vs. 40%) with 81% power assuming a Type I error of 0.05 using a two-sided binomial test. The feasibility of the above within 1 year is possible, as Winship performs roughly 50 autologous transplants for NHL a year at our institution and roughly 70-80 for myeloma. No patients are expected to be lost to follow-up for the assessment of the primary endpoint.

Survey scores and 6MWT distances were compared using Wilcoxson rank sum tests. Historical controls at Emory matched for age, disease status, conditioning, stem cells infused, and use of stimulating factor were used to compare median time to neutrophil engraftment.

Descriptive statistics were used to summarize patient characteristics. Categorical variables were summarized using frequencies and percentages, and continuous variables such as quality of life assessments, neutrophil recovery time, absolute lymphocyte count at 15 days, and biomarker endpoints over time were summarized using mean, median, standard deviation, and range.

Statistical Analyses

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Usual PA prior to diagnosis and subsequent survival

From 2002 to 2012, 4,087 participants were enrolled in the MER at the Mayo Clinic, and of these, 3,129 participants completed an RFQ, of which 3,060 were evaluable for usual level of PA prior to diagnosis (baseline mLSI). The baseline characteristics of the evaluable patients are shown in Table 1 and in Figure 1, a consort diagram.

Compared to the participants who were evaluable for mLSI (N=3,060), the 1,027 participants enrolled but not evaluable for mLSI were more likely to be male (65% vs. 58%), have aggressive histology (44% vs. 37%), ECOG performance status ≥ 2 (9% vs. 5%), be obese (BMI $\geq$30, 35% vs. 29%) and have missing co-morbidity data (31% vs. 20%) (Table 2). At baseline, the median mLSI was 28 (IQR 13-43); 1392 (46%) of patients could be classified as active (mLSI ≥ 24). Correlates of level of usual adult mLSI (active vs insufficiently active) are shown in Table 3. Participants who were active had a lower median BMI than those who were insufficiently active based on mLSI, and were similar on other factors.

At a median follow-up of 8.9 years from diagnosis, there were 863 total deaths, 440 of which were attributable to lymphoma. Survival curves for mLSI by active vs insufficiently active are shown in Figure 2a. Compared to participants who were insufficiently active, those who were active had significantly superior OS (HR=0.82, 95% CI 0.72-0.94, p=0.004) and LSS (HR=0.74, 95% CI 0.61-0.90, p=0.003) with a trend towards better EFS (HR=0.92, 95% CI 0.82-1.02, p=0.114). Baseline mLSI modeled as

a continuous score and by tertiles was significantly associated with OS, LSS and EFS (Figure 2b).

PA at FU3 and subsequent survival

Of 3,060 participants with a baseline LSI, 368 died prior to FU3 and 93 who had an event within 6 months of FU3 were excluded. Baseline characteristics for those evaluable (N=1,371, Table 2) and not evaluable (N=1,321, Table 2) for LSI at FU3 were comparable, except that co-morbidity information was more likely to be missing (26% vs. 14%) in those not evaluable (Table 2). At FU3, the median LSI at FU3 was 23 (IQR 9-40); 544 (40%) of patients were classified as active (LSI≥ 24). Compared to the insufficiently active, FU3 survivors who were active were more likely to be younger, male, have aggressive lymphoma histology, have lower BMI, have fewer co-morbidities and have higher baseline mLSI (Table 3). For EFS analysis beyond FU3, participants who had an event prior to FU3 (N=267) were excluded and only participants who achieved EFS36 (N=1104) were included.

At a median follow-up of 2.3 years from FU3, there were 225 total deaths, 84 of which were attributable to lymphoma. Participants who were active had significantly better OS (HR=0.64, 95% CI 0.46-0.88, p=0.006) and LSS (HR=0.32, 95% CI 0.18-0.59, p<0.001) with a trend towards better EFS (HR=0.82, 95% CI 0.61-1.10, p=0.188) compared to those who were insufficiently active (Figure 3a). FU3 mLSI modeled as a continuous score and by tertiles was significantly associated with OS, LSS and EFS (Figure 3b).

Change in PA from baseline to FU3 and subsequent survival

1,371 participants had both baseline mLSI and FU3 LSI available to assess change in PA and subsequent survival after FU3. The median change in mLSI from baseline to FU3 was -3 (IQR -18 to +10). After accounting for baseline mLSI, the continuous mLSI change score (per 10-point change) was associated with significantly superior OS (HR=0.88, 95% CI 0.82-0.95, p=0.001), LSS (HR=0.74, 95% CI 0.65-0.84, p<0.001) and EFS (HR=0.92, 95% CI 0.85-0.98, p=0.016). The change in mLSI had an approximately linear association with OS, LSS and EFS, as confirmed by spline plots (Figure 5). Based on their change score, participants were divided into three groups: the highest (mLSI increase>5), middle (stable mLSI -12 to 5) and lowest (mLSI decrease < -12) tertiles. After accounting for baseline mLSI, category of change in mLSI was associated with OS and LSS (Figure 4a) but not EFS. Compared to patients with stable mLSI, patients with increased mLSI had marginally superior OS (HR=0.70, 95% CI 0.49-1.00, p=0.09), more strikingly superior LSS (HR=0.49, 95% CI 0.26-0.94, p=0.006) but not EFS (HR=0.79, 95% CI 0.57-1.10, p=0.282). There was no association of decreased mLSI with OS (HR=1.05, 95% CI 0.74-1.49), LSS (HR=1.56, 95% CI 0.90-2.71) or EFS (HR=1.04, 95% CI 0.73-1.48).

Self-perceived change in PA from diagnosis to FU3 was also associated with OS, LSS and EFS (Figure 4b). Compared to no change, patients who perceived a reduction in their PA at FU3 had inferior OS (HR=1.93, 95% CI 1.50-2.47, p<0.001), LSS (HR=2.58, 95% CI 1.70-3.93, p<0.001) and EFS (HR=1.40, 95% CI 1.05-1.87, p=0.073), while a perceived increase in PA was not associated with OS (HR=0.86, 95%CI 0.49-1.50), LSS

(HR=0.68, 95%CI 0.24-1.93) or EFS (HR=1.22, 95% CI 0.75-1.96), noting the latter estimate was based on a small number of events leading to wide confidence intervals.

Sub-group analysis:

In order to determine if the survival benefit from increasing PA was specific to any particular subgroup of patients, analyses by age (<60 vs. ≥60 years), sex (male vs. female), BMI (<30 vs. ≥30), co-morbidity score (0 vs. ≥1 vs. missing), Vitamin D insufficient or not, disease histology (aggressive vs. indolent; individual subtypes DLBCL, CLL and FL), patients with and without events by FU3 (EFS36 achievers vs. non-achievers), and any treatment vs. no treatment by FU3 were performed. These results showed superior OS, LSS and EFS was consistently associated with higher mLSI at baseline and higher LSI at FU3 among all the subgroups analyzed. Figure 6 a-c illustrates the subgroup analysis for change in mLSI from baseline to FU3 demonstrating a consistent survival benefit from increasing PA among all the lymphoma survivors.

Feasibility Study Preliminary Results:

Since April 2018, 10 pts have enrolled and completed the feasibility PA study, with 2 denying participation due to pain or lack of interest. Median age was 62, 70% male gender, 40% NHL, 50% African American and 50% Caucasian (table 4). 100% were chemotherapy sensitive at time of transplant. Conditioning regimens included BEAM (30%), Melphalan (60%) and busulfan/cytoxan/etoposide (10%). Granulocyte colony stimulating factor was used in 60% of pts. Median follow up was 22 days. Six of 9 (67%, 95% CI 0.30-0.93) patients were able to adhere to a PA regimen while hospitalized by self-report, with one patient having missing data. Eight of ten patients wore their watch regularly for HR analysis. Six of eight patients consistently reached HR goal

during their PA. Of the 6 patients who met PA goal by self-report, 4 (67%, 95% CI 0.22-0.96)) consistently met HR goals during PA (sample heart rate data, figure 7). QoL scores measured by FACT-lymphoma and FACT-MM showed no significant decrease in total score from pre-intervention to post-discharge follow up (median score difference -2.5 points, std dev 10.65, *p-value=0.72*). Individual sections of FACT surveys showed no significant differences except emotional well-being (median score difference baseline vs post-discharge follow up, -3 points, std deviation 1.84 *p=0.008*). Physical function by 6MWT decreased by a median of 97 meters (pre-test median of 435 meters, post-test median of 333.5 meters, std deviation 59.75, *p-value=0.016*). Compared to 20 historical controls, median time to engraftment was similar (12 days vs 12.5 days).

DISCUSSION

Our study shows that lymphoma patients with a higher level of usual PA during adult life prior to lymphoma diagnosis had significantly better OS and LSS after diagnosis compared to those who are less physically active. Higher level of PA in 3-year survivors was also associated with improved survival beyond the 3-year landmark. A change in the level of PA from baseline to FU3 had a stronger association with survival than baseline PA alone and this association was linear. Self-perceived decrease in PA from diagnosis to FU3 was associated with inferior survival. These associations held true irrespective of age, sex, co-morbidities, BMI, lymphoma histology at diagnosis by subtype and group, disease course and treatment. More importantly, the survival associations held true 3 years after lymphoma diagnosis and PA seems to impact LSS to a greater degree than OS.

This is the first study, to our knowledge, to measure the effect of change in PA after lymphoma diagnosis on subsequent OS and LSS. Prior studies in lymphoma have shown that baseline PA after adjusting for BMI associates with lymphoma survival outcomes (13). Our study argues, after adjusting for other covariates such as comorbidity score, age, sex, and stratifying by lymphoma subtype, for increased PA having a causal role in reducing mortality outcomes for lymphoma patients. This study attempts to address reverse causation by excluding those patients who had an event within 6 months of FU3 questionnaire.

While many epidemiologic studies have shown an association of physical activity with survival outcomes in solid tumors, this is the first study in a lymphoma population to show a dose-response relationship between PA levels and survival outcomes (1-4, Figure

5). Given the paucity of randomized controlled PA intervention trials in lymphoma patients, this study serves as a rationale to pursue other rigorous studies to strengthen causal inference as suggested by our data (16).

Limitations of the study include selection bias, especially a healthy adherer effect in the patients who chose to enroll in this cohort. Unmeasured confounding is always possible in an observational cohort study. Information bias is likely in this study as well, as self-reported PA will often lead to measurement error and possible misclassification of outcomes. Further misclassification is possible as the initial assessment of usual adult PA prior to diagnosis used different questions than the Godin questionnaire. However, we were able to use data on frequency, duration and intensity of PA to develop a surrogate of the LSI. The calculated mLSI and self-perceived PA change results broadly paralleled each other even though they measured PA differently.

The strengths of our study include prospective enrollment and follow-up of participants; detailed clinical data; measurement of PA at enrollment and at FU3, allowing assessment of change; ability to adjust for important potential confounding factors including level of comorbidity and BMI; and the length of follow-up.

The mechanism by which PA affects OS in lymphoma patients may be explained in part by decreased cardiovascular events, as is well established in the non-cancer population (50, 51). The mechanism of disease-specific survival benefit from PA is likely multifactorial and not well understood (28, 52). One possible explanation could be that patients who are more physically active are more likely to tolerate and complete lymphoma treatments (16). Other explanations might include changes in metabolism, sex hormones, vitamin D angiogenesis, and immune function, although these have been

mainly studied in breast or colorectal cancer patients to date (29-31). One possible biological link is the role of PA and vitamin D levels, with a deficiency in vitamin D shown to have worse outcomes in more indolent lymphomas (14, 15). A possible hypothesis is that those who perform more PA have more sun exposure and thus have sufficient vitamin D levels. Very few studies have examined the effect of PA on lymphoma biology, although there is a suggestion in animal models that tumor progression is retarded with PA via immunomodulatory mechanisms (53). Further studies are needed to elucidate mechanism of PA's effects on prognosis for lymphoma survivors as we did see a trend towards improved event free survival with increased PA.

Cancer survivors commonly ask what they can do to decrease the risk of recurrence or progression. Our study strongly suggests that providers should counsel patients on the important role for PA in lymphoma survivorship. Many efforts have been undertaken to improve upon the outcomes following standard chemotherapy in NHL, particularly in DLBCL, the most common subtype. With the exception of consolidative radiotherapy in bulky disease, most of these efforts have proven unsuccessful (54). Herein, we found that PA is associated with improved overall and lymphoma-specific survival. These data provide a strong rationale for further investigating the role of PA in the care of lymphoma patients through intervention trials. Our study supports current national exercise guidelines for lymphoma survivors and suggests a benefit with even a modest increase in PA for those who cannot meet the guideline thresholds. Future studies are needed to elucidate the underlying biologic mechanisms as well as overcome barriers to effective delivery of exercise interventions to lymphoma patients.

Next Steps: Our findings support the feasibility of studying an inpatient PA intervention for ASCT pts using traditional and novel methods. Nearly 70% of pts who participated were successful in adhering to a PA regimen of 150 minutes of exercise. Ongoing assessment by research staff to encourage pts to adhere to prescribed exercise, as well as use of an Apple Watch to validate PA by HR data was feasible. A specific flow cytometry panel is being developed in our lab to measure immune reconstitution to further study the effect of PA in ASCT. Currently, this pilot study is near completion with a planned multi-center randomized controlled trial as a follow up.

With the assistance of a 2 year mentorship award from the Lymphoma Research Foundation from 2019-2021, I have designed a future study with the following aims: 1) Complete a multi-site randomized controlled trial to a) evaluate QOL in validated surveys such as the FACT-BMT and b) evaluate the impact of PA on transplant and disease outcomes including rehospitalization, transplant-related mortality, and event-free survival, 2) Utilize wearable digital health technology to validate an unsupervised PA intervention, and 3) Explore impact of PA on immune reconstitution and vitamin D status (55).

The intervention will randomize patients to a prescribed physical activity regimen of 150 minutes of moderate PA or to usual care during their ASCT. Given the potential confounding of a smart watch initiating health behavioral change, we will use an internal control of 20 additional patients in control arm with no watch, analyzing by descriptive analysis if there are differences with and without a watch in the control arm. All other patients will receive a smartwatch to monitor heart rate. Our primary end point is the overall well-being difference on FACT-BMT surveys at day 30 of ASCT compared to

baseline. Secondary endpoints include validation of PA by HR monitoring, functional PA assessment, overall QOL, sleep quality, vitamin D status, lymphoma outcomes such as event-free survival, and transplant outcomes such as non-relapse mortality, and rehospitalization.

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Table 1: Baseline characteristics of patients evaluable for mLSI at baseline and at 3-year follow-up (FU3)

	Baseline, N= 3060	**3-year follow-up, N= 1371**
Median age at diagnosis (range), years	62 (18-92)	61 (18-91)
Male	1,770 (58%)	771 (56%)
Race: Caucasian	2,973 (98%)	1339 (98%)
ECOG performance status:		
Missing	12	3
<2	2,894 (95%)	1319 (96%)
≥2	154 (5%)	49 (4%)
Co-morbidity score*:		
Missing	612 (20%)	190 (14%)
0	1962 (64%)	951 (69%)
≥1	486 (16%)	230 (17%)
BMI:		
Missing	72	26
<18.5	18 (1%)	8 (1%)
18.5-24.9	868 (29%)	384 (28%)
25.0-29.9	1202 (40%)	533 (40%)
30.0-34.9	579 (19%)	277 (21%)
>/=35	318 (11%)	143 (11%)
Stage:		
Missing	48	18
Rai 0	422 (14%)	211 (16%)
Rai I-II	318 (11%)	147 (11%)
Rai III-IV	38 (1%)	15 (1%)
Ann Arbor I-II	854 (28%)	387 (29%)
Ann Arbor III-IV	1380 (46%)	593 (44%)
B-symptoms:		
Missing	207	105
Yes	408 (14%)	159 (12%)
No	2,445 (86%)	1107 (87%)
Histology:		
Unclassified	40	15
Aggressive[ε]	1131 (37%)	462 (34%)
Indolent[γ]	1889 (62%)	894 (65%)

* MER co-morbidity score components (1 point each): other cancer diagnosis within 3 years of lymphoma diagnosis (except non-melanoma skin cancer), coronary artery disease, congestive heart failure, diabetes, hip fracture, hepatitis, autoimmune disease, and elevated creatinine. Missing co-morbidity score was used as a category for adjustment of Cox models.

ε Aggressive histologies: Diffuse large B-cell (DLBCL), Follicular (FL) grade 3, Burkitt, primary CNS, PTLD, high grade B-cell not otherwise specified, mediastinal B-cell, classical Hodgkin, peripheral T cell, angioimmunoblastic T cell, anaplastic large cell systemic, extra nodal NK/T cell nasal, enteropathy type T cell, Sézary syndrome, Precursor T/B lymphoblastic.

ϒIndolent histologies: Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL), Follicular grade 1 and 2, marginal zone, mantle cell, low grade lymphoma not otherwise specified, lymphoplasmacytic, mycosis fungoides, primary cutaneous B-cell, cutaneous T-cell, anaplastic large cell, large granular T-cell.

Table 2: Baseline Characteristics of Patients Evaluable vs. Not Evaluable

	Baseline			FU3		
	Evaluable for mLSI N= 3060	**Not evaluable for mLSI N=1027**	**p-value**	**Evaluable for LSI N= 1371**	**Not evaluable for LSI N= 1321**	**p-value**
Median age at diagnosis (range), years	62 (18-92)	61 (18-90)	0.06	61 (18-91)	61 (18-92)	0.28
Male	1770 (58%)	669 (65%)	**<0.001**	771 (56%)	764 (58%)	0.40
ECOG performance status:			**<0.001**			
Missing	12	13		3	4	0.32
<2	2894 (95%)	926 (90%)		1319 (96%)	1260 (96%)	
≥2	154 (5%)	88 (9%)		49 (4%)	57 (4%)	
Co-morbidity score*:			**<0.001**			**<0.001**
Missing	612 (20%)	317 (31%)		190 (14%)	347 (26%)	
0	1962 (64%)	549 (54%)		951 (69%)	789 (60%)	
≥1	486 (16%)	161 (16%)		230 (17%)	185 (14%)	
BMI:			**<0.001**			0.79
Missing	69 (2%)	33 (3%)		26 (2%)	29 (2%)	
<18.5	18 (1%)	15 (2%)		8 (1%)	8 (1%)	
18.5-24.9	870 (28%)	258 (25%)		384 (28%)	388 (29%)	
25.0-29.9	1203 (39%)	360 (35%)		533 (40%)	513 (39%)	
30.0-34.9	581 (19%)	226 (22%)		277 (20%)	239 (18%)	
>/=35	319 (10%)	135 (13%)		143 (10%)	144 (11%)	
Stage:			0.06			0.82
Missing	48 (2%)	31 (3%)		18 (1%)	21 (2%)	
Ann Arbor I-II	854 (28%)	280 (27%)		387 (28%)	397 (30%)	
Ann Arbor III-IV	1380 (45%)	469 (46%)		593 (43%)	543 (41%)	
Rai 0	422 (14%)	131 (13%)		211 (15%)	198 (15%)	
Rai I-II	318 (10%)	99 (10%)		147 (11%)	145 (11%)	
Rai III-IV	38 (1%)	17 (2%)		15 (1%)	17 (1%)	
B-symptoms:			0.10			0.24
Missing	207 (7%)	72 (7%)		105 (7%)	80 (6%)	
Yes	408 (13%)	164 (16%)		159 (12%)	163 (12%)	
No	2445 (80%)	791 (77%)		1107 (81%)	1078 (87%)	
Histology:			**<0.001**			0.99
Unclassified	40 (1%)	23 (2%)		15 (1%)	14 (1%)	
Aggressive[ε]	1131 (37%)	453 (44%)		462 (28%)	448 (29%)	
Indolent[γ]	1889 (62%)	551 (54%)		894 (62%)	859 (60%)	

* MER co-morbidity score components (1 point each): other cancer diagnosis within 3 years of lymphoma diagnosis (except non-melanoma skin cancer), coronary artery

disease, congestive heart failure, diabetes, hip fracture, hepatitis, autoimmune disease, and elevated creatinine.

[ε] Aggressive histologies: DLBCL, Follicular grade 3, Burkitt, primary CNS, PTLD, high grade B-cell not otherwise specified, mediastinal B-cell, classical Hodgkin, peripheral T cell, angioimmunoblastic T cell, anaplastic large cell systemic, extra nodal NK/T cell nasal, enteropathy type T cell, Sezary syndrome, Precursor T/B lymphoblastic.

[ϒ]Indolent histologies: CLL/SLL, Follicular grade 1 and 2, marginal zone, mantle cell, low grade lymphoma not otherwise specified, lymphoplasmacytic, mycosis fungoides, primary cutaneous B-cell, cutaneous T-cell, anaplastic large cell, large granular T-cell.

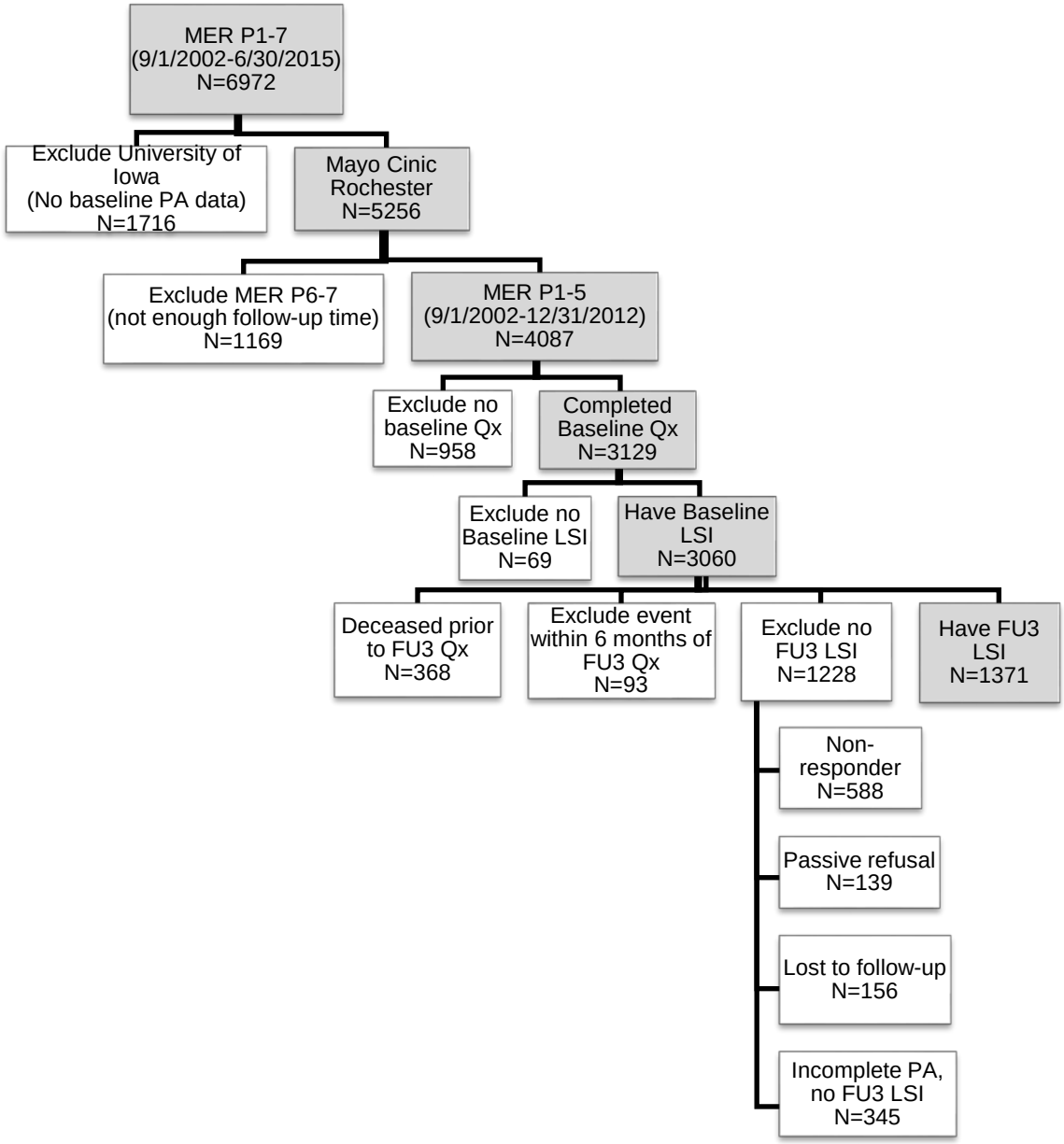
Table 3: Baseline Characteristics of Patients Meeting (active) versus not meeting (insufficiently active) American Cancer Society exercise guideline recommendations

	Baseline mLSI			**3-year follow-up LSI**		
	Active N=1392	**Insufficiently Active N=1668**	**p-value**	**Active N=516**	**Insufficiently active N=855**	**p-value**
Baseline mLSI, median (IQR)	45 (37-57)	15 (6-23.5)	**<0.001**	37 (23-51)	23.5 (9-38.5)	**<0.001**
FU3 LSI, median(IQR)				43 (39-57)	15 (6-20)	**<0.001**
Age in years, median (range)	62 (18-92)	62 (18-91)	0.98	57 (18-83)	62 (21-91)	**<0.001**
Male	800 (58%)	970 (58%)	0.70	322 (62%)	449 (52%)	**<0.001**
Baseline BMI, median (IQR)	26.8 (24.2-30.2)	27.8 (24.8-31.7)	**<0.001**	26.6 (17.4-60.4)	27.8 (24.9-32.2)	**<0.001**
Baseline ECOG performance status <2	1331 (96%)	1563 (94%)	0.06	501 (97%)	818 (96%)	0.23
Co-morbidity score ≥1	217 (16%)	269 (16%)	0.42	82 (16%)	148 (17%)	**0.034**
Stage III-IV	651 (47%)	767 (46%)	0.96	219 (42%)	389 (46%)	0.51
B-symptoms present	166 (12%)	242 (15%)	0.08	63 (12%)	96 (11%)	0.47
Aggressive Histology	512 (37%)	619 (37%)	0.57	180 (35%)	282 (33%)	**0.039**

Table 4 – Baseline Characteristics of Feasibility Study PA intervention in ASCT patients

Baseline Char	**Overall (N=10)**
Age (Years, median)	62 (range 40-70)
Female	3 (30%)
Caucasian	5 (50%)
African American	5 (50%)
Disease Subtype	
Non-Hodgkin Lymphoma	4 (40%)
Multiple Myeloma	6 (60%)
Conditioning Regimen	
Melphalan	6 (60%)
BEAM or Bu/Cy/VP-16	4(40%)

Figure 1. CONSORT diagram



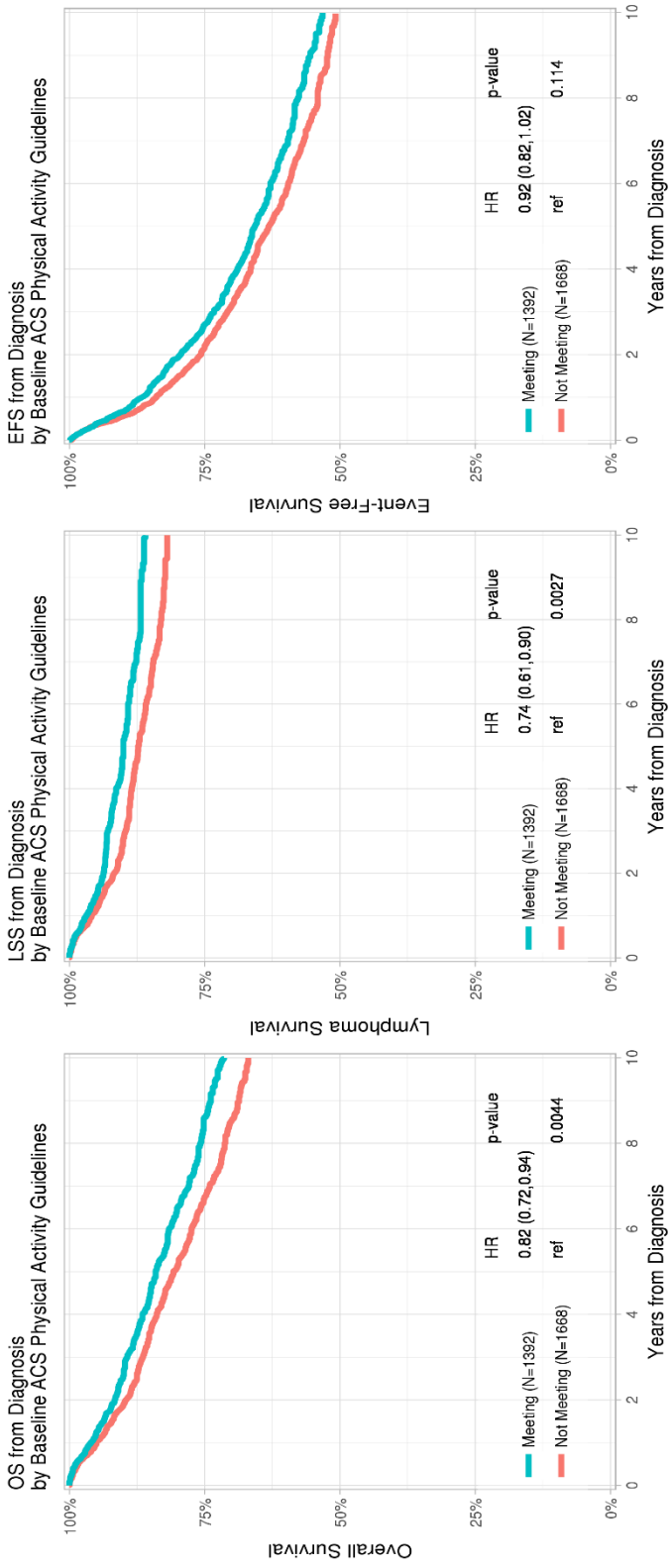


Figure 2a: Kaplan-Meier plots of Overall, Lymphoma-specific and Event-free survival by baseline mLSI meeting (active) versus not meeting (insufficiently active) the American Cancer Society physical activity guideline.

*HRs adjusted for age, sex, baseline BMI and comorbidity score

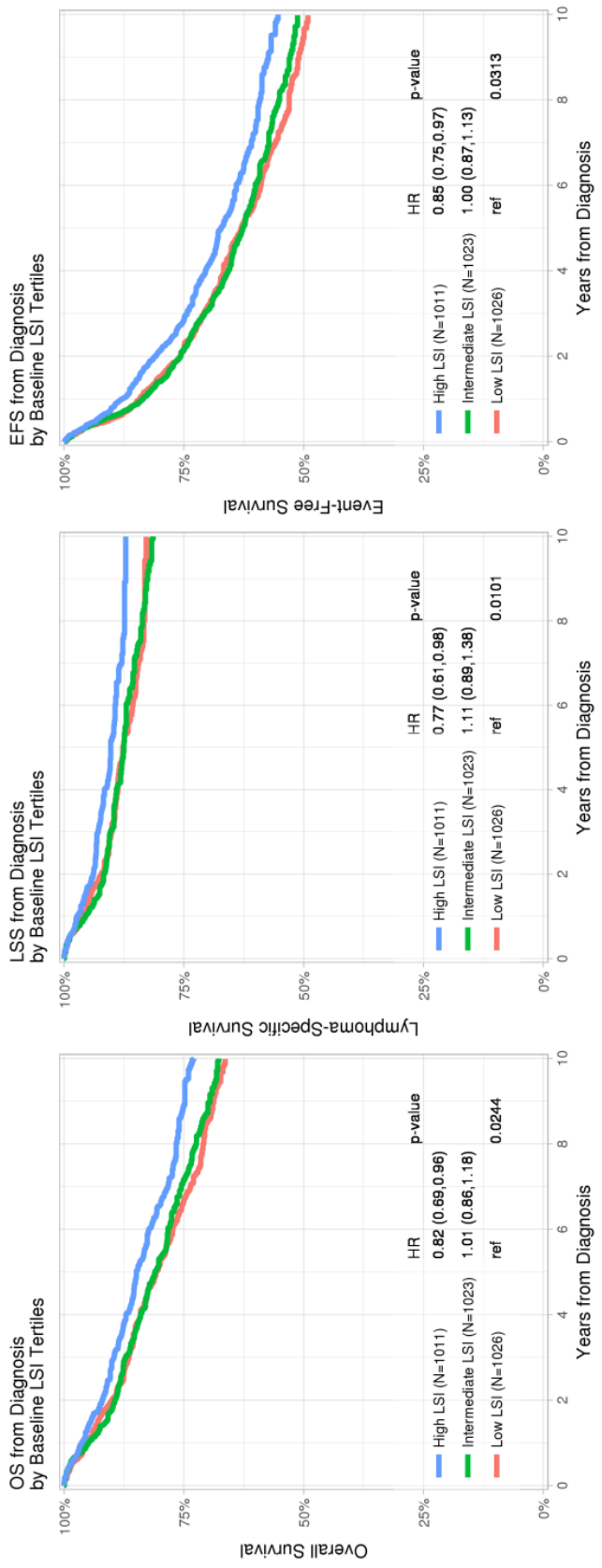


Figure 2b. Kaplan Meier survival curves of OS, LSS and EFS by mLSI tertiles at baseline

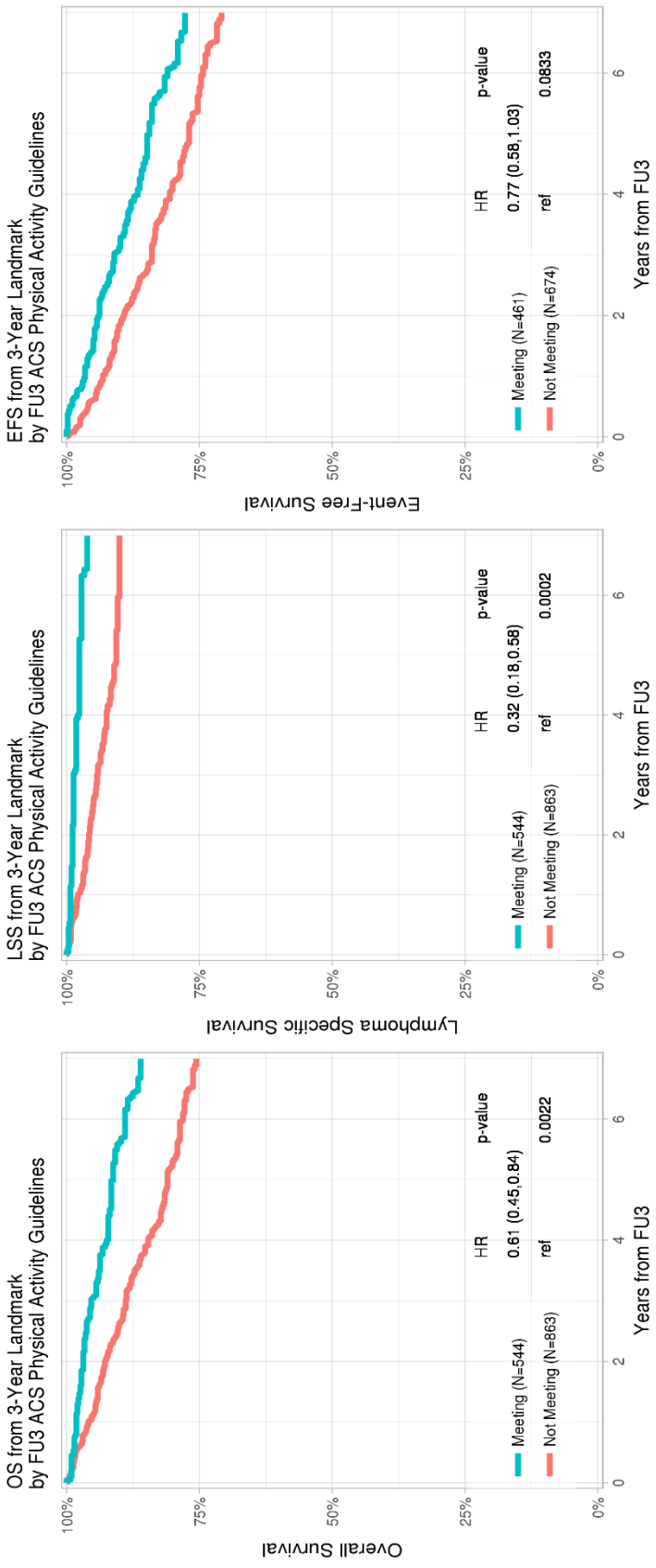


Figure 3a: Kaplan-Meier plots of Overall, Lymphoma-specific and Event-free survival by FU3 mLSI meeting (active) versus not meeting (insufficiently active) the American Cancer Society physical activity guideline

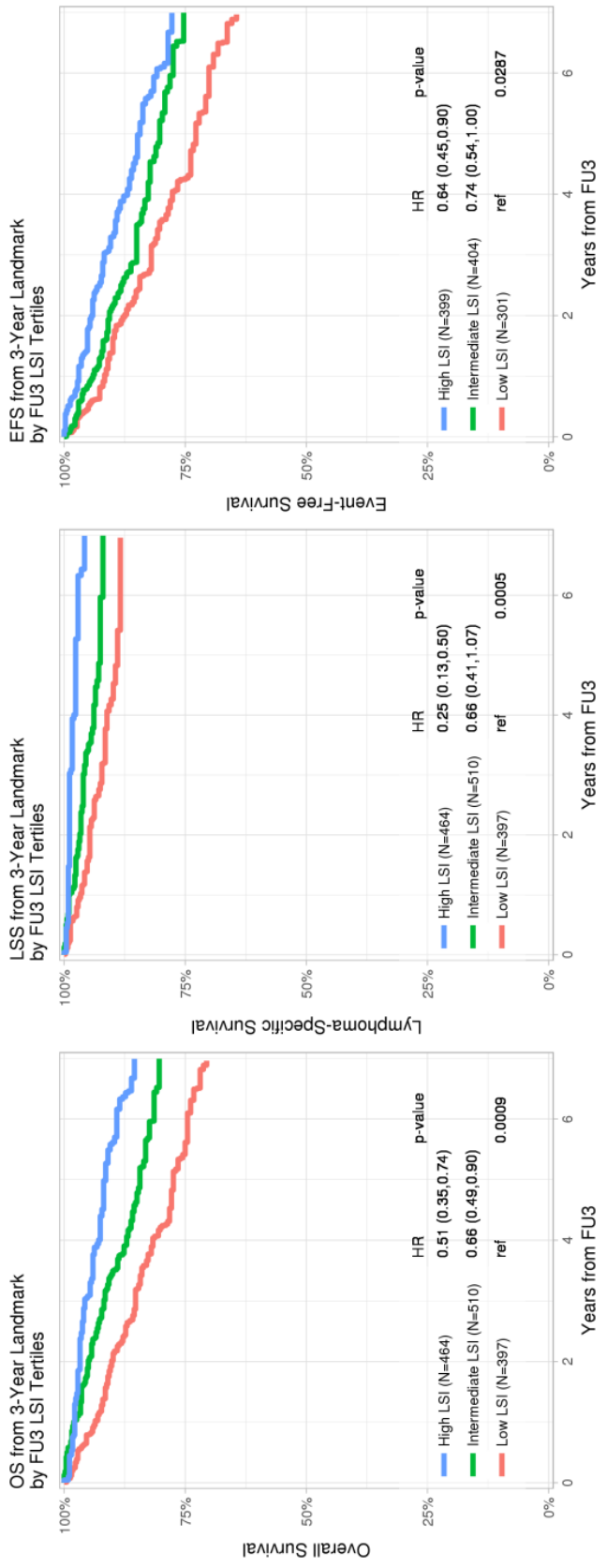


Figure 3b. Kaplan Meier survival curves of OS, LSS and EFS by mLSI tertiles at FU3

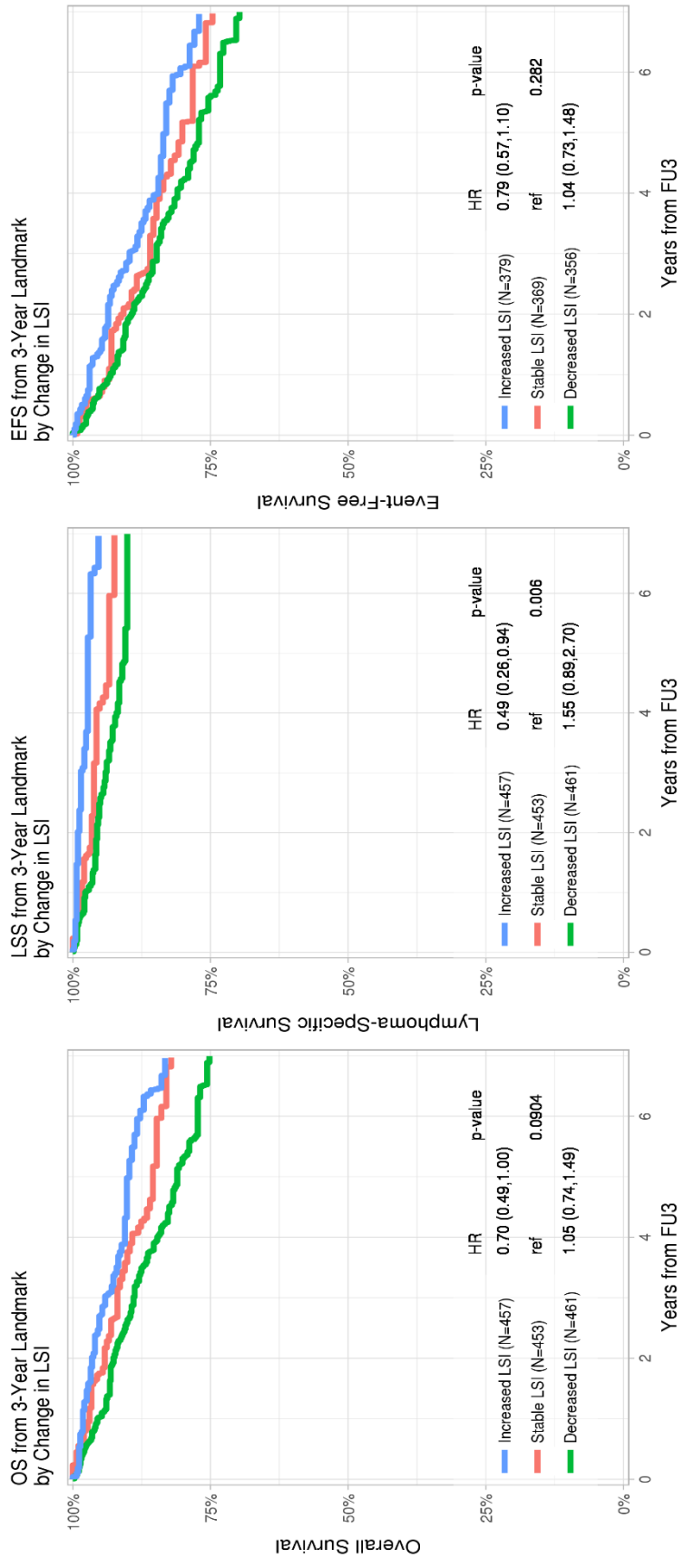


Figure 4a: Kaplan-Meier plots of Overall, Lymphoma-specific and Event-free survival by change in mLSI from baseline to FU3

*HRs adjusted for age, sex, baseline BMI, comorbidity score and baseline mLSI

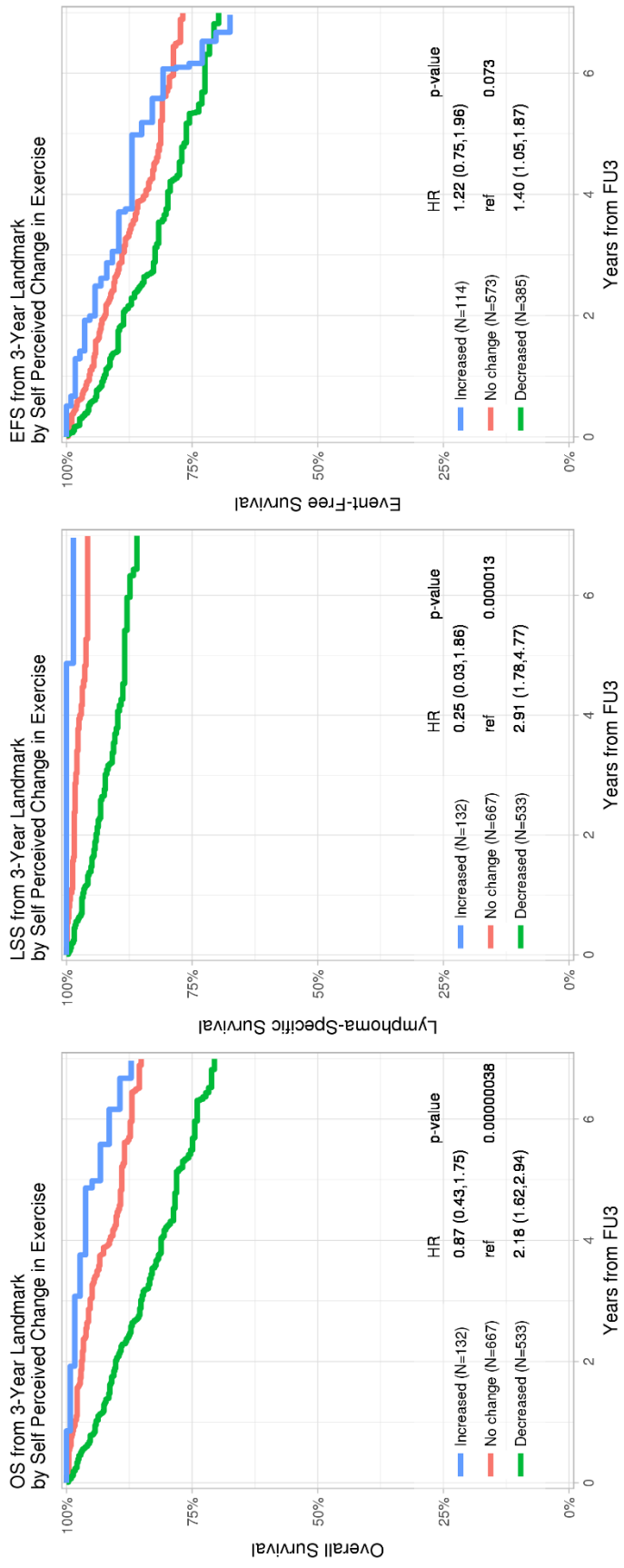
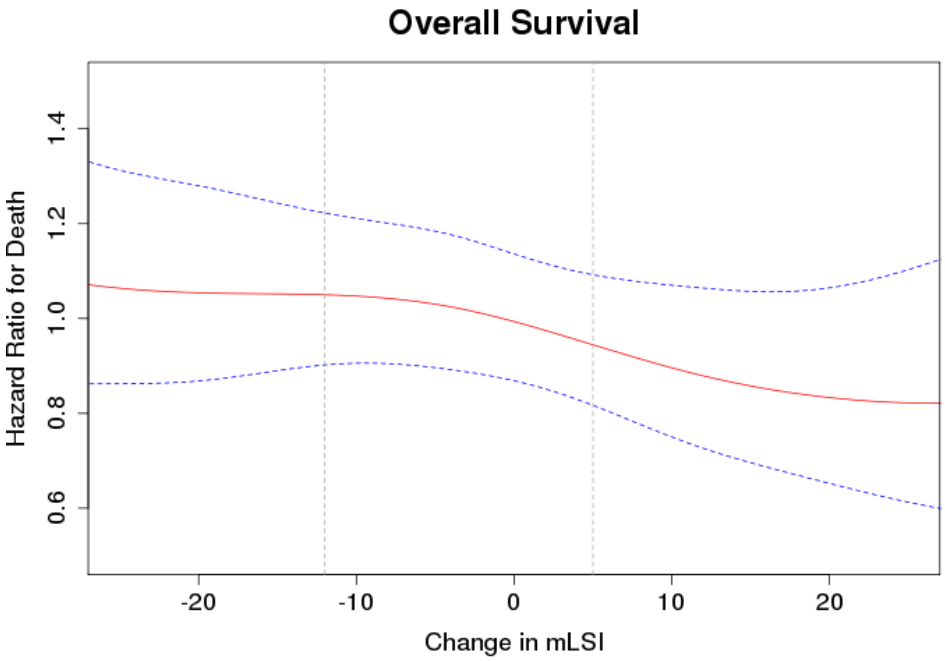
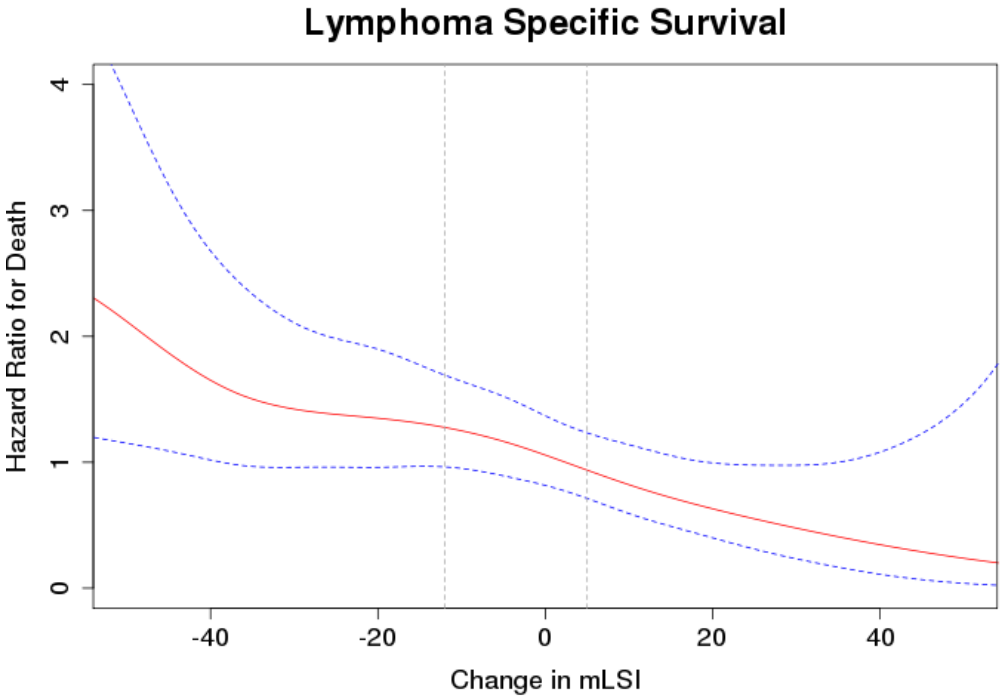


Figure 4b: Kaplan-Meier plots of Overall, Lymphoma-specific and Event-free survival by self-perceived change in physical activity from baseline to FU3

Figure 5. Spline plots of change in mLSI with a) Overall survival b) Lymphoma-specific survival





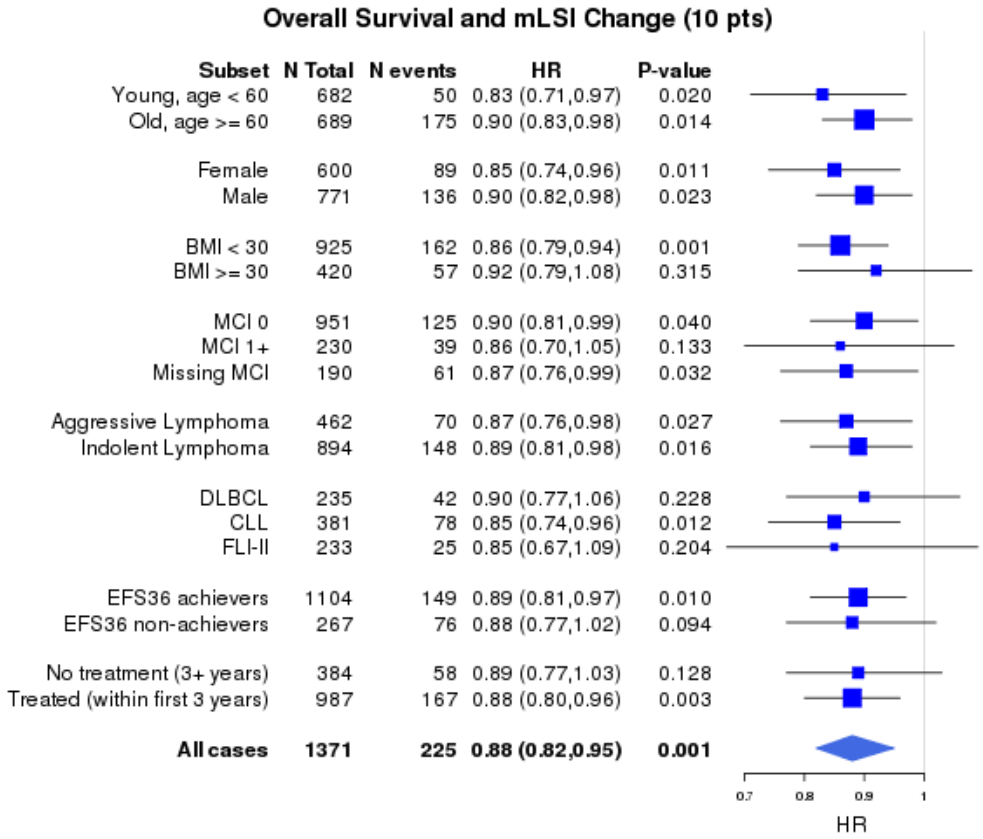


Figure 6a: Forest plot of subgroup analyses of association of continuous change in mLSI (per 10-point change) with Overall survival

*HRs adjusted for age, sex, baseline BMI, co-morbidity score and baseline mLSI

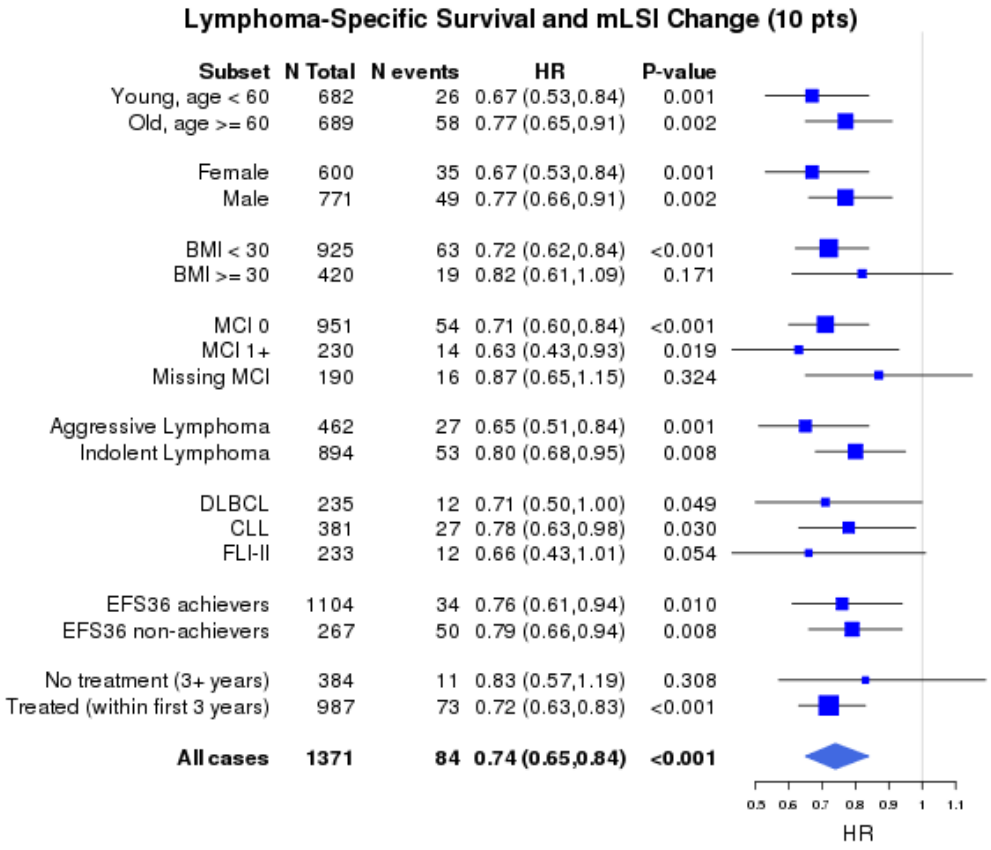


Figure 6b: Forest plot of subgroup analyses of association of continuous change in mLSI (per 10-point change) with Lymphoma-specific survival

*HRs adjusted for age, sex, baseline BMI, co-morbidity score and baseline mLSI

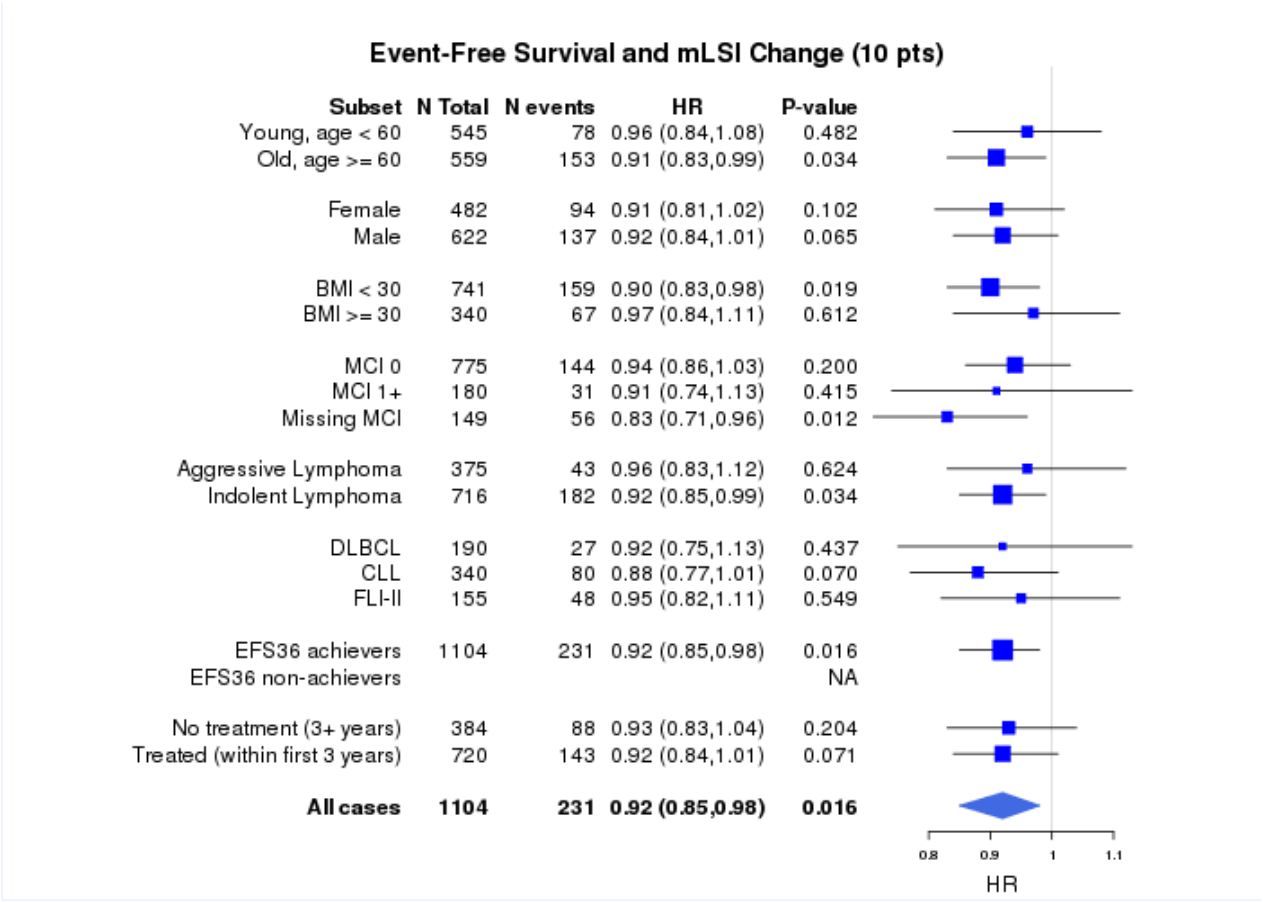


Figure 6c: Forest plot of subgroup analyses of association of continuous change in mLSI (per 10-point change) with Event-free survival

*HRs adjusted for age, sex, baseline BMI, co-morbidity score and baseline mLSI

Figure 7. Individual Workout Heart rate data from Apple Watch