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## Pediatric lymphoma patients in Malawi present with poor health-related quality of life at diagnosis and improve throughout treatment and follow-up across all Pediatric PROMIS-25 domains

Grace K. Ellis<sup>1</sup>, Hutton Chapman<sup>2</sup>, Agness Manda<sup>1</sup>, Ande Salima<sup>1</sup>, Salama Itimu<sup>1,3</sup>, Grace Banda<sup>1</sup>, Ryan Seguin<sup>1</sup>, Geoffrey Manda<sup>3</sup>, Mercy Butia<sup>3</sup>, Minke Huibers<sup>3,4</sup>, Nmazuo Ozuah<sup>3,4</sup>, Alyssa Tilly<sup>2</sup>, Angela M. Stover<sup>2</sup>, Ethan Basch<sup>2</sup>, Satish Gopal<sup>1,2</sup>, Bryce B. Reeve<sup>5</sup>, Katherine D. Westmoreland<sup>1,2</sup>

<sup>1</sup>UNC Project-Malawi

<sup>2</sup>University of North Carolina at Chapel Hill

<sup>3</sup>Texas Children's Cancer and Hematology Centers, Global Hematology-Oncology Pediatric Excellence (HOPE) Program

<sup>4</sup>Baylor College of Medicine

<sup>5</sup>Duke University School of Medicine

### Abstract

**Background:** Patient-reported outcomes (PROs) that assess health-related quality of life (HRQoL) are increasingly important components of cancer care and research that are infrequently used in sub-Saharan Africa (SSA).

**Methods:** We administered the Chichewa Pediatric Patient-Reported Outcome Measurement Information System Pediatric (PROMIS)-25 at diagnosis, active treatment, and follow-up among pediatric lymphoma patients in Lilongwe, Malawi. Mean scores were calculated for the six PROMIS-25 HRQoL domains (Mobility, Anxiety, Depressive Symptoms, Fatigue, Peer Relationships, Pain Interference). Differences in HRQoL throughout treatment were compared using the minimally important difference (MID) and an ANOVA analysis. Kaplan-Meier survival estimates and Cox hazard ratios for mortality are reported.

**Results:** Seventy-five children completed PROMIS-25 surveys at diagnosis, 35(47%) during active treatment, and 24(32%) at follow-up. The majority of patients died (n= 37, 49%) or were lost-to-follow-up (n=6, 8%). Most (n=51, 68%) were male, median age was 10 (IQR 8–12), 48/73

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**Corresponding Author:** Dr. Kate Westmoreland, kawestmo@email.unc.edu, US Mobile: +1 (336) 414-8811, Malawi Mobile: +265 996 466 771, Fax: +1 (919) 966-7629, USA Address: 170 Manning Drive, Campus Box 7236, Chapel Hill, NC 27599, Malawi Address: UNC Project Malawi, Private Bag 104A, Lilongwe, Malawi.

**Author Contributions:** KDW designed the study and provided oversight and mentorship throughout the project. GKE and KDW analyzed and interpreted the data with assistance from BBR. GKE and HC wrote the first draft of the paper and KDW performed significant edits and revisions. SG, BBR, NO, MH, AMS, AT, GM, and EB provided edits and comments. AS, SI, and GB conducted PROMIS surveys with participants. KDW, NO, MH, GM, and MB provided clinical care. RS provided project setup and management.

**Availability of Data:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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(66%) presented with advanced Stage III/IV, 61(81%) were diagnosed with Burkitt lymphoma and 14(19%) Hodgkin lymphoma. At diagnosis, HRQoL was poor across all domains, except for Peer Relationships. Improvements in HRQoL during active treatment and follow-up exceeded the MID. On exploratory analysis, fair-poor PROMIS Mobility<40 and severe Pain Intensity=10 at diagnosis were associated with increased mortality risk and worse survival, but not statistically significant.

**Conclusions:** Pediatric lymphoma patients in Malawi present with poor HRQoL that improves throughout treatment and survivorship. Baseline PROMIS scores may provide important prognostic information. PROs offer an opportunity to include patient voices and prioritize holistic patient-centered care in low-resource settings.

### Keywords

health-related quality of life; patient-reported outcomes; pediatric oncology; sub-Saharan Africa; Burkitt lymphoma; Hodgkin Lymphoma

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### Introduction

Children and adolescents with cancer in low- and middle-income countries (LMICs) have poor outcomes and improving their care is a significant global health priority.<sup>1</sup> Five-year survival rates for children with cancer in high-income countries (HICs) are approximately 80%, but are estimated to be only 30% in LMICs.<sup>1-4</sup> In sub-Saharan Africa (SSA), pediatric cancer experiences are often marked by high rates of treatment failure, due to poor treatment access, high treatment abandonment, and high treatment-related mortality.<sup>1,2,4-6</sup> Additionally, palliative and supportive care capacity is limited for children with cancer in SSA.<sup>4</sup> Ongoing efforts in SSA to improve survival rates include numerous initiatives to identify and implement context-specific adaptations of standard HIC approaches.<sup>1,4,7-9</sup>

Patient-reported outcomes (PROs) offer an important opportunity to incorporate patients' voices and experiences in evidenced-based interventions across SSA. PROs have become a routine part of oncologic care in many HICs and measure how mental, physical, and social health-related quality of life (HRQoL) are affected by cancer diagnosis, treatment, and survivorship. PROs provide critical information to complement clinical assessments, monitor disease- and treatment-related adverse events, and guide symptom management.<sup>10-16</sup> Standardized instruments for self-reporting HRQoL domains were created by the United States National Institutes of Health Patient-Reported Outcomes Measurement Information System® (PROMIS®) initiative. Patient-reported HRQoL measures are a more sensitive measure of functional status than clinician-reported assessments, and incorporating PROs into cancer treatment can improve outcomes and survival.<sup>14,16</sup> Despite their utility and frequent use in HICs, PROs are rarely used in SSA.

We believe that patient-reported HRQoL would have particular utility in Malawi, where curative-intent treatments are often limited, advanced stage diagnoses are common, the risk for treatment-related toxicity is high, and supportive care infrastructure is often insufficient. The Pediatric PROMIS measures have been validated among pediatric and adolescent cancer patients in the United States.<sup>17-19</sup> In prior work, our group has translated and validated the Pediatric PROMIS-25 questionnaire into Chichewa, Malawi's national language, which

was the first Pediatric PROMIS translation and validation into a Bantu language for use in SSA.<sup>20</sup> The Pediatric PROMIS-25 is a short form composed of 25 questions assessing mental, physical, and social components of HRQoL. We measured HRQoL among pediatric lymphoma patients using the Chichewa Pediatric PROMIS-25 instrument at diagnosis in our initial cohort of 54 participants, and found our patients had poor HRQoL at diagnosis compared to the PROMIS pediatric reference population of children with cancer in the United States.<sup>20</sup> We extend our prior observations to expand on the baseline cohort and to describe longitudinal changes in HRQoL from diagnosis through active treatment and follow-up. We aimed to longitudinally measure HRQoL among pediatric lymphoma patients in Malawi to determine change throughout cancer treatment and association with survival.

## Methods

### Setting

Kamuzu Central Hospital (KCH) is a national teaching hospital in Lilongwe, the capital of Malawi, and is one of two hospitals in the country that provides pediatric cancer treatment. KCH receives cancer referrals from the northern and central regions, serving half of the estimated 18 million people in Malawi. The KCH pediatric cancer ward consists of 24–30 beds and is staffed by the Texas Children’s Cancer and Hematology Centers Global Hematology Oncology Pediatric Excellence (HOPE)-Malawi program. Collaboration with the University of North Carolina (UNC) Project-Malawi provides additional support including a pediatric hematologist-oncologist, clinical research staff, comprehensive diagnostic services through the KCH-UNC Pathology Laboratory.<sup>21</sup>

### Participants

We implemented the Chichewa Pediatric PROMIS-25 measure to assess HRQoL of patients aged 5–18 years with lymphoma who were diagnosed at KCH between June 2016 and September 2018. All patients were enrolled in the KCH Lymphoma study, an observational prospective cohort study that began in 2013, and were followed for two years after treatment completion.<sup>2,22,23</sup>

Patients were staged using physical examination, chest radiography, abdominal ultrasound, unilateral bone marrow biopsy, and cerebrospinal fluid cytology, as previously described.<sup>2,22</sup> The clinician-reported Lansky performance score (LPS), routinely used in cancer clinical trials for children <16 years, was obtained at diagnosis.<sup>24</sup> All lymphoma diagnoses were pathologically confirmed using tissue biopsies and immunohistochemistry and were interpreted during real-time weekly telepathology conferences.<sup>21</sup>

Standard chemotherapy regimens were administered and evolved during the study period, and as previously described: Hodgkin lymphoma patients received ABVE-PC regimen (doxorubicin, bleomycin, vincristine, etoposide – prednisone, cyclophosphamide); low-risk Burkitt Lymphoma patients received COMP (cyclophosphamide, vincristine, methotrexate, and prednisone); and high-risk Burkitt lymphoma initially received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and more recently

received modified COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate).<sup>2,22,23</sup> Radiotherapy is not available in Malawi.

### Study Design and Procedures

We previously reported Chichewa translation and validation of the Pediatric PROMIS-25 survey.<sup>20</sup> We also previously reported the HRQoL of the initial 54 participants at the time of diagnosis,<sup>20</sup> and this analysis expands on that data by including an additional 21 participants for a total of 75 participants. The Chichewa Pediatric PROMIS-25 short form was administered at diagnosis (at the time of study enrollment prior to initiation of chemotherapy), during active treatment (within 30 days of last receiving chemotherapy, typically on day 0 of the next scheduled chemotherapy) and at follow-up (patients returning for a scheduled follow-up clinic visit between 6 months and 2 years after treatment completion). If patients progressed or relapsed and were receiving second line chemotherapy at the time of the PROMIS-25 administration, then this was categorized as active treatment. If they progressed or relapsed, but were on palliative care and not receiving chemotherapy, then this was categorized as follow-up.

For children 8 years old, the Chichewa Pediatric PROMIS-25 was administered directly to the child. The parent-proxy version was used for children 5–7 years old, cognitively impaired, or too ill to complete the questionnaire themselves.<sup>20,25–27</sup> Questionnaires were read aloud to the child/parent via a non-provider research assistant trained in survey methodology and recorded on a paper form. This modification was deemed necessary in our setting due to low literacy in the target population. The parent/child had an answer choice sheet in front of them so they could point to choose their answers, a method previously used by our team in Malawi and validated for other PRO-HRQoL instruments targeting young children.<sup>20,28</sup>

After treatment completion, some patients were lost to follow-up (LTFU) from clinic but reachable by phone. We encouraged these patients to return to clinic in person, and when unsuccessful we administered the PROMIS-25 survey via phone. Prior work has demonstrated that in person and telephone administration of English Pediatric PROMIS measure does not affect validity, although this has not been demonstrated for the Chichewa version.<sup>29,30</sup>

### Analysis

The Pediatric PROMIS-25 measured six HRQoL domains (Mobility, Anxiety, Depressive Symptoms, Fatigue, Peer Relationships, Pain Interference) by asking four questions per domain using a five-point Likert scale (e.g., *never, almost never, sometimes, often, almost always*; or, *with no trouble, with a little trouble, with some trouble, with a lot of trouble, not able to*). Additionally, a single-item PROMIS Pain Intensity item was measured on a scale of 0 to 10. All items have a 7-day recall period.

Within each domain, a raw score was calculated as the sum of the answers to the four question items. Raw scores were transposed to standardized domain T-scores using tables provided by the PROMIS scoring manual, with a mean of 50 and standard deviation of 10.<sup>31</sup> The PROMIS standardized T-score is composed from a mixed calibration sample of United

States children in good health and children with a wide range of chronic conditions.<sup>32</sup> Higher PROMIS scores for Mobility and Peer Relationships reflect better functioning and relationships, with scores < 40 (1 standard deviation (SD) below the mean) considered fair to poor.<sup>33</sup> Higher symptom scores reflect worse symptom experiences (Anxiety, Depressive Symptoms, Fatigue, Pain Interference), with scores > 55 (1 SD above the mean) indicating moderate to severe symptom burden.<sup>33</sup>

Differences between diagnosis, active treatment, and follow-up domain mean T-scores were compared to published minimally important difference (MID) estimates of 2–3 points, and also analyzed using an ANOVA test.<sup>34</sup> For sensitivity analyses, parent proxy-reported surveys were removed, as it has been demonstrated that caregivers consistently overestimate symptoms and underestimate function relative to child self-reports.<sup>35</sup> In a sub-analysis, we report the individual trajectories of the PROMIS-25 HRQoL domains scores for only the patients who completed a PROMIS survey at all 3 timepoints (diagnosis, active treatment, and follow-up), which allows interpretation of longitudinal HRQoL trends in our cohort without potential effects of survivor bias.

Cohort characteristics were summarized using simple descriptive statistics. Patients were followed from enrollment until death, LTFU, or administrative censoring on January 31, 2020. We conducted an exploratory analysis to compare outcomes among patients for those with poor versus adequate HRQoL domain scores at diagnosis. Kaplan-Meier methods were used to estimate overall survival and risk factors for mortality were assessed using univariate and multivariate Cox proportional-hazards regression analysis to estimate hazard ratios (HR) of quantitative predictor variables. Risk factors with a p-value <0.20 on univariate analysis were included in the multivariate Cox proportional-hazards regression analysis. LTFU events were analyzed as death in our survival analyses. Analyses were conducted using R 3.5.2 (New York, New York) and survival analysis were conducted using STATA version 13.1 (College Station, TX).

## Ethical Approval

All participants gave written informed consent by their legal guardian, and children 7 years also provided pediatric assent. This study was approved by the UNC Institutional Review Board and Malawi National Health Sciences Research Committee.

## Results

Seventy-five children had Chichewa Pediatric PROMIS-25 surveys administered at diagnosis prior to initiation of chemotherapy, 35 (47%) during active treatment, and 24 (32%) at follow-up (Figure 1, Table 2). Median age was 10 years (Interquartile range (IQR) 8–12) and 51 (68%) were male. Sixty (80%) patients were diagnosed with Burkitt lymphoma and 15 (20%) with Hodgkin lymphoma. Most patients presented with advanced stage III/IV disease (n=48/73, 66%), poor performance status with a LPS of 70 (n=50/71, 70%), and moderate-to-severe acute malnutrition (n=54/73, 74%). Median lactate dehydrogenase (LDH) was 555 IU/L (IQR 378–895), with 30/61 (49%) > 2x LDH upper limit of normal for their age. (Table 1)

Of the 75 surveys at diagnosis (Figure 1), patients reported poor HRQoL, with low Mobility and high Anxiety, Depressive Symptoms, Fatigue, and Pain Interference mean domain scores (Table 1, Table 2, Figure 3). Patients also presented with high pain intensity, with 32 (43%) reporting the maximum Pain Intensity of 10 on a scale of 0 to 10 at diagnosis (Table 1, Table 2). Peer Relationships were strong at diagnosis (Table 1, Table 2).

Of the 35 surveys during active treatment (Figure 1), the median time of survey administration was 113 days (IQR 61–210) after diagnosis (Table 2). Mean HRQoL domain scores significantly improved in all domains ( $p < 0.001$ ) (Table 2), and differences between diagnosis and active treatment domain scores exceeded accepted MID thresholds (Table 2, Figure 3). Pain Intensity decreased from a median of 9 (IQR 4–10) at diagnosis to a median of 1 (IQR 1–1) during active treatment (Table 2).

Of the 24 follow-up surveys (Figure 1), two patients (14%) had relapsed lymphoma and were receiving palliative care during follow-up. Median follow-up time was 720 days (IQR 486–1014) since diagnosis (Table 2). All mean HRQoL domains showed continued improvement from diagnosis to active treatment to follow-up timepoints that surpassed the MID (Table 2, Figure 3). Notably, median Pain Intensity score was 0 (IQR 0–0) at follow-up (Table 2).

Of 134 total Pediatric PROMIS-25 surveys administered across the 3 time points, 100/134 (75%) were to patients and 34/134 (25%) were to parents. Of the 34 surveys completed by parent proxy, 14/34 (41%) were for children younger than 8 years, 20/34 (59%) for older children who were too ill to complete the survey on their own. Improvements in HRQoL remained when proxy reports were removed from the analysis (Supplemental Table 1). Almost all surveys (125/134, 93%) were conducted in person, aside from 9/134 (7%) follow-up surveys administered over the phone.

Of the 75 patients enrolled at diagnosis, 37 (49%) of patients died—34/37 (92%) Burkitt, 3/37 (8%) Hodgkin—and 6 (8%) were LTFU (Figure 1). The median follow-up time was 11.8 months for the entire cohort and 25.3 months for those who survived. Kaplan-Meier overall survival was 49% (95% CI [37–59%]) at 1-year and 42% (95% CI [30–53%]) at 2-years. On exploratory analysis, statistically significant risk factors for increased mortality risk on univariate analysis include: diagnosis of Burkitt lymphoma (univariate Hazard ratio (HR) = 4.88, 95% CI [1.51–15.82],  $p = 0.008$ ), poor performance status with a LPS 70 (univariate HR = 2.75, 95% CI [2.75–6.25],  $p = 0.015$ ), and moderate-to-severe acute malnutrition (univariate HR 2.27, 95% CI [1.00–5.12],  $p = 0.049$ ); and only diagnosis of Burkitt lymphoma remained statistically significant on multivariate analysis (Table 1).

On exploratory analysis, we specifically focused on a patients' functional status at diagnosis as it relates to risk for mortality and survival outcomes. Patients with physician-reported poor performance status (LPS 70) also had a statistically significant worse 12-month overall survival compared to those with LPS > 70 (39%, 95% CI [26–52%] vs. 76%, 95% CI [51–89%],  $p = 0.012$ ) (Table 1, Figure 2A). In comparison, a poor patient-reported fair-poor PROMIS Mobility domain score (< 40) at diagnosis was also associated with increased mortality risk (univariate HR=2.40, 95% CI [0.86–6.74],  $p = 0.095$ ) and worse 12-month

overall survival compared to those with Mobility scores  $\geq 40$  (45%, 95% CI [33–57%] vs. 67%, 95% CI [34–86%],  $p=0.084$ ) (Table 1, Figure 2C). Likewise, patients with the highest patient-reported PROMIS Pain Intensity score of 10/10 at diagnosis also had increased mortality risk (univariate HR=1.71, 95% CI [0.93–3.11],  $p=0.081$ ) and worse 12-month overall survival compared to those with a Pain Intensity score  $< 10$  (36%, 95% CI [20–52%] vs. 58%, 95% CI [42–71%],  $p=0.078$ ) (Table 1, Figure 2B). Although clinically meaningful, both PROMIS Mobility and Pain Intensity risk factors were not statistically significant.

Domain score trajectories were plotted for the 17 patients who completed PROMIS surveys at all three time points (diagnosis, active treatment, and follow-up) to visualize individual changes in HRQoL throughout care (Figure 4). This sub-analysis allows interpretation of longitudinal HRQoL trends in our cohort without potential effects of survivor bias. Overall, HRQoL improvements were observed for most patients ( $n=15$ , 88%), with the exception of two patients (12%) who had relapsed disease and worse HRQoL at follow-up.

## Discussion

We report the first longitudinal assessment of HRQoL using PROs in SSA among pediatric cancer patients. We used the Chichewa Pediatric PROMIS-25 to serially measure HRQoL among pediatric lymphoma patients in Malawi. We found that pediatric lymphoma patients in Malawi present with poor HRQoL that improves throughout treatment and survivorship. Our experience highlights important disparities in pediatric cancer care experiences and suggests incorporating assessments of HRQoL via PROs in SSA generates clinically meaningful data to inform supportive care interventions, and may provide prognostic information.

Our cohort presented with overwhelmingly advanced disease, exemplified by late stage at diagnosis, high LDH, and poor performance status, which is common across SSA.<sup>2,36</sup> We have previously demonstrated that HRQoL at diagnosis is poorer among Malawian patients than the PROMIS reference population and similar pediatric oncology populations in the United States, likely reflecting more advanced disease.<sup>32</sup> In HICs, children with cancer are frequently diagnosed early in their disease course with no/minimal symptom burden and have preserved HRQoL.<sup>17,37</sup> In contrast, our patients reported poor HRQoL and extremely high pain intensity, with 32/75 (43%) of patients reporting a maximum 10/10 pain score at diagnosis. Pain medication is available in Malawi, but the extreme pain burden among our patients suggests their pain may not have been identified or adequately managed prior to referral and/or diagnosis. Efforts to educate providers on appropriate pain management in children and ensure reliable medication access, as well as outreach to facilitate early cancer diagnosis and referral are priorities.<sup>1,38–40</sup>

Patients reported significantly improved HRQoL during active treatment that far exceeded ( $>12$  points) the MID thresholds of 2–3 points, with the exception of peer relationships which improved by 3.3 points. These improvements likely reflect reduced tumor burden and improved symptom management during active treatment. HRQoL continued to improve after treatment completion and through follow-up. In contrast, children with cancer in HICs typically have no/ minimal symptom burden at diagnosis, and report decreased

HRQoL during cancer treatment due to therapy-related adverse effects, which then improves following treatment completion.<sup>17,37</sup>

One unique observation was that peer relationships were strong throughout all timepoints. Despite most patients having to travel long distances and being apart from their families and friends for weeks at a time during their treatment, patients in our cohort receive treatment in an open pediatric oncology ward and are able to develop strong friendships with other children undergoing similar experiences. The patients and their caregiver sleep together in the open ward, cook and eat together, and the children play together. In between treatment cycles, the families return home and remain socially connected in their home villages, where they live in close proximity with their neighbors, family, and friends, and continue to attend school. The preservation of peer relationships throughout cancer treatment in Malawi may also be common in other LMICs but is not observed among pediatric cancer patients in HIC. In HIC, children with cancer are typically treated in private rooms and with infection control restrictions, thus experiencing significant decreases in social HRQoL with poor peer relationship scores during treatment.<sup>17,18,20,41,42</sup>

We are sad to report that mortality in our cohort was high. Most of our patients died (37/75, 49%) or were LTFU (6/75, 8%), an indication of unverifiable death in our setting.<sup>43</sup> One-year overall survival was 49% (95% CI [37–59%]), which is consistent with historical and published survival rates for lymphoma across SSA, and is significantly worse than reported survival rates of >90% in HIC.<sup>2,22–23,43–47</sup> It was expected that a diagnosis of Burkitt lymphoma had the highest risk for mortality. In the parent KCH lymphoma cohort, we have reported a 29% 18-month overall survival for pediatric Burkitt lymphoma and a 61% 2-year overall survival for pediatric Hodgkin lymphoma in Malawi.<sup>2,23</sup> Given the high mortality and the challenges associated with cancer treatment in resource-poor health systems, appropriate risk stratification of patients is critical in SSA, where administering aggressive treatment to optimize survival must be weighed against toxicity risks for vulnerable children.

Giving a specific focus on functional status and outcomes, we found that poor LPS has consistently been identified as a risk factor for mortality in research from both LMICs and HICs.<sup>2,22,45,46,48</sup> Further, emerging data from HICs suggest PROs offer superior assessment of performance status when compared to traditional physician-reported measures.<sup>49</sup> We observed significantly increased mortality risk and worse survival in our cohort among patients with physician-reported poor performance status with a LPS  $\geq 70$  and patient-reported. In contrast, patient-reported moderate-severe PROMIS Mobility domain scores < 40 and severe Pain Intensity of 10/10 at diagnosis also increased risk of mortality and worse overall survival, but this trend was not statically significant in our exploratory analysis. Further evaluation of the potential prognostic utility of Pediatric PROMIS-25 in a larger patient cohort with adequate power is necessary to understand how PROs can assist with treatment risk stratification in SSA.

PROs are especially important in SSA, where providers are often over-worked, healthcare infrastructure/access is limited, and shared decision making between patients and providers is not the norm. Assessments of HRQoL via PROMIS can assist providers in quickly identifying and prioritizing patients for referral to ancillary, multidisciplinary providers, such

as physiotherapists and palliative/supportive care specialists. Further, PROMIS measures mental wellbeing, which is often overlooked in pediatric oncology despite being a significant problem, and can screen patients for anxiety and depression to facilitate referrals for psychosocial support.<sup>50</sup> In addition to generating clinically meaningful data, Pediatric PROMIS-25 surveys were feasible to administer at clinical visits while patients were receiving chemotherapy infusions or waiting to be seen by the provider.

Study strengths include prospective design, longitudinal data collection, and use of the first rigorously validated Bantu-language pediatric PRO instrument to assess HRQoL among pediatric cancer patients in SSA. Our data are limited by high mortality, which is comparable to other pediatric lymphoma studies across SSA, and LTFU, which is low compared to other studies in the region.<sup>2,22,44,51,52</sup> This may have introduced survivorship bias in observed HRQoL improvements during active treatment and follow-up. However, among the 17 patients who completed surveys at all three timepoints, we observed substantial improvements across all HRQoL domains, except for two patients with relapsed disease. An additional limitation is the use of parent-proxy reporting for some children (35/140, 25%), as parents tend to report worse HRQoL than children self-report.<sup>35</sup> However, our sensitivity analysis without parent proxy-reported surveys showed that HRQoL mean domain scores did not significantly differ. Finally, raw PROMIS-25 scores were transposed to T-scores based on the Pediatric PROMIS reference population of children in the United States. As PROMIS is increasingly translated and incorporated into care throughout the world, region-specific reference populations will facilitate better interpretation of patient HRQoL scores. In our future work, we are developing voice-enabled tablet-based software to administer PROMIS-25 surveys without an intermediary to allow for a truly patient-reported measure in our low-literacy patient population.

## Conclusion

Children with lymphoma in Malawi present with poor HRQoL at diagnosis that improves during active treatment and follow-up across all PROMIS-25 domains. The Chichewa Pediatric PROMIS-25 generates clinically meaningful data that can inform multidisciplinary supportive care interventions, and may provide useful prognostic information among pediatric cancer patients. The use of translated PROMIS-25 surveys in both research and routine clinical care includes patient voices in decision making, with a focus on mental, physical, and social HRQoL, and can strengthen holistic patient-centered oncology care across SSA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Abbreviations:**

<b>PROs</b>	patient-reported outcomes
<b>HRQoL</b>	health-related quality of life
<b>SSA</b>	sub-Saharan Africa
<b>PROMIS</b>	Patient-Reported Outcome Measurement Information System
<b>LMICs</b>	low- and middle-income countries
<b>HICs</b>	high-income countries
<b>KCH</b>	Kamuzu Central Hospital
<b>UNC</b>	University of North Carolina
<b>HOPE</b>	Hematology-Oncology Pediatric Excellence
<b>LPS</b>	Lansky performance score
<b>LTFU</b>	lost to follow-up
<b>MID</b>	minimally important difference
<b>LDH</b>	lactate dehydrogenase
<b>ULN</b>	upper limit of normal
<b>SD</b>	standard deviation
<b>IQR</b>	interquartile range

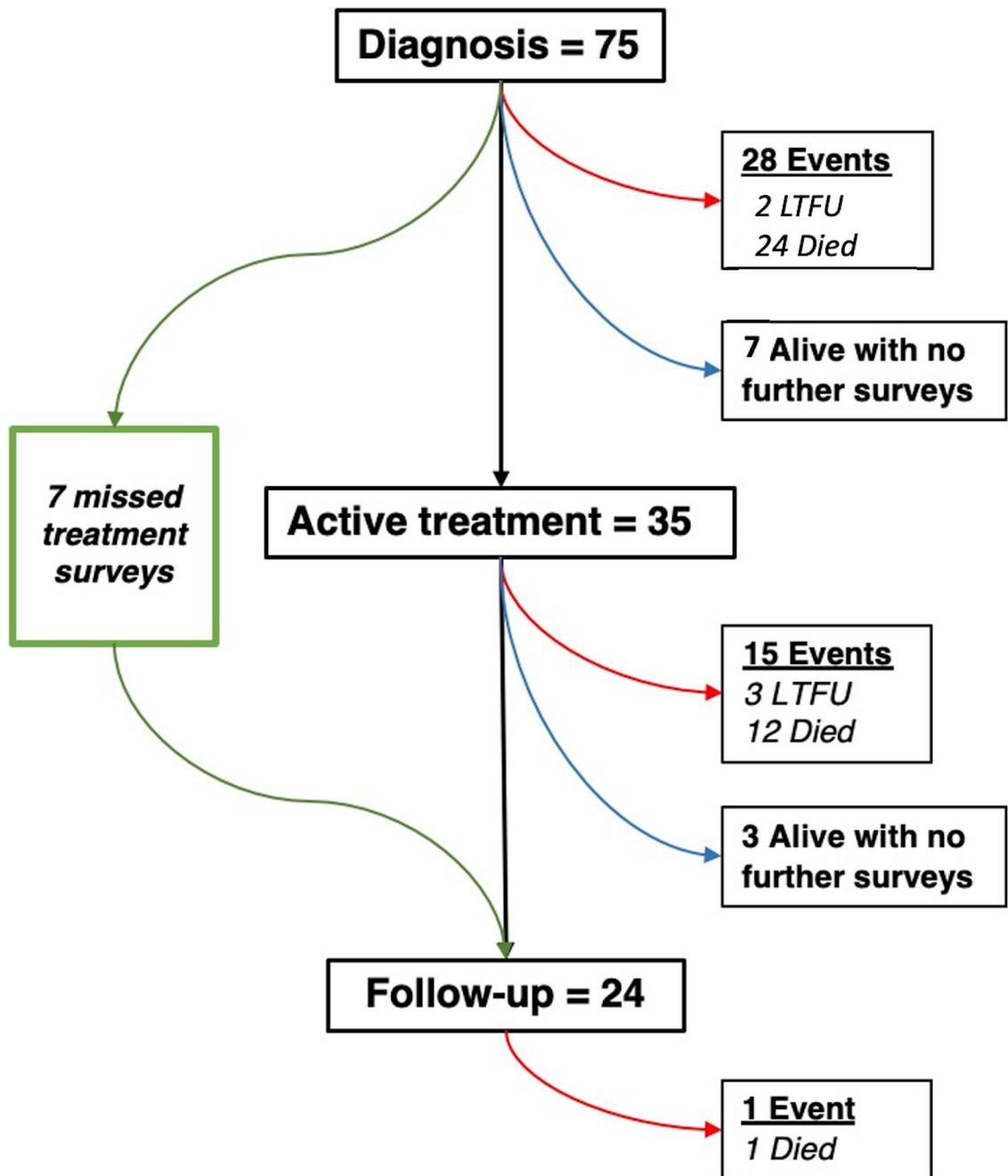
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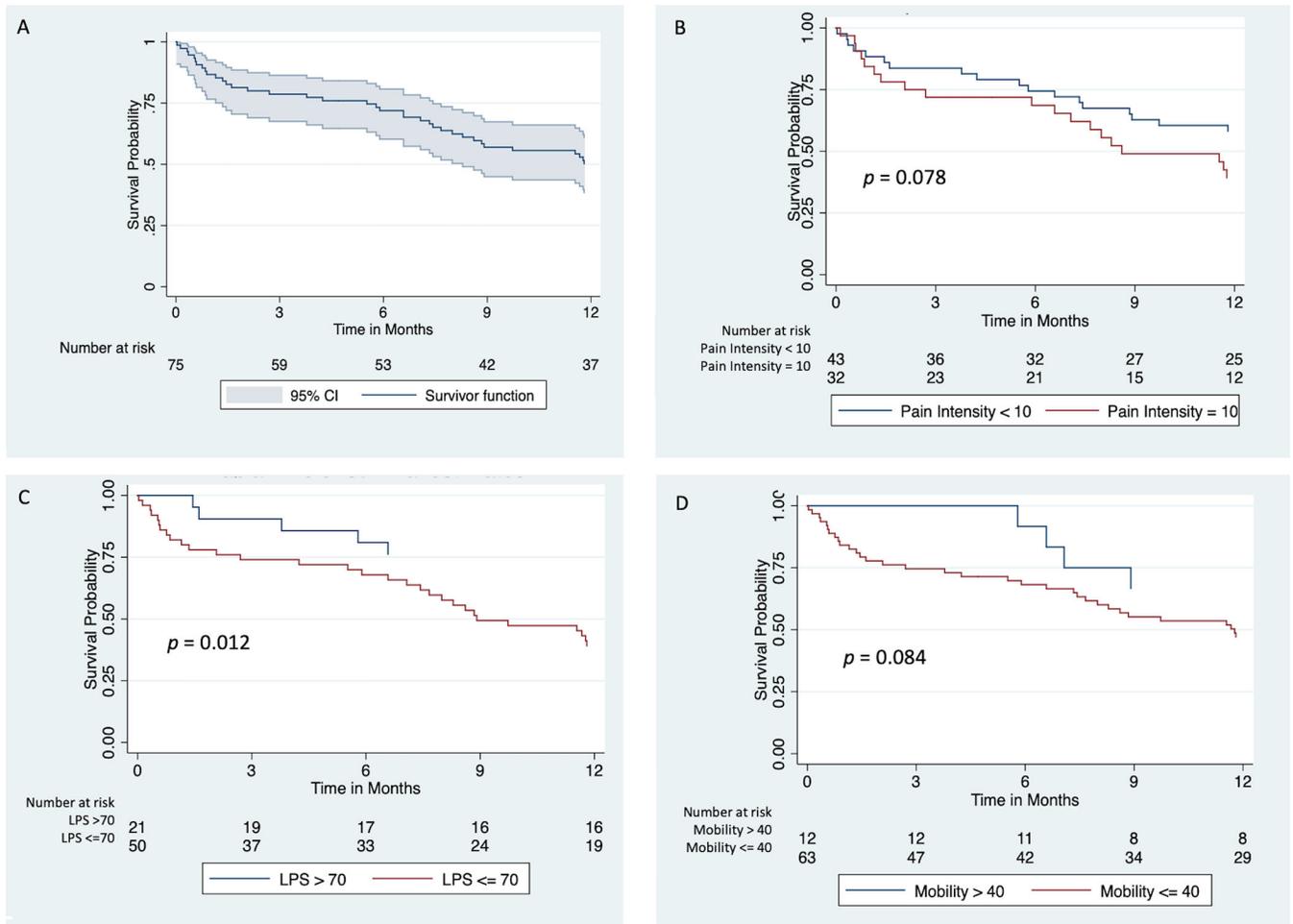
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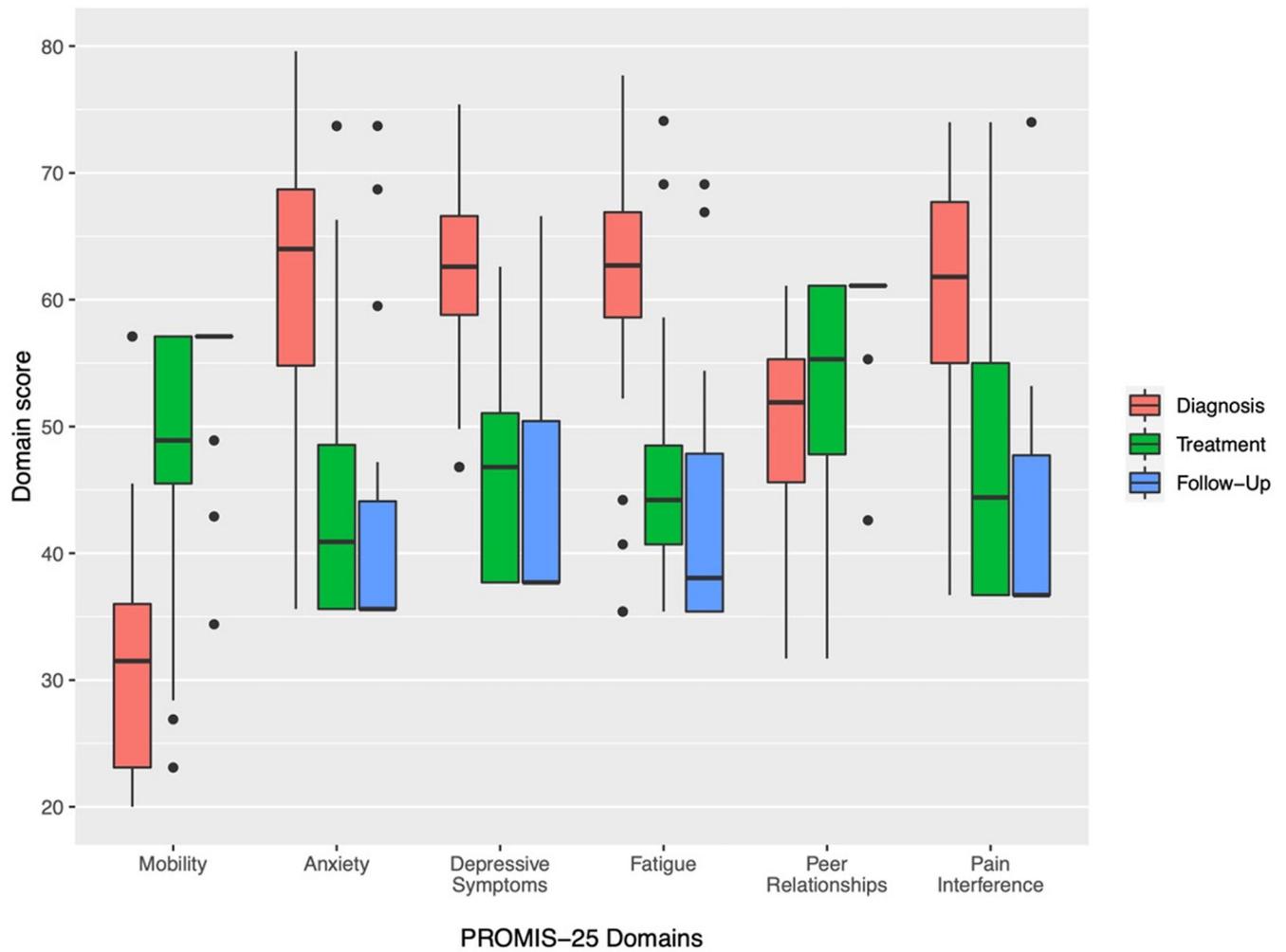
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**Figure 1. Flow chart for Pediatric PROMIS-25 surveys completed by participants receiving lymphoma care in Lilongwe, Malawi.**  
LTFU = lost to follow-up.

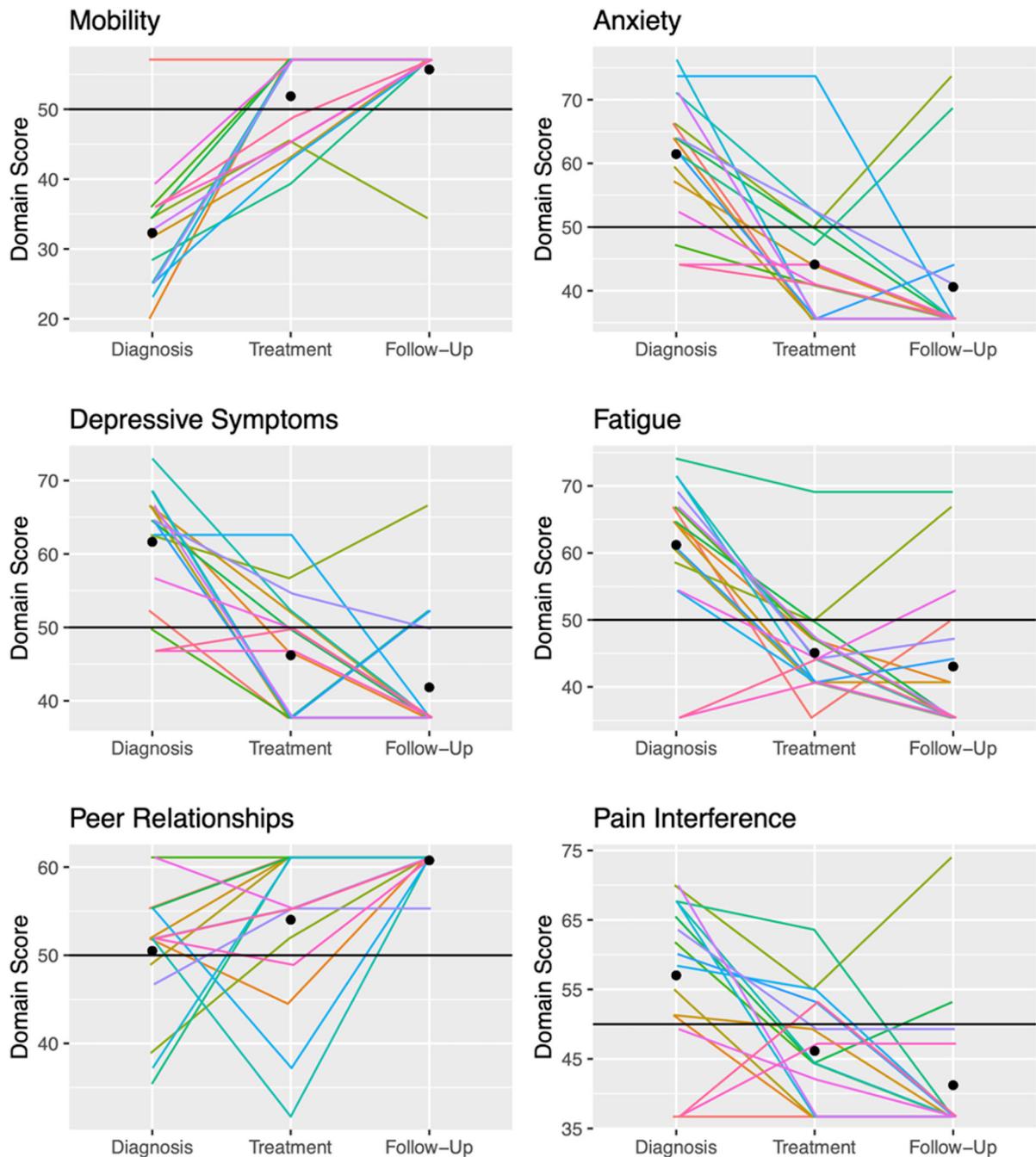


**Figure 2. Exploratory analysis of Kaplan-Meier 1-year overall survival curves for pediatric lymphoma patients at KCH in Lilongwe, Malawi with a focus on functional status.**  
 A. Overall cohort with 95% confidence intervals; B. Stratified by patient-reported PROMIS severe Pain Intensity score (10/10); C. Stratified by poor physician-reported performance status (Lanksy Performance Score (LPS) > 70); D. Stratified by fair-poor patient-reported PROMIS Mobility score (< 40).



**Figure 3. Distribution of PROMIS-25 HRQoL domain scores between diagnosis (n=75), active treatment (n=35), and follow-up (n=24) for pediatric lymphoma patients treated in Lilongwe, Malawi.**

Higher PROMIS scores for Mobility and Peer Relationships reflect better functioning and relationships; lower symptom scores reflect better symptom experiences.



**Figure 4. Trajectories of PROMIS-25 HRQoL domain scores throughout cancer care at KCH in Lilongwe, Malawi among patients who completed surveys at all time points (n=17).** Unique patient trajectory indicated by colored line; mean domain score at each timepoint indicated by black dot; mean reference T-score of 50 indicated by black horizontal line. Higher PROMIS scores for Mobility and Peer Relationships reflect better functioning and relationships; lower symptom scores reflect better symptom experiences.

**Table 1.**

Characteristics of pediatric lymphoma patients at diagnosis who completed Pediatric PROMIS-25 surveys in Lilongwe, Malawi, stratified by outcome and their univariate and multivariate hazard ratios for mortality.

<i>Patient Characteristics at Diagnosis, n (%)</i>										
	All patients N = 75	Alive N = 32	Died/LTFU N = 43	p-value	Univariate HR	95% CI	p-value	Multivariate HR	95% CI	p-value
Age 10	45 (60)	16 (50)	29 (67)	0.131	1.56	0.82-2.96	0.171	1.75	0.84-3.61	0.133
Male sex	51 (68)	20 (62)	31 (72)	0.385	1.42	0.73-2.78	0.297			
HIV-positive	2/68 (3)	1/27 (4)	1/41 (2)	0.732						
<i>Diagnosis</i>										
Burkitt lymphoma	60 (80)	20 (62)	40 (93)	0.001	4.88	1.51-15.82	0.008	5.70	1.70-19.10	0.005
Hodgkin lymphoma	15 (20)	12 (38)	3 (7)	0.001						
Stage III/IV	48/73 (66)	18/32 (56)	30/41 (77)	0.134	1.84	0.92-3.67	0.084	0.88	0.35-2.21	0.789
Lactate dehydrogenase > 2x ULN, n (%) *	30/61 (49)	11/27 (41)	19/34 (56)	0.247	1.36	0.69-2.67	0.378			
Poor Performance Status (LPS 70)	50/71 (70)	17/31 (55)	33/40 (83)	0.011	2.75	1.21-6.25	0.015	2.39	0.81-7.08	0.114
Moderate-Severe Acute Malnutrition	54/73 (74)	20/32 (63)	34/41 (83)	0.049	2.27	1.00-5.12	0.049	2.09	0.86-5.03	0.101
<i>PROMIS-25 Domain Scores at Diagnosis, n (%)</i>										
Fair-Poor Mobility (Score <40)	63 (84)	24 (75)	39 (91)	0.068	2.40	0.86-6.74	0.095	1.49	0.47-4.80	0.496
Moderate-Severe Anxiety (Score >55)	54 (72)	23 (72)	31 (72)	0.984	1.01	0.53-2.00	0.937			
Moderate-Severe Depressive Symptoms (Score >55)	64 (85)	27 (84)	37 (86)	0.842	1.21	0.51-2.88	0.660			
Moderate-Severe Fatigue (Score >55)	61 (81)	24 (75)	37 (86)	0.230	1.75	0.74-4.15	0.204			
Fair-Poor Peer Relationships (Score <40)	13 (17)	7 (22)	6 (14)	0.376	0.64	0.27-1.52	0.319			
Moderate-Severe Pain Interference (Score >55)	58 (77)	24 (75)	34 (79)	0.682	1.11	0.53-2.31	0.786			
Severe Pain Intensity (Score = 10/10)	32 (43)	10 (31)	22 (51)	0.087	1.71	0.93-3.11	0.081	1.36	0.68-2.72	0.391

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Higher PROMIS scores for Mobility and Peer Relationships reflect better functioning and relationships, with scores < 40 (1 standard deviation (SD) below the mean) considered fair to poor.<sup>33</sup> Higher symptom scores reflect worse symptom experiences (Anxiety, Depressive Symptoms, Fatigue, Pain Interference), with scores > 55 (1 SD above the mean) indicating moderate to severe symptom burden.<sup>33</sup>

\* LDH Upper Limit of Normal (ULN) for age: Age 2–12 = 295 U/L, Age 13–17 = 190 U/L.

LTFU = Lost to Follow-up; HR = Hazard Ratio, HIV= Human Immunodeficiency Virus; ULN= Upper limit of normal; LPS= Lankys Performance Score

PROMIS-25 Pediatric Health-related Quality of Life domain scores and Pain Intensity throughout pediatric lymphoma treatment in Lilongwe, Malawi.

**Table 2.**

	Diagnosis	Treatment	Follow-Up	
	N = 75	N = 35	N = 24	
Days since Diagnosis, median [IQR]	0 [0-0]	113 [61-210]	720 [486-1014]	
Patient Reported, n (%)	57 (76)	27 (77)	16 (67)	
Caregiver Reported, n (%)	18 (14)	8 (13)	8 (33)	
<b>PROMIS HRQoL Domains</b>	<b>Mean score (SD)</b>	<b>Mean score (SD)</b>	<b>Mean score (SD)</b>	<b>p-value</b>
Mobility	31.5 (9.1)	49.8 (9.2)	55.1 (5.6)	<0.001
Anxiety	61.9 (9.8)	44.1 (10.4)	41.7 (10.8)	<0.001
Depressive Symptoms	62.2 (6.7)	46.7 (7.9)	42.6 (8.5)	<0.001
Fatigue	61.7 (9.2)	45.9 (8.3)	42.6 (10.1)	<0.001
Peer Relationships	49.3 (7.3)	52.6 (9.2)	60.1 (3.9)	<0.001
Pain Interference	59.6 (9.5)	47.2 (9.8)	41.9 (8.9)	<0.001
Pain Intensity, median [IQR]	9 [4-10]	1 [1-1]	0 [0-0]	<0.001

\* Higher PROMIS scores for Mobility and Peer Relationships reflect better functioning and relationships; lower symptom scores reflect better symptom experiences.

\*\* = Difference in mean domain score between timepoints. Minimally Important Difference (MID) is 2-3 points.<sup>33</sup>

PROMIS = Patient-Reported Outcomes Measurement Information System; HRQoL = Health-related quality of life; IQR = Interquartile range; SD = Standard Deviation.