



Qualitative Findings on the Impact of Disease in Epstein–Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Patients, as Measured by EQ-5D, SF-36, and the FACT-LYM

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ABSTRACT

Introduction: There are no validated patient-reported outcome (PRO) instruments for Epstein–Barr virus-driven post-transplant lymphoproliferative disease (EBV⁺ PTLD). The aim of this study was to assess the content applicability for three frequently used PRO instruments from the perspective of patients with EBV⁺ PTLD.

Methods: A moderated focus group comprising adult patients with EBV⁺ PTLD was conducted using a concept confirmation and an open-ended concept elicitation approach. The domains of the EuroQoL Group-5 Dimension (EQ-5D) instrument, Short Form Health Survey-Version 2 (SF-36v2) questionnaire, and Functional Assessment of Chronic Illness Therapy–Lymphoma (FACT-LYM) questionnaire were discussed. The concept elicitation portion

was a general discussion of symptoms and patient burden of EBV⁺ PTLD.

Results: Six patients participated in this study: five women and one man. Most participants reported acute pain in the location of their EBV⁺ PTLD. All participants reported significant physical fatigue and experienced productivity loss. Patients reported emotional fatigue, feelings of dissociation, lack of motivation, and persistent fear of disease progression, including mortality. Patients described their social functioning as disjointed, behaving differently with loved ones/caregivers than when alone. The EQ-5D was relevant for the pain/discomfort and anxiety/depression domains; most SF-36v2 domains were relevant, with the exception of the general health perception domain, which was not applicable; all domains in the FACT-LYM were relevant. The open-ended portion drew no new content.

Conclusions: This qualitative research identified meaningful concepts in patients with EBV⁺ PTLD, with physical, emotional, and social functioning being impacted. The FACT-LYM questionnaire was the most relevant of the three PROs studied, with all domains relevant to this population. It is important to properly analyze PRO data in patients with EBV⁺ PTLD.

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Key Summary Points

There are no validated patient-reported outcome (PRO) instruments for Epstein–Barr virus-driven post-transplant lymphoproliferative disease (EBV⁺ PTLD).

This study assessed the content applicability for three frequently used PROs from the perspective of patients with EBV⁺ PTLD.

This qualitative research identified meaningful concepts in these patients, with physical, emotional, and social functioning being impacted.

The Functional Assessment of Cancer–Lymphoma questionnaire was the most relevant instrument of the three PROs studied, with all domains relevant to this population.

It is important to properly analyze PRO data in patients with EBV⁺ PTLD.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12988640>.

INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is an ultra-rare disease that is classified as a type of lymphoma that can result from allogeneic hematopoietic stem cell transplantation or solid organ transplantation [1–3]. PTLD can be aggressive and is often deadly, especially in those who do not respond to initial treatment. Patients undergoing transplantation are severely immunocompromised and have a substantially higher risk of developing a lymphoma

compared to the general population [3–6]. PTLD can be Epstein–Barr virus (EBV) positive (EBV⁺) or EBV negative (EBV⁻). EBV⁺ PTLD has a known origin that is often the direct result of unchecked EBV infection in immunocompromised patients [1–3]. In immunocompetent individuals, EBV infection is controlled by a strong immune response of virus-specific and nonspecific T cells that eliminate the majority of EBV-infected B cells. However, in post-transplant patients, hyperproliferation of EBV-infected B cells, either due to reactivation of the virus after transplantation or from primary EBV infection, occurs as a result of profound immune suppression, which may lead to EBV⁺ PTLD [7, 8].

Several factors increase the risk of PTLD. Whereas PTLD can affect post-transplant patients of all ages, the risk of PTLD is influenced by a number of factors, including age and EBV status. Specifically, there is a higher incidence of PTLD in the pediatric population (0–18 years) as children are more likely to be EBV negative at transplantation and are more susceptible to primary EBV infection, resulting in a significantly higher risk of EBV⁺ PTLD compared to adults [4–6, 9].

Over the past 20 years, patient-centered outcomes (PCOs; instruments that capture the patient's voice from the patient, a physician, a caregiver, or other source) and specifically patient-reported outcomes (PROs; those reported by the patient about the patient) have evolved to be an important and indispensable assessment tool in healthcare systems. PRO instruments are used to better understand the disease and treatment experiences and health conditions from the patient's perspective, without any interpretation from a third party, be it a caregiver or healthcare provider [10]. Additionally, guidance documents issued by the U.S. Food and Drug Administration (FDA) has emphasized the importance of including disease-specific PROs that reflect the patient voice in drug development programs [11, 12]. This guidance includes best practices in qualitative research, including conducting interviews to gather meaningful and relevant information on aspects of symptoms and impacts of the disease that are important to patients.

The clinical presentation of EBV⁺ PTLD is heterogenous, ranging from an incidental asymptomatic finding to a fulminant presentation including organ failure and spontaneous tumor lysis [13]. In order to measure the efficacy of the treatment for patients with EBV⁺ PTLD, it is essential to understand the patient's experience and unmet medical needs directly from the patient's point of view. Unfortunately, there are no PRO instruments that have been validated for use in the EBV⁺ PTLD patient population. One commonly used PRO instrument in oncology that is potentially appropriate for patients with EBV⁺ PTLD is the Functional Assessment of Cancer Therapy–Lymphoma (FACT-LYM) questionnaire, which was developed by Cella and colleagues [14, 15]. The FACT-LYM combines the Functional Assessment of Cancer Therapy-General (FACT-G) instrument, which consists of 7-item subscales on physical well-being, social well-being, and functional well-being and a 6-item subscale on emotional well-being [16], with a 15-item lymphoma-specific subscale on additional concerns. The FACT-LYM was originally developed in the non-Hodgkin's lymphoma patient population but has since become the standard PRO instrument for assessing multiple patient populations, such as those with relapsed/refractory mantle cell lymphoma and Hodgkin lymphoma. This instrument was developed primarily based on input from hematologists and oncologists. The content of the FACT-LYM was validated with non-Hodgkin's lymphoma patients, however, its development process did not include patient input [15, 17]. Although EBV⁺ PTLD is a type of lymphoma, patients with this disease are immunocompromised and may respond differently to treatment and questionnaires than other lymphoma patients, making it difficult to determine the applicability and accuracy of the interpretation of scores for the patients with EBV⁺ PTLD [18]. Thus, in order to obtain more accurate data from patients with EBV⁺ PTLD, it is important to confirm the applicability of this PRO instrument to this patient population.

There are two additional commonly used PRO instruments that may be of value in the EBV⁺ PTLD patient population: the EuroQoL

5-Dimension (EQ-5D) instrument [19] and the Short Form Health Survey Version 2 (SF-36v2) questionnaire [20]. The EQ-5D is a preference-based measure with a descriptive system of health-related quality of life (HRQoL) states, or conditions, that defines health through five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D also has a visual analog scale (VAS), and participants are asked to rate their overall health using this scale during the interview. The EQ-5D is designed for easy completion by the patient, has been translated into more than 100 languages, and is widely used across the healthcare spectrum [19].

Similarly, the SF-36v2 is a general health, multi-item instrument designed to assess eight domains: limitations in physical activities due to health problems; limitations in social activities due to physical or emotional problems; role limitations due to physical health problems; role limitations due to emotional problems; pain; general mental health (psychological distress and well-being); vitality; and general health perceptions [20]. Additionally, scores are also measured for individual physical component and mental component summaries. Similar to the EQ-5D, the SF-36-v2 is available in over 100 languages and has been used in thousands of research studies.

As of January of 2020, no known study has investigated conceptual domains for any PCOs, including PROs, in the EBV⁺ PTLD patient population. For patients with EBV⁺ PTLD, for whom no validated PRO instruments for assessing disease and treatment effectiveness are available, difficulties may arise when attempting to analyze PROs, as many measures may not be meaningful to this population or may change due to the disease or treatment. Thus, it is important to understand just what is meaningful to patients with EBV⁺ PTLD and the significance of the instruments that contain these measures.

The objective of this study was to better understand the applicability of the conceptual domains for three frequently used general and lymphoma-specific PROs (EQ-5D, SF-36v2, and FACT-LYM) from the perspective of patients with EBV⁺ PTLD.

METHODS

Participant Selection and Eligibility

Patients who previously had EBV⁺ PTLD and survived were recruited from attendees of a patient advocacy meeting to participate in the focus group. Among these prospective participants, two patients were referred for the focus group by their physicians and six were self-identified patients who previously had EBV⁺ PTLD and who were identified and contacted through social media. Invitation letters to participate in the focus group were sent to all eight patients; six accepted and were included in the focus group. Prior to the session, patients completed an informed consent form. The focus group format was a concept confirmation approach whereby patients were queried on the domains found within the EQ-5D, SF-36v2, and FACT-LYM and on how these domains were impacted by their EBV⁺ PTLD. This concept confirmation approach was then followed by a concept elicitation portion aimed at uncovering additional unaddressed or under-addressed symptom- and disease-related themes for the participants.

Only one focus group was planned and conducted due to the small number of patients with EBV⁺ PTLD, difficulty in recruitment, and health status of the patients (i.e., healthy enough to attend the focus group in person and surviving the disease). Patients were excluded from participating in the focus group if they were < 18 years of age and/or did not speak English. Additionally, moderators may have disqualified a participant if there were concerns about his/her physical, emotional, or cognitive ability to complete the focus group session.

Conduct of Focus Group Session

Patients were requested to complete a brief demographic questionnaire prior to the start of the session to gain a better understanding of the study sample. The focus group session was conducted using a moderator discussion guide designed for the study and was executed by two facilitators working in tandem. The moderator

guide detailed the session format and content, a review of existing PRO conceptual frameworks and domains from the targeted PROs, and a general discussion of patient HRQoL and burden of illness.

The focus group lasted 90 min and was audio-recorded and transcribed. Main concepts were analyzed and derived from the transcripts. The moderator guide, study protocol, and informed consent form were reviewed by the New England Institutional Review Board (NE-IRB), which determined the study to be exempt from IRB requirements because the research was observational and only included interactions involving educational tests, survey procedures, interview procedures, and/or observation of public behavior (including visual or auditory recording) (finalized on 21 February 2019; referenced as WO# 703). All patients completed an informed consent form (ICF) indicating their willingness to participate in this research and to allow publication of study findings.

The three PRO instruments utilized in the focus group are described in Table 1. Key concepts from the EQ-5D, SF-36v2, and FACT-LYM were assessed. The steps taken for the concept confirmation approach were: (1) ask patients open-ended questions about their experiences with EBV⁺ PTLD; (2) probe to get full information on any topic raised and evaluate if others have had similar experiences; and (3) only after the group has run out of concepts they bring up, the moderators ask about remaining domains from the three PROs not already discussed to determine their relevancy to the group. Domains from the PROs were linked based on relevance to feedback generated from the focus group. Key insights were generated for each individual domain discussed, i.e., social, physical, and emotional functioning, during the focus group. After completing the discussion of domains derived from the aforementioned PROs, we used open-ended questions to determine if there were other aspects of their EBV⁺ PTLD experience not previously discussed. Once no new concepts were raised, we moved to completion of the focus group.

Table 1 Patient-reported outcomes instruments assessed in the study

PRO measure/instrument	Description
Euro-QoL-5D (EQ-5D)	A preference-based measure with a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)
Short Form Health Survey-Version 2 (SF-36v2)	Generic health instrument assessing 8 domains, including physical functioning, role limitations due to physical problems, pain, general health perceptions, vitality, role limitations due to emotional problems, social function, mental health. It also provides scores for more general measures of a physical component summary (PCS) score and mental component summary (MCS) score
Functional Assessment of Chronic Illness Therapy Lymphoma (FACT-LYM)	An instrument consisting of the FACT General (FACT-G) and a 15-item subscale ‘lymphoma-specific additional concerns’ (LYM). The FACT-G consists of three 7-item subscales (physical well-being, social well-being, and functional well-being) and a 6-item subscale on emotional well-being

HRQoL Health-related quality of life, *PRO* patient-reported outcome

RESULTS

Participant Demographics and Characteristics

The focus group session was held in Houston, Texas, and consisted of five women and one man as participants, with a mean age of 35.3 (range 26–48) years. The average time since their primary diagnosis of EBV⁺ PTLD was 11.8 year (range of 8 months to 20 years). The average time from resolution of their EBV⁺ PTLD was 11.3 years (range 2 months to 19 years).

Qualitative Results

Three major themes emerged from the analysis of the PRO domains: physical functioning, emotional functioning, and social functioning. Table 2 summarizes some key messages for each of the major themes.

Physical Functioning

All participants felt that EBV⁺ PTLD significantly affected their physical functioning,

especially at the direct location of their PTLD. General physical abilities, such as walking or daily self-care routines, were not affected to the same degree unless the location of the PTLD interfered with that activity.

Most participants reported that they suffered from severe acute pain in the direct location of their PTLD, which in turn affected their HRQoL. Additionally, most patients reported significant physical fatigue to be the most limiting factor of their activities of daily living (ADLs; e.g., bathing, getting ready for the day). The participants also had a reduced overall desire to partake in daily activities, especially those for fun (i.e., they experienced anhedonia).

All participants experienced and were significantly impacted by work productivity loss as they missed times from school or work due to symptoms or treatment of EBV⁺ PTLD.

Participants also described significant fatigue and fatigue-related pain (see Table 2). For some of the participants, the pain and fatigue were so severe that it resulted in hospitalization, severely limited their ability to make decisions, and significantly impacted their ADLs, such as eating and sleeping.

Table 2 Meaningful concepts of the patient-reported outcomes

Domain	Concept	Patient testimonial (verbatim)
Physical functioning	Pain	<p>“...For me personally I was in such pain, it was painful leading up to being in the hospital...Once the lymph node started swelling it was horribly painful. So, it was just physically very painful for me”</p> <p>“...I have severe abdominal pain. Pretty much every single instance where I couldn’t stand straight, and it was painful to lay down and couldn’t eat a couple times as well. And so, there was significant appetite loss, not eating resulted in weight loss as well”</p>
	Fatigue	<p>“...I’d say sometimes even like the showering and getting out of bed was hard, but I was able to do it, but you had to make energy decisions and just wherever you’re going to use it”</p> <p>“...Fatigued. I got too much sleep, I felt like I can never get my energy back”</p>
Emotional functioning	Lack of self-confidence and motivation	<p>“...For me, so I went through this when I was a teenager so total lack of self-confidence and with that lack of energy not being able to function like a normal human, but also with treatments not looking like a normal teenager either. I think those were kind of the biggest impacts for me emotionally, just not being able to do what a normal person does and knowing that I could have that potential”</p>
	Dissociation/isolation	<p>“...Numbness. I dissociated completely, dissociated and experienced fear. I was afraid of dying”</p> <p>“...Happiness was very elusive, I might have said I was happy, but it was fake happy. It was like it was painful to feel joy, but on the other hand it was a relief to feel joy but being able to do that with friends with the social aspect, feeling that being among friends was hard”</p> <p>“...I had lack of motivation and also some isolation. We didn’t tell anybody what I was going through. I didn’t talk to anybody about what I was going through and so was difficult. I was very kind of lethargic or apathetic. I didn’t really want to do much”</p>
Social functioning	Two worlds	<p>“...I lived in two worlds because I felt like I had to be happy in front of, my social circle”</p>
	Isolation	<p>“...I never communicated it with anybody other than my parents, my caregivers. And so, from a social standpoint, because of that, I had some isolation”</p>
	Social media	<p>“...I mean I was generally just scared to go in public places in general and things like that so it really kept me from doing all the things with my friends, but I found that things like care pages [and] posts [are] kind of really interesting ways to [connect]... [I am] hopeful of getting emails back”</p>

Emotional Functioning

Many participants indicated that EBV⁺ PTLD affected emotional functioning (Table 2), especially their emotional and mental fatigue. Participants reported experiencing a lack of self-confidence and motivation. Some felt “dissociated” or “isolated,” “numb to everything,” “down in the dumps,” “deep despair,” and “extreme emotions.” A few participants indicated that immunosuppression led to emotional distress since it created an omnipresent fear of contracting a new illness, including the possibility of contracting another PTLD. One participant even described feeling numb and disassociated from the possibility of such reality.

Participants also expressed feeling conflicted when it came to reality, or the perception of reality. They described how everyone around them assumed that they should be happy given their transplant, but internally they often felt sad. This duality resulted in a decreased desire to spend time with their friends and family, further contributing to their feelings of isolation. Indeed, some participants stated that their sense of isolationism became exacerbated post-transplant because their follow-up treatment locations were far away from their home, where it was more difficult for their family and friends to visit.

Some of the patients also noted a special case of pervasive anxiety. Specifically, these participants talked about pervasive anxiety, even after PTLD resolution, stating that there is always a fear that the cancer could return and that it is “in the back of your mind that you are a cancer survivor.” This specific aspect of pervasive anxiety goes beyond the specific content of what is included in any of the examined PROs but is a more extreme extrapolation of content within emotional functioning.

Social Functioning

All patients agreed there were social challenges associated with EBV⁺ PTLD. A highly endorsed perception was that of living in “two worlds” as patients reported behaving differently with friends/family compared to when they were alone (Table 2). Despite having family and caregivers for primary social support, participants still voiced their feelings of isolation.

Interestingly, participants felt supported from care group websites and online chat forums where they were able to participate at their leisure; the hope of getting responses back made them feel connected. Online social pages were important outlets as participants felt they were able to engage on a regular basis. This is likely because other outlets, such as more physically strenuous leisure or recreational social activities (i.e., sports), were unavailable due to the participants’ physical fatigue.

Concept Elicitation Findings

There were additional findings in the concept elicitation portion that expanded on the domains reviewed during concept confirmation. A few items were endorsed by either one or two participants. One participant suffered anxiety on the visual cues associated with PTLD (if present, depending on the location of PTLD). Another participant expressed concern with the management of life after PTLD, which included various medications.

Relevance of PROs Instruments

The findings from the focus group provide important insights on the HRQoL among patients with EBV⁺ PTLD. During the focus group session, topics of discussion were based on the PROs of interest (i.e., EQ-5D, SF-36v2, and FACT-LYM). The relevance of these concepts or domains for this population was elucidated from participant responses. Results from this analysis are shown in Table 3 together with the degree of relevance of the domains (i.e., no relevance, some relevance, and high relevance). None of the instruments provided a fully comprehensive measure of the concerns of EBV⁺ PTLD measures, but all instruments had a number of relevant aspects. The FACT-LYM, a tool developed for lymphoma patients, had the greatest relevance for its content domains among patients with EBV⁺ PTLD as all of its domains had some relevance.

EQ-5D Instrument

Participants indicated that PTLD did not affect their physical mobility in general (only if their

Table 3 Relevant domains that are impacted by Epstein–Barr virus-driven post-transplant lymphoproliferative disease

PROs measure	Conceptual domain/domain	Degree of relevance
EQ-5D	Mobility	Not applicable
	Self-care	Not applicable
	Usual care	Not applicable
	Pain/discomfort	High
	Anxiety/depression	High
SF-36v2	Physical functioning	High
	Physical role limitations	High
	Bodily pain	High
	General health perceptions	Not applicable
	Energy/vitality	High
	Social functioning	High
	Emotional role limitations	High
	Mental health	High
FACT–LYM	Physical well-being	High
	Social/family well-being	High
	Emotional well-being	High
	Functional well-being	Somewhat
	Lymphoma-specific questions	High

PTLD was in a specific location); consequently, the first three domains of the EQ-5D (i.e., mobility, usual care, and self-care) were assessed as not relevant (Table 3). Alternatively, most participants professed that they experienced pain and indicated that the pain/discomfort domain of the EQ-5D was very relevant, especially at the PTLD site. Lastly, the anxiety/depression domain was considered to be highly relevant by participants as they reported experiencing anxiety and depression during the treatment phase.

SF-36v2 Questionnaire

Participants in the focus group found that most domains of the SF-36v2 were relevant for the signs and symptoms of the disease (Table 3). The domains of physical functioning and physical role limitations of the SF-36v2 were

considered relevant to patients with EBV⁺ PTLD as the items in these domains query a lack of energy and fatigue. Overall, the items in the general health perception domain of the SF-36v2 are related to health status. Participants indicated that a “healthy” scale (i.e., items in domain general health perceptions) was not appropriate for someone with EBV⁺ PTLD. Participants reported that their social life was greatly impacted by EBV⁺ PTLD and, therefore, they also felt an inability to lead a normal social life. Thus, the social functioning domain of SF-36v2 was considered by this patient population to be very relevant. The emotional and mental health domains were also considered to be quite relevant as participants expressed that they were significantly impacted as they faced extreme emotions, loneliness, fear, and anxiety of developing new symptoms.

FACT-LYM Questionnaire

The FACT-LYM was developed to assess HRQoL in patients with non-Hodgkin's lymphoma; consequently, the lymphoma-specific questions under "additional concerns" surrounding treatment side effects, lymphoma symptoms, and emotional responses to such symptoms were considered to be particularly applicable to this population. All domains of the FACT-LYM were rated as highly relevant, with the exception of the functional well-being domain that was rated as having some relevance. Participants cited productivity and work loss as well as an inability to fully enjoy life but did not cite any specifically sleep-related problems due to their disease.

DISCUSSION

Patient-focused drug development is a systematic approach to ensure that patients' experiences, perspectives, and priorities are included and incorporated in programs of drug development and evaluation [11, 12]. The inclusion of the patient voice is critical to this approach. Additionally, assessment of patient-centered outcomes in the treatment of nearly any condition is now considered to be an essential cornerstone of the evaluation of a treatment's efficacy and benefit to medical care [11, 12]. However, given the lack of prior research on relevant concepts of PROs for patients with EBV⁺ PTLD, a patient population which may differ from other lymphoma populations since the former are immunocompromised, it is important to understand just what is meaningful to this population to better understand and analyze data within clinical trials. The current study fills this knowledge gap and identifies domains of importance for these patients with an ultra-rare disease. Despite the small sample size, we were able to obtain high agreement among the participants on many of the PRO domains. Researchers now have the first empirically-based recommendations on the types of domains to assess for patients with EBV⁺ PTLD patients: physical functioning (pain and fatigue), emotional functioning (lack of confidence and motivation as well as dissociation/isolation), and social functioning (feeling

like they are living in two worlds, isolation, and social media connectedness).

All three PROs evaluated had at least one domain that was considered to be relevant by the participants in the focus group to patients with EBV⁺ PTLD. The pain/discomfort and anxiety/depression domains of the EQ-5D were considered to be particularly relevant, while the other domains in this instrument (i.e., physical mobility, self-care, and usual care) were not considered to be relevant or would not change due to EBV⁺ PTLD. Most domains of the SF-36v2 were considered to be relevant, with the exception of the general health perception domain, which the participants assessed as not being applicable. The FACT-LYM was the most relevant scale of the three PROs studied, with all domains assessed to be relevant to the studied population, especially the emotional well-being domain and the lymphoma-specific questions.

Given the widespread views that including the voice of the patient in clinical research is a critical component in assessing treatment success, the finding from the current study should help advance clinical research and subsequent medical practice, especially within this patient population with an ultra-rare disease. On the clinical research side, there is now objective information on the domains to assess PROs. This research helps identify key domains that are impacted by EBV⁺ PTLD and are meaningful to patients; in particular, it identifies those domains more likely to change with treatments. By identifying these relevant domains, we can better analyze PRO data in clinical trials.

Medical practice may also benefit from an understanding of the conceptual domains most relevant to patients. The advancement of new treatments can illuminate which aspects of a patient's health are measurable by PROs and related to overall positive health outcomes for this disease. Having positive results or changes in outcome measures that are meaningful to patients can better demonstrate the effectiveness of a treatment.

While PROs such as the FACT-LYM were developed for patients with lymphoma, there are no other known studies in which PROs are qualitatively evaluated among patients with EBV⁺ PTLD. Studies such as these aid

researchers, providers, and patients to further understand the relevance and benefits of PRO use in assessing patient experiences, especially pertaining to conditions where patient experience is highly subjective. As EBV⁺ PTLD demonstrates heterogeneity in terms of histopathologic and immunophenotypic presentations, it is critical to understand experiences and unmet clinical needs directly from the patients' point-of-view. Here, we describe findings from the first known focus group dedicated to exploring disease and clinical outcome from the point-of-view of the EBV⁺ PTLD patient.

A key limitation of this study, as with most qualitative research, is that data relevance is reliant on patient reports, which are highly subjective across individuals. Other limitations of this study are largely related to limitations of conducting research in patients with EBV⁺ PTLD. The ultra-rare nature of the disease and high mortality rate associated with EBV⁺ PTLD limit the patient advocacy/support network and number of patients available for PRO research, with the consequence that only responders to treatment for this disease were selected as participants (e.g., non-responders quickly die due to the aggressiveness of this disease). Due to these limitations, this study was conducted with a small number of patients ($n = 6$), represented by a single focus group, and some patients had long recall periods. Since many of the six participants were in high agreement on nearly all of the concepts, it is possible to reach saturation with this small number of patients in the most common forms of saturation assessment. For example, splitting the sample into three subgroups of two patients each would achieve saturation for nearly every permutation (see Table 4 in [21]). Another common approach is to review interviews for new concepts until two consecutive interviews with no new concepts are obtained. If the current focus group data used this individual interview approach, saturation would also be quickly obtained. As noted in Patrick et al. [21], concept elicitation for PROs assessing broad concepts can more quickly obtain saturation than concepts with much more details and nuances. This is likely why our study obtained such high

agreement among the participants. Lastly, understanding which domains may be the most appropriate for examining change due to treatment and additional domains of importance with these patients were not assessed in this study, although most domains are likely represented in the evaluated PROs. Further research is needed to fully understand all concepts that are important to the patient experience in EBV⁺ PTLD (e.g., a full concept elicitation study).

CONCLUSIONS

This research study identified meaningful concepts in a small sample of patients with EBV⁺ PTLD and demonstrated a high burden of illness that impacts physical, emotional, and social functioning. When mapping these concepts to existing PRO instruments, we found that the FACT-LYM was considered by our participants to be the most relevant, with all domains considered to be applicable to patients with EBV⁺ PTLD. Identifying and understanding the concepts of interest to this patient population contribute to a proper analysis of PRO data that is relevant to this population as well as to a more holistic understanding of the needs of these patients. Findings of this study also uncovered the highly favorable effects of online support groups and other social media that allow patients with EBV⁺ PTLD to speak with one another regardless of where they live and/or get their treatment. Additional future studies like these could also demonstrate the same benefit in understanding patients' experiences, needs and general HRQoL in areas of physical, emotional, social functioning.

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Compliance with Ethics Guidelines. The moderator guide, study protocol, and informed consent form were reviewed by the New England Institutional Review Board (NE-IRB), which determined that the study was exempt from IRB requirements (finalized on 21 February 2019; referenced as WO# 703). All patients completed an informed consent form (ICF) indicating their willingness to participate in this research and to allow publication of study findings.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available to maintain

compliance with protecting protected health information.

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REFERENCES

1. Leblond V, Sutton L, Dorent R, et al. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. *J Clin Oncol.* 1995;13(4):961–8.
2. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Crit Rev Oncol Hematol.* 2005;56(1):155–67.
3. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. *Curr Hematol Malig Rep.* 2013;8(3):173–83.
4. Allen UD, Preiksaitis JK. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant.* 2013;13(Suppl 4):107–20.
5. Nijland ML, Kersten MJ, Pals ST, Bemelman FJ, Ten Berge IJ. Epstein-Barr virus-positive posttransplant lymphoproliferative disease after solid organ transplantation: pathogenesis, clinical manifestations, diagnosis, and management. *Transplant Direct.* 2016;2(1):e48.

6. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. *N Engl J Med*. 2018;378(6):549–62.
7. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. *Transpl Infect Dis*. 2001;3(2):70–8.
8. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res*. 2004;10(3):803–21.
9. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. *Am J Hematol*. 2011;86(2):206–9.
10. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: a new era in clinical research. *Perspect Clin Res*. 2011;2(4):137–44.
11. U.S. Food and Drug Administration (FDA). Patient-focused drug development: collecting comprehensive and representative input. [Draft guidance]. 2018. <https://www.fdanews.com/ext/resources/files/2018/06-12-18-DrugDevelopment.pdf>. Accessed Oct 2019.
12. U.S. Food and Drug Administration (FDA). Patient-focused drug development: methods to identify what is important to patients guidance for industry, Food and Drug Administration staff, and other stakeholders. [Draft guidance]. 2019. <https://www.fda.gov/media/131230/download>. Accessed Oct 2019.
13. San-Juan R, Comoli P, Caillard S, et al. Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. *Clin Microbiol Infect*. 2014;20(Suppl 7):109–18.
14. Cella D, Webster K, Cashy J, et al. Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: the functional assessment of cancer therapy-lymphoma (FACT-Lym). *Blood*. 2005;106(11):750. <https://doi.org/10.1182/blood.V106.11.750.750>.
15. Hlubocky FJ, Webster K, Beaumont J, et al. A preliminary study of a health related quality of life assessment of priority symptoms in advanced lymphoma: the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy—Lymphoma Symptom Index. *Leuk Lymphoma*. 2013;54(9):1942–6.
16. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–9.
17. Hlubocky F, Webster K, Cashy J, Beaumont J, Cella D. The development and validation of a measure of health-related quality of life for non-Hodgkin's lymphoma: the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym). *Lymphoma*. 2013;2013:147176. <https://doi.org/10.1155/2013/147176>.
18. Haynes SN, Richard DC, Kubany EW. Content validity in psychological assessment: a functional approach to concepts and methods. *Psychol Assess*. 1995;7(3):238–47.
19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–36.
20. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–83.
21. Patrick DL, Burke LB, Gwaltney CJ, Kline Leidy N, Martin ML, Molsen E, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluations: ISPOR PRO Good Research Practices Task Force Report: part 1—eliciting concepts for a new PRO instrument. *Value Health*. 2011;14:967–77.