Applying the thresholds for clinical importance for fourteen key domains of the EORTC QLQ-C30: A Latent Class Analysis of Cancer Survivors.

Abstract

A person's quality of life is impacted from the beginning of their oncology experience. One of the most common tools to measure quality of life is the EORTC QLQ-C30. The absolute scores it produces can be difficult to interpret in the clinical setting and thresholds to help identify those who require intervention have recently been introduced. The aim of this research was to identify heterogeneity of these thresholds for clinical importance using latent class analysis in cancer survivors (those undergoing and those who have completed treatment) attending a hospital in the north west of Ireland. We identified 3 distinct classes of cancer survivors, using Mplus 6.11: high clinical impact (13.9%), compromised physical function (40.3%) and low clinical impact (45.9%). The compromised physical function group were slightly more likely to be older (OR=1.042, p<.05, CI=1.000–1.086), not employed (OR=8.347, p<.01, CI=2.092–33.305), have lower PG-SGA scores (OR=.826, p< .001, CI=.755-.904), and not have been diagnosed in the last two years (OR=.325, p<.05, CI= .114-.923) compared to the high clinical impact group. The low clinical impact group were more likely to be female (OR=3.288, p<.05, CI=1.281–1.073), not employed (OR=10.129, p< .01, CI=2.572-39.882), have a lower BMI (OR=.921, p<.05, CI=.853-.994) and lower PG-SGA scores (OR=.656, p<.001, CI=.573-.750) than the high clinical impact group. Functional and symptom issues impact on quality of life and therefore identifying those of clinical importance is crucial for developing supportive care strategies.

Keywords: Clinical Importance, Quality of Life, Symptom Burden, Functioning, Thresholds

Introduction

A person's quality of life is impacted from the beginning of their oncology experience [1] and those with cancer often report strong impairments in Quality of Life (QoL) compared to healthy populations [2, 3]. Side effects of treatment such as anxiety, depressed mood, pain, fatigue, dyspnea and appetite loss can impair activities of daily living in those with cancer, impacting on QoL [4, 5] Cancer-related fatigue, experienced as emotional, physical or cognitive exhaustion, is one of the most commonly reported side effects of cancer and treatment [6-8] and can significantly impair multiple domains of QoL including physical functioning, cognitive functioning and emotional functioning [9, 6, 8]. Correlations with survival rates have been reported for several QoL domains [10-12] and therefore it has received much focus as a variable of importance.

One of the best ways to determine impacts of cancer on QoL is to ask patients themselves and there are a number of tools available to measure QoL in this way. One of the more commonly used is the European Organization for Research and Treatment of Cancer quality of Life Questionnaire (EORTC QLQ-C30) [13, 14]. This questionnaire assesses not just global health status but also five different functioning domains, eight symptom domains as well as financial impact. While it was often used as an outcome measure for trials it is more increasingly being used in clinical practice [15], where it appears to improve clinician-patient communication [16]. The absolute scores it produces however, can be difficult to interpret in this setting and do not indicate clearly indicate which functioning or symptom subscales require attention [17].

To better interpret the scores that this questionnaire generates, researchers have investigated cut-offs and thresholds for each of these scales to try to aid clinicians in easily identifying clinically important impairment of function or symptom burden. These have varied significantly over the years and all come with their own inherent limitations, such as using the same threshold for each of the domains [18] or use of percentiles with a general population reference point [19]. Giesinger et al., have recently developed thresholds for clinical importance based on mixed-methods work with patients and healthcare professionals to determine what makes a symptom or burden clinically important [20].

In clinical practice these thresholds will help the clinician to be able to identify symptom and functional health problems that require attention. The aim of this research was to apply these thresholds to a cohort of Irish Cancer Survivors (both undergoing and completed treatment) and to examine heterogeneity of these thresholds for clinical importance using latent class

analysis. A secondary aim was to determine whether these groups differed by select demographic and health characteristics.

Method Section

Sample

Participants were recruited through the oncology day ward and outpatient department in Sligo University Hospital between September 2019 and March 2020. Ethical approval was granted by the Research Ethics Committee at Sligo University Hospital.

Measures

Individuals completed a demographic questionnaire (age, gender, cancer duration, education, employment, treatment status), the EORTC QLQ-C30 [13], the Patient Generated Subjective Global Assessment Short Form (PG-SGA SF) [21] questionnaire and a handgrip strength test using a handgrip dynamometer (dominant hand, result measured in kg). Weight and height was measured by an oncology nurse and Body Mass Index (BMI) was calculated using the formula weight/height^2.

The PG-SGA SF is a screening tool for malnutrition risk which is considered the reference method to assess malnutrition in an oncology setting [22], it is not however, an oncology specific tool. It consists of four sections to be completed by the patient which address weight history (patient is asked to indicate current weight and height, weight one month ago, weight six months ago and also to answer the following: during the past two weeks my weight has increased, decreased, stayed the same), food intake (compared to my normal intake, I would rate my food intake during the past month as unchanged, more than usual, less than usual; individuals are then asked what type of food e.g. normal food, liquids, nutritional supplements), nutrition impact symptoms (e.g. I have had the following problems that have kept me from eating in the last two weeks, tick all the apply – list of 14 impact symptoms and option to choose and specific 'other') and activities/function (rate activity over the last month from

normal to severe limitations/bed bound). These were scored using standardised guidelines with a minimum of 0 and a maximum of 36 points being achievable [21]. A higher score reflects a greater risk of malnutrition.

The EORTC QLQ-C30 is a validated measure for determining Quality of Life in cancer patients. This provides scoring (0-100) for five functioning scales (physical, role, emotional, cognitive and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea) and perceived financial impact. Example questions include, in the past week have you have difficulty remembering things; did you feel depressed; have you had trouble sleeping; were you limited in doing either your work or other daily activities? For the current study, the five items of the functioning subscales had favourable factor loads [23] and yielded a favourable level [24] of internal consistency (α = .77). Likewise, for the symptom and financial subscales all nine items had favourable factor loads [23] and yielded a favourable level [24] (Kline, 2000) of internal consistency (α = .70).

The thresholds for clinical importance (TCI's) for each of the quality of life subscales was determined using the validated measures developed by Giesinger et al., [20]. Individuals were then binary categorised as meeting or not meeting this threshold. The TCI's for the five functioning scales were: Physical Functioning (83); Role Functioning (58); Social Functioning (58); Emotional Functioning (71) and Cognitive Functioning (75). While the TCI's for the symptom scales were: Fatigue (39); Pain (25); Nausea/vomiting (8); Sleep Disturbance (50); Dyspnoea (17); Appetite Loss (50); Constipation (50); Diarrhoea (17) and Financial Impact (17).

Materials

Proposed analytical approach

For the analysis we undertook a two-stage approach to the research. We employed Latent Class Analysis (LCA) as the main statistical approach to investigate the number of possible latent typologies within the TCI data. Using the binary observed TCI indicators, it was expected that it would identify possible typologies [25, 26] as LCA is seen as a 'person-centred' statistical process [26]. For each of the latent classes identified we defined a conditional model using

each of the ten binary indicators; and furthermore, all models were estimated using Mplus 6.11 [27] along with robust maximum likelihood [28]. Also, in order to avoid solutions based on local maxima, 100 random sets of start value were used alongside 20 final stage optimisations. Model fit was assessed using several information theory-based fit statistics; Akaike Information Criterion (AIC) [29], Bayesian Information Criterion (BIC) [30] and the sample-sized-adjusted BIC (ssaBIC) [31]. The model that produces the lowest values on each of these is the best fitting model. Additionally, the Lo-Mendell-Rubin adjusted Likelihood Ratio Test (LRT) [32] has also been employed to assist in class enumeration, where a non-significant value suggests a class lower should be considered. Nylund et al. [33] have identified the benefits of the LRT [32] over the BIC in aiding decision making over the number of classes to accept.

Multinominal Logistic Regression

Two multinominal logistic regressions were carried out to explore the relationship between (i) key demographic variables (age, education (Primary/Non-Completed Secondary; Completed Secondary/Training; Third Level (BA, BSc, Diploma); Graduate Degree/Higher), gender, and employment (this binary variable allowed participants to be classified as (1 = No) not working (retired/unemployed) and (Yes = 0) working (full-time, part-time, or self-employed) at present) and (ii) health related factors (BMI (kg/m^2), Handgrip (kg), PG-SGA score, diagnosis duration ($\leq$2 years or >2 years) and treatment status (currently receiving treatment or completed treatment)) with participant classifications.

Results Section

Characteristics

232 participants were recruited. The cohort had a mean age of 63.5 (±11.9) years. The majority were female (n=138, 61.1%), diagnosed less than five years (n=167, 73.9%) and almost half (n=112, 48.5%) were retired. The majority were currently receiving treatment (n=159, 70.4%). The main treatment type being received was chemotherapy (n=129, 81.1% of those receiving treatment), followed by hormonal therapy (n=19, 11.9% of those receiving treatment). The

most common diagnosis was breast cancer (n=58, 25.7%), followed by colorectal (n=32, 13.8%), haematological (n=28, 21.1%), lung (n=12, 5.2%) and upper gastrointestinal/liver (n=10, 4.3%). Gynaecological, urinary, head and neck, skin and bone cancers made up the remaining cases.

Descriptive trends of indicators

Table 1 presents the descriptive breakdown for each of the TCI indicators to be included within the LCA model. A total of fourteen indicators were employed and each was measured on a No (0) or Yes (1) binary response set. Descriptive analysis reported that the most experienced QOL-CI issue was dyspnoea (40.9%) while the least experienced were appetite loss (12.6%) and constipation (12.6%).

Fit indices and latent class analyses

To explore the number of TCI typologies, analysis started firstly with a one class model and continued until models failed to add significantly to the previous model. In other terms once the conditional model failed to add statistically to its predecessor, the analysis would cease. Each of the TCI model fit indices are displayed in **Table 2.** A three-class model was selected as the AIC was lower in the three-class solution (AIC = 3392.618) than the two-class solution (AIC = 3443.829). The BIC was reported to be more favourable for the three-class model (BIC = 3544.084) than the four-class model (BIC = 3575.481). Additionally, since the four-class model added nothing significantly (LRT = 50.240, p = .191) to the three-class model, the three-class model was preferred. Lastly, a three-class provides a more parsimonious explanation than a four-class.

Table 3 contains the posterior probabilities for each of the three-classes along with associated descriptive information. Regarding class size, it is clear from the table that the largest group is the second class (n = 106, 45.9%) and this group is characterised by very low probability of experiencing any of the TCI indicators. Posterior probabilities ranged from 0.01 to 0.23. Thus, this class of participants were labelled “low clinical impact” based on their probability of low clinical importance. The next largest in participant size was the third group (n = 93, 40.3%) and interestingly this class was characterised by three TCI indictors of higher clinical

importance. More specifically, higher posterior probabilities were reported for physical functioning (0.65), fatigue (0.52) and dyspnoea (0.52); thus, identifying this group as "compromised physical function". Lastly, the smallest class (n = 32, 13.9%) was characterised by reporting higher posterior probability scores than the other two groups. All indictors had a posterior probability score higher than 0.50 except for two indicators; namely appetite loss (.46) and constipation (.29). Examining the reported probabilities this group was labelled "high clinical impact". A graph was also developed to aid the interpretation of the probabilities and how the three classes distinguish from each other across each of the symptom indicators (**Figure 1**).

Multinominal Logistic Regression

In model 1, age had only a significant effect within Class 3 (impaired physical functioning) (OR = 1.042, $p < .05$, CI = 1.000 – 1.086) but not Class 2 (low clinical impact) in comparison to the reference group (high clinical impact). Individuals in this group were slightly more likely to be older than the reference Class. There was no significant effect by age for education across any of the classes. Gender was only reported significant in Class 2 (low clinical impact) (OR = 3.288, $p < .05$, CI = 1.281 – 1.073). Here individuals were over 3 times more likely to be female in this group in comparison to Class 1 (high clinical impact). Employment status was reported to have a significant effect on both Classes (Class 2: OR = 10.129, $p < .01$, CI = 2.572 – 39.882; Class 3: OR = 8.347, $p < .01$, CI = 2.092 – 33.305) in comparison to the reference Class; more specifically, non-workers were over 10 times more likely to be in Class 2 (low clinical impact) than the referent class (high clinical impact), while Class 3 individuals (impaired physical functioning) were over 8 times more likely to be not-working in comparison to the referent Class (**Table 4**).

Compared to Class 1 (high clinical impact) within Model 2, the odds of belonging to Class 2 (low clinical impact) decreased significantly by having higher BMI (OR = .921, $p < .05$, CI = .853 - .994) and PG-SGA (OR = .656 , $p < .001$, CI = .573 - .750) scores . Similarly, the odds of belonging to Class 3 (impaired physical functioning) decreased significantly for those with higher PG-SGA (OR = .826, $p < .001$, CI = .755 - .904), but also for those diagnosed within the past two years (OR = .325, $p < .05$, CI = .114 - .923). All other associations were reported non-significant (**Table 5**).

Discussion

We identified 3 distinct classes of cancer survivors based on the thresholds for clinical importance for each of the 14 subscales of the EORTC QLQ-C30. Approximately 46% of the cohort were classified as having a very low probability of meeting the threshold for clinical importance for any of the QoL scales. The remaining participants were classified into one of two classes which demonstrated clinical importance for either the majority of QOL scales or those related to physical functioning e.g. physical function, fatigue and dyspnoea.

The distinct classes of low clinical impact, compromised physical function and high clinical impact indicates that classifying quality of life by an average score may be limiting. In that case the clinical implications of the various domains may not be evident. Almost 41% of the total cohort met the threshold for clinical importance for dyspnoea, 43% for physical functioning and 36% for fatigue, none of which will be evident by looking at the overall Global Health Status score.

Those in the compromised physical function group represented 40% of the total cohort and are likely to experience clinically important impairments in physical function, fatigue and dyspnoea. Fatigue is one of the most common and impactful symptoms experienced by those with cancer and is associated with profound psychological distress [34, 6]. It has been rated as one of the more troublesome symptoms and impacts more negatively on activities of daily living than any other cancer related symptom [9, 35]. Physical function has been related to fatigue [36], is a frequent consequence of cancer and its treatments, and impacts on quality of life and contributes to disease burden and psychosocial distress [37]. Dyspnoea can impact on activities of daily living and in particular physical activities [4]. Increased physical activity has been associated with reduced cancer associated mortality [38] as well as a reduced symptom burden [39, 40]. Exercise interventions have been shown to have beneficial effects on QoL, physical function, social function, and fatigue [41]. All three symptoms in this class will impact on an individual's ability to undertake physical activity or partake in exercise-based rehabilitation and therefore prevent them from experiencing these benefits.

Fourteen percent of the cohort belonged to the high clinical impact group. Though the smallest group, they were the most important as they identified with higher clinical importance in most

of the QoL indicators, except for appetite loss and constipation. They were more likely to have higher PG-SGA scores, meaning a higher risk of malnutrition than those in the compromised physical function group and the low clinical impact group. Nutritional status has been shown to be a significant predictor of QoL in those with cancer and therefore this finding is not surprising [42]. Cancer and its treatment can lead to changes in physiological and psychological domains, which in turn can negatively influence a patients QoL through its impacts on nutritional status [43]. Nutrition support should therefore be included as part of all oncology care. The treatment of symptoms and impaired function will help improve overall quality of life.

Those in the high clinical impact group were more likely to be diagnosed in the last two years than those in the compromised physical function group. This indicates that while symptom burden may be higher in this cohort in the initial years after diagnosis the symptoms associated with physical function impairment such as fatigue can persist much longer. Previous work has indicated that up to 30% of cancer survivors can experience this symptom for several years after diagnosis [44]. Those in the higher symptom burden group were also more likely to be younger than those in the impaired physical function group. This is a topic of debate where some studies have shown similar findings where those who were younger experienced a higher symptom burden [45], while other studies have not agreed with this [46, 47]. Some potential reasons for younger individuals being more likely to be in the high clinical impact group could be that there is a higher likelihood of them receiving aggressive therapies [48], a higher level of functioning and therefore greater expectations for the resumption of pre-cancer abilities [49] or in some cases a higher prevalence of advanced cancers [50].

Interestingly, those in the low clinical impact group were more likely to be female than those in the high clinical impact group. Gender based differences in symptom burdens experienced by those with cancer tends to be inconsistent across the literature [51, 52, 45]. The only socioeconomic based difference that was observed in class membership was that those in the compromised physical function and low clinical impact group were more likely to not be working, however a large proportion of our cohort was retired which may account for this finding. Those in the low clinical impact group were more likely to be older which would support this. In addition, those in the compromised function group were more likely to be

female and this is a group that can be more likely to be homemakers or work part-time which could also explain this finding.

Importantly, this research through the identification of these distinct classes will allow clinicians to better identify those at need for intervention. This is the first study to implement the thresholds for clinical importance using LCA and therefore there are no previous studies to compare to, however previous work which implemented LCA for the health related QoL scores reported four distinct classes in lung cancer survivors, three of which are similar to those reported in this study: high health related quality of life (HRQOL), low HRQOL and mobility/usual activities impairment [53]. This study also reported 46% of the cohort in the high HRQOL class, identical to the 46% we report as being in the low clinical impact group.

There are limitations to our study. First, the current findings are specific to our cohort and analysis should be repeated to validate our findings. Second, for those who have completed treatment the EORTC QLQ-C30 may not adequately reflect the physical and psychosocial problems experienced during this stage. Issues such as fear of recurrence or returning to work may become more common, however the EORTC QLQ-C30 focusses more on acute and treatment-related symptoms. Finally, the data was collected into the early months of 2020 and therefore some domains could have been impacted by the early stages of the Covid-19 pandemic.

Conclusion

This research identified three distinct classes of cancer survivors based on the thresholds of clinical importance for fourteen key domains of the EORTC QLQ-C30 questionnaire that will help clinicians to better identify those at need for intervention. Functional and symptom issues impact on quality of life and therefore identifying those of clinical importance is crucial for developing supportive care strategies.

Acknowledgements

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Tables

Table 1**:** QOL-CI indicators experienced by the cohort

Indicators of Clinical Importance	**No**		**Yes***	
	n	**%**	**n**	**%**
Physical Functioning	131	57%	99	43%
Role Functioning	176	76.2%	55	23.8%
Emotional Functioning	162	71.4%	65	28.6%
Cognitive Functioning	157	68%	74	32%
Social Functioning	170	73.9%	60	26.1%
Fatigue	148	64.3%	82	35.7%
Nausea	171	74%	60	26%
Pain	166	71.9%	65	28.1%
Dyspnoea	136	59.1%	94	40.9%
Sleep Disturbances	156	67.8%	74	32.2%
Appetite Loss	202	87.4%	29	12.6%
Constipation	202	87.4%	29	12.6%
Diarrhoea	178	77.1%	53	22.9%
Financial	145	63.3%	84	36.7%

*indicates individuals meet the threshold for clinical importance for this quality of life measure

Table 2: Latent class fit indices for two to four class solutions

Classes	**LL**	**Par**	**AIC**	**BIC**	**LRT**	***p***
1	-1865.728	14	3759.456	3807.649	--	--
2	-1692.914	29	3443.829	3543.659	345.627	.000
3	**-1652.309**	**44**	**3392.618**	**3544.084**	**81.211**	**.039**
4	-1627.189	59	3372.378	3575.481	50.240	.191

Note. AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LRT = Lo-Mendell-Rubin likelihood ratio test. Best fitting LCA model in bold.

Table 3: Descriptive information regarding that three classes that arose from LCA*

Indicators	High Clinical Impact	Low Clinical Impact	Compromised Physical Function
Physical Functioning	**0.85**	0.08	**0.65**
Role Functioning	**0.65**	0.04	0.30
Emotional Functioning	**0.78**	0.07	0.34
Cognitive Functioning	**0.69**	0.12	0.40
Social Functioning	**0.82**	0.05	0.29
Fatigue	**0.93**	0.00	**0.52**
Nausea	**0.82**	0.11	0.22
Pain	**0.87**	0.08	0.29
Dyspnoea	**0.63**	0.22	**0.52**
Sleep Disturbances	**0.80**	0.20	0.28
Appetite Loss	0.46	0.01	0.13
Constipation	0.29	0.04	0.15
Diarrhoea	**0.57**	0.19	0.15
Financial	**0.64**	0.32	0.33
Percentage	**13.9**	**45.9**	**40.3**
n	**32**	**106**	**93**

Note: Higher probabilities (>0.50) for meeting the threshold of clinical importance for each of the QoL domains are bolded
*231 were successfully classified by LCA.

Table 4: Odds ratios, confidence intervals (95%) for demographic factors

					95% Confidence Interval	
Reference Group: Class 1		**B**	**SE**	**OR**	**Lower**	**Upper**
Class 2						
	Age	.030	.021	1.030	.989/	1.073
	Education	.353	.289	1.423	.808/	2.506
	Gender (M = 0, F = 1)	1.190	.481	3.288 *	1.281/	8.441
	Employment (Y = 0, N = 1)	2.315	.699	10.129 **	2.572/	39.882
Class 3						
	Age	.041	.021	1.042 *	1.000/	1.086
	Education	-.059	.291	.942	.533/	1.666
	Gender (M = 0, F = 1)	.221	.487	1.248	.481/	3.238
	Employment (Y = 0, N = 1)	2.122	.706	8.347 **	2.092\	33.305

Note: B = Estimate, SE = Standard Error, OR = Odds Ratio, * = p < .05, ** p < .01, *** p < .001

Table 5: Odds ratios, confidence intervals (95%) for health-related factors

				95% Confidence Interval	
Reference Group: Class 1	**B**	**SE**	**OR**	**Lower**	**Upper**
Class 2					
BMI (kg/m2)	-.083	.039	.921 *	.853	.994
Handgrip (kg)	.044	.030	1.045	.985	1.108
PG-SGA	-.422	.069	.656 ***	.573	.750
Diagnosed within past 2yrs (N = 0, Y = 1)	-.914	.575	.401	.130	1.238
Receiving treatment (N = 0, Y = 1)	-.428	.586	.652	.207	2.055
Class 3					
BMI (kg/m2)	-.059	.036	.943	.878	1.012
Handgrip (kg)	-.006	.029	.994	.940	1.052
PG-SGA	-.191	.046	.826 ***	.755	.904
Diagnosed within past 2yrs (N = 0, Y = 1)	-1.124	.533	.325 *	.114	.923
Receiving treatment (N = 0, Y = 1)	-.237	.538	.789	.275	2.265

Note: B = Estimate, SE = Standard Error, OR = Odds Ratio, * = $p < .05$, ** $p < .01$, *** $p < .001$

Figures

Figure 1: Probability of clinical importance for each of the latent classes for the 14 domains of the EORTC QLQ-C30.

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