Characteristics and patient-reported outcomes associated to dropout in severely affected oncological patients

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Research article

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Abstract

Background

Patient-reported outcome measures (PROMs) are commonly used and are surrogates for clinical outcomes in cancer research. In the research setting of very severe diseases such as cancer, it is difficult to avoid the problem of incomplete questionnaires from drop-out or missing data due to patients who deceased during observation period. We aimed to explore patient characteristics and patient-reported outcomes associated with the time-to-dropout.

Methods

In the Oncological Social Care Project (OSCAR) study the condition of participants was assessed four times within 12 months (t0: baseline, t1: 3 months, t2: 6 months, and t3: 12 months) by validated PROMs. We performed competing-risks regression based on Fine and Gray’s proportional sub-distribution hazards model for exploring factors associated with time-to-dropout. Death was considered as competing risk.

Results

Three hundred sixty-two participants were analyzed in the study. 193 (53.3%) completed follow-up at 12 months, 67 (18.5%) patients dropped out, and 102 patients (28.2%) died during the study period. Poor subjective social support was related to higher risk for drop-out (SHR=2.10; 95%CI: 1.01 – 4.35). Lower values in health-related quality of life were related to drop-out and death. The subscales global health status/QoL, role functioning, physical functioning, and fatigue symptom in the EORTC QLQ-C30 were key characteristics associated with early drop-out.

Conclusion

Severely affected cancer patients with poor social support and poor quality of life seem more likely to drop out of studies compared to patients with higher levels of social support and quality of life. This should be considered when planning studies assessing cancer patients. Methods to monitor drop-outs timely and handle missing outcomes might be used. Results of such studies have to be interpreted with caution in light of the particular drop-out mechanisms.

Introduction

Patient-reported outcome measures (PROMs) are tools for assessing patients’ physical and emotional wellbeing, satisfaction with care, symptoms, or quality of life (QoL) (1). Patient-reported outcomes (PROs) are usually measured with questionnaires, which combine several items into subscales or total scales. Oncology research often focuses on PROs as primary outcomes (2) and repeatedly measured PROs are typically observed for exploring and monitoring the change in health status in cancer patients (3, 4). Since cancer patients are often severely affected by the disease, missing data due to drop-out from deterioration in health state and mortality are common (5).
Drop-out happens in a longitudinal study when a participant discontinues the study completely. Rates of drop-out vary from 30–50% (6–8) in oncology studies, but reasons for drop-out are in most cases not recorded (7). In cancer research, numerous factors have been identified to be related to dropping out. Older age, male sex, not being married, low education, or low economic status are associated with early dropout. However, the relevance of some of those factors is less consistent than others, as for example some studies showed that women are more likely to drop out (6, 9). Generally, symptom burden and health condition are the main factors related to the discontinuation of studies (6, 7, 10). High rates of drop-out not only result in reduced statistical power, they also cause biased results if subpopulations are over or under-represented in the remaining sample (10). Knowledge of patients’ characteristics related to the risk of drop-out, will enable application of strategies for the minimization of data loss, for example continuous monitoring, reminders, and use of modern technology (e.g. application on tablet or mobile phone, online questionnaire) to measure data (11) result in more complete and reliable data, just as estimation procedures for missing data.

Investigating patients’ characteristics associated with drop-out in cancer research is useful for study planning with regard to estimation of sample size, more appropriate definition of patient inclusion criteria, decreasing insufficient enrollment by improved inclusion criteria, increasing patient retention over study periods, improve monitoring and possible post-recruitment and purposing appropriate statistical analysis to challenge missing data. The aim of this study was to assess patients’ characteristics and patient-reported outcomes associated with time-to-dropout when accounting for death as a competing risk.

**Material And Methods**

**Study population**

A protocol for the Oncological Social Care Project (OSCAR) has been reported previously (12). In brief, the OSCAR was developed as an intervention in oncological care by the German company health insurance fund Pronova BKK. A non-randomized, controlled, multi-center intervention study was conducted at three study sites in Germany from January 2018 to February 2020. Three hundred sixty-two participants above the age of 18 with different cancer types were included (see the inclusion criteria in the original published protocol (12)). One hundred fifty patients in the intervention group and 212 patients in the control group were studied. Patients answered the EORTC QLQ-C30 questionnaire monthly in the intervention group. The EORTC QLQ-C30 questionnaire for the control group and other PROMs for both groups were assessed at baseline (t0), 3 months (t1), 6-months (t2), and 12 months (t3). Refusal to participate was documented for each follow-up visit and those who dropped out were asked whether they want to discontinue the study because of health-related or other reasons. In the following analysis we focus on drop-out (health-related or other reasons) and death.

**Data collection**

Demographic data was collected at baseline, e.g. age, sex, time since diagnosis, cancer diagnosis, family status, and education. Education and professional qualification were classified based on the CASMIN
Assessment of subjective social support is based on the Oslo Three-Item Social Support Scale (OSSS-3) (14), where the total score ranges from 3 to 14 points, which is categorized into poor (3 to 8), moderate (9 to 11), and strong (12 to 14).

The following five PROMs were assessed in this study:

1. The EORTC QLQ-C30 (version 3.0) is a generic tool for assessing the quality of life (QoL) of various cancer patients and is provided by the European Organisation for Research and Treatment of Cancer (15). It consists of 30 questions and incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social functioning); three symptoms scales (fatigue, pain, and nausea/vomiting); six single item scales (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties); and a global health status/QoL scale. The total score is calculated by averaging items within scales and transforming them to the range from 0 to 100, where higher values of a functional scale represent high or healthy level of functioning, whereas higher values of a symptom scale or item represent a high level of symptomatology or problems.

2. The Patient reaction assessment (PRA-D) (16) is an instrument to assess the perceived quality of the doctor-patient relationship. In OSCAR, we modified five questions using five-point instead of seven-point Likert scales. The total score is transformed using the formula \( y = 1.5 \times x - 0.5 \) (17) and ranges from 5 to 35. Higher values indicate better doctor-patient relationships.

3. The German modified version of the Autonomy Preference Index (API-DM) (18) consists of two preferences: decision making and information seeking. The decision making and information seeking preferences consist of four items and seven items, respectively. The total score of each preference is transformed to achieve score ranges from 0 to 100. Higher values indicate higher preference in decision making and information seeking.

4. The Decision Conflict Scale (DSC) (19) is a self-reported questionnaire to evaluate the decision conflicts and comprises ten items, where the sum score ranges from 0 to 100. Higher values indicate higher decision conflicts.

5. The European health literacy survey (HLS-EU-Q6) (20) is a 6-item short version of the European Health Literacy Survey (HLS-EU) for assessing health literacy (HL). The sum score is averaged and categorized into three groups: insufficient (\( \leq 2 \) scores), problematic (2-3 scores), and sufficient (\( \geq 3 \) scores) health literacy.

### Statistical analysis

The study outcome was discontinuation of the study due to either dropout or death. Baseline characteristics were presented separately by participants who completed the study or who dropped out. For continuous variables, mean and standard deviation (SD), or median and interquartile range (IQR) are presented depending on their distribution. For categorical data, absolute and relative frequencies are reported.
Demographic data at baseline, the PROMs at baseline and at the visit before dropping out or death were used for exploring the association with time-to-dropout. Fine and Gray’s proportional sub-distribution hazards models were performed assuming that death is a competing risk. Cox regression models were used for assessing the association between participant characteristics and death. Time-to-event was defined from enrollment date to date of death, date of drop-out, or censored at 12 months. Multinomial logistic regression models were used for comparing characteristics related to drop-out or death as a sensitivity analyses.

Statistical testing was done within an exploratory framework at a two-sided significance level of $\alpha=0.05$ without adjustment for multiple testing. Due to multi-collinearity within PROs e.g. the high correlation within the EORTC QLQ-C30 between global health status/QoL and subscales of functional or symptoms, as well as PROs between baseline and visit prior to drop-out and restricted by the number of observations in some variables e.g. family status and HLS-EU-Q6, we used bivariate models only. All statistical tests were performed using Stata IC15 (StataCorp, 2017, College Station, TX, USA).

Results

Participants’ characteristics and dropout rate

Three hundred sixty-two participants were analyzed in the study. 193 (53.3%) completed follow-up at 12 months, 102 patients died during follow-up (28.2%), and 67 patients dropped out the study (18.5%) (Additional file 1: Table S1). Rates of drop-out and death combined were 14.4% at 3 months, 31.5% at 6 months, and 46.8% at 12 months, respectively. Participants who dropped out or died were older than participants who completed the study; however, there was almost no age difference between participants who dropped out and those who died. Proportion of patients who died was higher in participants with malignant neoplasm of bronchus and lung (22.6%) and malignant neoplasm of pancreas (15.7%) when compared with participants who dropped out and compliant participants (Additional file 1: Table S1). Participants who dropped out or died had lower values in global health status/QoL, physical functioning, and role functioning at baseline compared to participants who completed the study (Additional file 1: Table S2).

Characteristics associated with drop-out or death during follow up

In our study, family status and poor subjective social support were related to drop-out (Table 1). Lower global health status/QoL and role functioning of the EORTC QLQ-C30 at baseline were associated with a higher risk of drop-out, as a difference in global health status/QoL and role functioning by 10 points resulted in a 12% (95%CI: 1% – 21%) and 9% (95%CI: 1% – 16%) higher risk of drop-out, respectively. In addition, low physical functioning of the EORTC QLQ-C30 at the visit before drop-out was associated with a higher likelihood of drop-out when considering death as a competing risk (Figure 1).

Characteristics associated with shorter time to death were malignant neoplasm of pancreas compared to acute leukemia (HR=2.48; 95%CI: 1.27 – 4.85), low levels of EORTC QLQ-C30 at baseline, as well as low
global health status/QoL, low physical functioning, low role functioning, worse outcomes at symptom scale (fatigue, nausea and vomiting, dyspnea, and appetite loss) at the visit before death (Table 1 and Figure 2). Low quality of the doctor-patient relationship at baseline was also associated with shorter time to death. There were additionally study site differences with regard to time to death. Sensitivity analyses showed similar results, meaning that study sites, family status, and the EORTC QLQ-C30 were important factors for both, drop-out and death (Additional file 1: Table S3-5).

The trajectories of the EORTC QLQ-C30 over time are substantially different between participants who dropped out, those who deceased during study time, and those who completed the study visits (Figure 3a and 3b). For participants who died it is more clear than for those who dropped out insofar that participants who died had worse values in QoL, functioning, and symptoms whereas in those who dropped out the QoL values did in all cases decrease before drop-out. However, patients who have low baseline values in global health status/QoL and worse functionalities of the EORTC QLQ-C30 were somewhat more likely to drop out or die early.

**Discussion**

The purpose of this study was to investigate the patient characteristics and PROs associated with drop-out and death in a non-randomized intervention study in severely cancer patients. Family status, subjective social support, low values of global health status/QoL and role functioning of the EORTC QLQ-C30 at baseline and low value of physical functioning at the visit before drop-out were associated with time-to-dropout whereas study site, diagnosis, low values of global health status/QoL, physical functioning, and role functioning, high values of symptoms (e.g. fatigue, nausea and vomit, and appetite lose) of the EORTC QLQ-C30 at both baseline and the visit before death were associated with time-to-death.

Around 50% of subjects completed all study visits in OSCAR. In other words, there was a relatively high drop-out rate in our study compared to prior oncological studies (6, 7, 9, 21, 22). The major reasons for non-completion were early death, accounting for approximately 60% (102/169) of discontinuation. A high rate of early death is expected in this population of severely affected cancer patients and it was vulnerably related to the patient’s recruitment which having severely cancer diagnosis. However, this expectation has to be considered when planning a further study with advanced cancer patients e.g. closely continue monitoring after the patient misses an assessment, shorter time windows between follow up visits, post-recruitment and shorter studies (6). Although we have rate of deceased patients, the overall attrition (drop-out) rate in the OSCAR of 18.5% (withdrawal, 15.2%; loss-to-follow up, 2.8%; other reasons, 0.5%) was considerably modest compared to rates reported in other oncological studies, which ranges between 18% and 31% (6, 9, 23).

Our results show that PROs are in fact characteristics associated with both drop-out and death. Cancer patients with poor quality of life and high symptom burden at baseline and at the visit before drop-out or death played an important role in the likelihood of early drop-out and death in our study. These findings
are similar to those of other studies (6, 7, 21, 22). In addition, regarding specific reasons to drop-out, we found that participants who dropped out due to illness and other reasons had a lower disease burden and better functionalities than participants who died. In specific, we found that fatigue, nausea and vomiting, and appetite loss were associated with early death for both time points at baseline and at the visit before drop-out. These symptoms have been identified as early signs of upcoming death in cancer patients, especially fatigue symptoms (24). In other words, our results showed that patients who early died prematurely tend to show a trend of progressive deterioration, indicated by reduction on their health-related quality of life scores as well as lower baseline scores while the patients who completed the study showed a stable of progressive throughout the study.

The probability of early death differed between study sites and it could relate to the difference of the distribution of diagnosis between the study sites. We found that study site 3 had enrolled around 70% of cancer patients with malignant neoplasm of bronchus and lung, metastatic colorectal cancer or colon carcinoma, and malignant neoplasm of pancreas, whilst study site 1 enrolled around 15% of those cancer types and about 60% of cancer patients with acute leukemia and aggressive lymphoma (data not shown). It is relevant to our finding that patients who were diagnosed with malignant neoplasm of pancreas had a higher risk of early death. This result has implications to research design, patient selection, and further data interpretation.

Older age was not markedly related to drop-out or death in our study, although there was a weak association between older age and early death. This result is in line with previous cancer studies (6, 7, 21), some studies reported contrary findings (9, 10). Males seemed more likely to early drop-out compared to females in our study; however, this association was reversed in some other studies (22, 23). Additionally yet other studies found no association between sex and the probability of drop-out (7, 9). Participants with lower educational status presented early drop-out, but this association was only weak in our study. Similarly, Spiers et al. and Roick et al. found that low education was associated with loss to follow-up (9, 10). Another finding in this study was that being divorced or widowed was related to drop out. Similar findings were observed among cancer patients in a cluster-randomized controlled trial (9), other studies could not confirm this association (6, 7). Moreover, lack of social support was associated with early drop-out among cancer patient. These findings are in line with ours, where family status is playing a role as social support and it has a positive effect on patients’ health, quality of life, and coping behavior (25). Therefore, lack of social support from family or friends might be one explanation for the lack of motivation to continue a study.

Surprisingly, there was no marked differential drop-out between intervention and control groups, despite our expectation of lower drop-out rates in the control group. In contrast we found slightly higher rates of drop-out and death in the intervention group compared to the control group. Yielding unbiased results depend on the appropriate handling of missing data within the analytical approach (26). Our findings, that baseline characteristics and QoL were associated to drop-out, could be useful to determine the potential missing data mechanism, which is a prerequisite to considering the choice of handling missing PROs data e.g. imputation methods. In addition, poor baseline QoL scores should prompt researchers to
assess more auxiliary data such as Eastern Cooperative Oncology Group (ECOG) performance status and reasons for incomplete PROMs questionnaires are collected to assist in determining the type of missingness and using those auxiliary data as covariate in the model or using in multiple imputation methods (27). In presence of the relationship between symptom severity and missing data in health-related QoL from drop out and death, the missing data mechanism is clearly not missing completely at random (MCAR). The pattern of PROs before drop out and death may suggest that missing at random (MAR) or missing not at random (MNAR) is present. The results suggest that OSCAR study needs appropriate consideration for a primary endpoint analysis. Complete case analysis or last observation carried forward (LOCF) method would not be appropriate, especially in health-related QoL outcomes. Alternative models such as pattern mixture models or joint models might be used if the PROs data are MNAR (27, 28). Independent of the particular statistical method used to handle missing PRO data, sensitivity analyses should be conducted and reported whatever the type of missing data mechanism is assumed (27).

Limitations of this study are: no information on the severity of a patient’s disease, as e.g. the stage of cancer, which could affect the time to death, and multivariable analyses were not possible and the statistical power was restricted, due to multi-collinearity within the PROs and a low number of observations in some variables e.g. education, family status, and HLS-EU-Q6. As there was no correction for multiple testing and without a multivariable analysis, p-values should be interpreted with caution and even small p-values cannot be interpreted as demonstrations of substantial effects.

Conclusions

Our study demonstrates that participants with low quality of life, worse symptoms, and poor social support seem to be more likely to discontinue the study early compared to patients with better values, resulting in a higher rate of missing patient-reported outcomes. This should be taken into account when planning any study in advanced cancer patients by shortly monitoring in those who has low baseline quality of life. Expected high mortality rates up to 50% during study time should be already considered in sample size calculations. Follow-up periods and study duration should be planned well. Continued monitoring is useful to characterize the study sample and to react fast to avoid a high drop-out rate. Methods to identify the factors related to drop-out similar to those we used here are useful to determine the missing data mechanism and informing choice of statistical methods for primary endpoint analysis. Methods for handling missing data might be applied appropriately, interpreting results of patient-reported outcomes should be done within caution, reasons for drop-out and how it may impact the finding should be discussed.

Abbreviations

API-DM: The German modified version of the Autonomy Preference Index

CI: Confidence interval
Declarations

Ethical approval and consent to participate

The OSCAR was approved by the ethics committees at Charité – Universitätsmedizin Berlin (EA2/192/17), the Medical Association of North Rhine (2017429), and German Clinical Trial Register (DRKS-ID: DRKS00013640). The participants were enrolled in the study after providing informed consent.

Consent for publication
Availability of data and materials

The datasets analyzed during the current study are not publicly available due to privacy and ethical concerns, neither the data nor the source of the data can be made available. The analysis code is available from the corresponding author on request.

Competing interests

The authors declared that they have no competing interests.

Funding

The OSCAR project received a grant from the Innovation Fund of the Federal Joint Committee (G-BA). Reference number: 01NVF17016. The G-BA had no role in the design of the study and collection, analysis and interpretation of data and in writing the manuscript.

Author contribution

PG drafted the manuscript and performed the statistical analysis.

JF, DS and LS participated in the design of the study and critical review.

UG and LS supervised the study.

UG was involved in the statistical design and verified the analytical methods.

All authors discussed the results and approved the final manuscript.

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References


scale.

Tables

Table 1 Participants’ demographic data as characteristics associated to time-to-dropout with early death as a competing risk
<table>
<thead>
<tr>
<th>Study group</th>
<th>n</th>
<th>Time-to-dropout with death as a competing risk</th>
<th>Death</th>
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<tr>
<td></td>
<td></td>
<td>SHR (95%CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Intervention</td>
<td>150</td>
<td>1.23 (0.76, 1.99)</td>
<td>1.26 (0.84, 1.88)</td>
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<td>Control</td>
<td>212</td>
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<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>362</td>
<td>1.01 (0.99, 1.03)</td>
<td>1.02 (1.00, 1.03)</td>
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<td>Study site</td>
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<td>Study site 1</td>
<td>119</td>
<td>1</td>
<td></td>
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<tr>
<td>Study site 2</td>
<td>98</td>
<td>1.77 (0.94, 3.33)</td>
<td>1.69 (0.99, 2.89)</td>
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<tr>
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<td>145</td>
<td>1.60 (0.87, 2.93)</td>
<td>1.99 (1.22, 3.26)</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>219</td>
<td>1.35 (0.82, 2.24)</td>
<td>0.75 (0.51, 1.11)</td>
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<td>Female</td>
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<tr>
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<td>1.68 (0.84, 3.38)</td>
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<td>Single</td>
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<td>1</td>
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<td>Divorced/Widowed</td>
<td>63</td>
<td>2.71 (1.12, 6.56)</td>
<td>0.89 (0.36, 2.20)</td>
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<td>Time since diagnosis</td>
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<tr>
<td>≤6 months</td>
<td>187</td>
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<td>1</td>
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<tr>
<td>7 – 12 months</td>
<td>49</td>
<td>0.43 (0.17, 1.08)</td>
<td>1.06 (0.58, 1.93)</td>
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<td>13 – 24 months</td>
<td>46</td>
<td>0.54 (0.22, 1.32)</td>
<td>1.53 (0.87, 2.67)</td>
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<td>&gt;24 months</td>
<td>80</td>
<td>0.97 (0.54, 1.72)</td>
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<td>Diagnosis</td>
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<td>(CI)</td>
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<td>Aggressive lymphoma</td>
<td>58</td>
<td>1.53</td>
<td>(0.64, 3.65)</td>
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<td>Malignant neoplasm of bronchus and lung</td>
<td>62</td>
<td>1.92</td>
<td>(0.84, 4.38)</td>
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<td>Metastatic colorectal cancer/colon carcinoma</td>
<td>78</td>
<td>1.39</td>
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<td>Malignant neoplasm of pancreas</td>
<td>32</td>
<td>1.94</td>
<td>(0.79, 4.77)</td>
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<tr>
<td>Multiple myeloma and malignant plasma cell neoplasms</td>
<td>24</td>
<td>1.24</td>
<td>(0.40, 3.83)</td>
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<tr>
<td>Metastasized malignant neoplasm of breast</td>
<td>9</td>
<td>0.91</td>
<td>(0.11, 7.21)</td>
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<tr>
<td>Others</td>
<td>30</td>
<td>2.13</td>
<td>(0.79, 5.74)</td>
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**Education**

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<th>SHR</th>
<th>(CI)</th>
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<th>(CI)</th>
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<td>(0.90, 3.81)</td>
<td>0.92</td>
<td>(0.39, 2.15)</td>
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<tr>
<td>Medium</td>
<td>101</td>
<td>1.27</td>
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<td>1.58</td>
<td>(1.02, 2.45)</td>
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<tr>
<td>High</td>
<td>206</td>
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**Social support (OSSS-3)**

<table>
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<th>Social support</th>
<th>n</th>
<th>SHR</th>
<th>(CI)</th>
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<th>(CI)</th>
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<tr>
<td>Poor (3 – 8)</td>
<td>35</td>
<td>2.10</td>
<td>(1.01, 4.35)</td>
<td>0.83</td>
<td>(0.39, 1.79)</td>
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<tr>
<td>Moderate (9 – 11)</td>
<td>158</td>
<td>1.32</td>
<td>(0.74, 2.36)</td>
<td>0.87</td>
<td>(0.56, 1.36)</td>
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<tr>
<td>Strong (12 – 14)</td>
<td>139</td>
<td>1</td>
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<td>1</td>
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</table>

n=number of observation, SHR=Sub-hazard ratio, HR=Hazard ratio, CI=Confidence Interval

**Figures**
Figure 3

Patterns of patients who (a) dropped out or (b) died: Subscales of the EORTC QLQ-C30 versus follow-up times, stratified by drop-out time or death time. The possible range of the EORTC QLQ-C30 is 0-100, with higher values indicating better QoL in global health status/QoL, physical functioning, role functioning, social functioning, and lower values indicating better symptom in fatigue and appetite loss.