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The distress thermometer as a prognostic tool for one-year survival among patients with lung cancer

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ABSTRACT

Introduction: The use of patient-reported outcome measures is increasingly advocated to support high-quality cancer care. We therefore investigated the added value of the Distress Thermometer (DT) when combined with known predictors to assess one-year survival in patients with lung cancer.

Methods: All patients had newly diagnosed or recurrent lung cancer, started systemic treatment, and participated in the intervention arm of a previously published randomised controlled trial. A Cox proportional hazards model was fitted based on five selected known predictors for survival. The DT-score was added to this model and contrasted to models including the EORTC-QLQ-C30 global QoL score (quality of life) or the HADS total score (symptoms of anxiety and depression). Model performance was evaluated through improvement in the -2 log likelihood, Harrell's C-statistic, and a risk classification.

Results: In total, 110 patients were included in the analysis of whom 97 patients accurately completed the DT. Patients with a DT score ≥ 5 (N = 51) had a lower QoL, more symptoms of anxiety and depression, and a shorter median survival time (7.6 months vs 10.0 months; P = 0.02) than patients with a DT score < 5 (N = 46). Addition of the DT resulted in a significant improvement in the accuracy of the model to predict one-year survival (P < 0.001) and the discriminatory value (C-statistic) marginally improved from 0.69 to 0.71. The proportion of patients correctly classified as high risk (≥ 85% risk of dying within one year) increased from 8% to 28%. Similar model performance was observed when combining the selected predictors with QoL and symptoms of anxiety or depression.

Conclusions: Use of the DT allows clinicians to better identify patients with lung cancer at risk for poor outcomes, to further explore sources of distress, and subsequently personalize care accordingly.

1. Introduction

Lung cancer is the second most common and deadliest cancer worldwide. It constitutes approximately 14 percent of all cancer diagnoses and 27 percent of all cancer deaths [1]. Most patients are diagnosed with either locally advanced or metastatic disease and are often faced with treatment-related toxicities and side-effects [2]. These factors contribute to a poor prognosis, high levels of distress, and a lower quality of life (QoL) among patients and their caregivers [3,4].

Despite this poor prognosis and limited survival, many patients with lung cancer receive aggressive treatments (e.g. chemotherapy) near the end of their life. Discussions focused on discussing the rationale for such

treatments or patient's goals and values either happen late in the disease course or are of insufficient quality [5]. Moreover, it may be difficult to accurately determine a patient's prognosis due to the unpredictability of the disease course. Indeed, previous work shows that current prognostic predictions by clinicians are frequently inadequate and largely based on disease-related characteristics [6,7]. Recent studies have thus suggested that addition of patient-reported outcome measures (PROMs) to such predictions can be useful to better approximate a patient's prognosis [8–11]. Use and subsequent discussion of such measures also leads to better symptom control, increased use of supportive care facilities or measures, and enhanced patient satisfaction [12].

A PROM has been defined as "a measurement of any aspect of a patient's health status that comes directly from the patient" [13]. International and consensus-based guidelines advocate the routine use of PROMs as an integral component of high-quality cancer care [9,11,14–16]. To date however, these measures are only sparsely incorporated in clinical care for patients with (lung) cancer [17,18]. One example of a possibly useful rapid assessment tool is the Distress Thermometer (DT). The DT is a single-item, visual analogue scale that can be immediately interpreted to rule out elevated levels of distress in patients with cancer [19,20]. The prognostic value or significance of this tool in terms of survival has not been confirmed among patients with lung cancer [21]. To this end, we sought to investigate the prognostic value of the DT when combined with sociodemographic and clinical predictors to assess one-year survival in patients with lung cancer. We also compared this model to models that included quality of life or symptoms of anxiety and depression.

2. Methods

2.1. Design and setting

This study represents a secondary analysis of data obtained from a randomised controlled trial (RCT) evaluating the effects of screening for distress using the DT, the associated Problem List (PL) and additional supportive care measures to those in need of such care. This study detailed on the effects of this intervention on QoL, mood, patient satisfaction, and end-of-life care. The primary results of this trial are detailed elsewhere [22]. The RCT was conducted at the University Medical Center Groningen among patients with newly diagnosed or recurrent lung cancer starting systemic treatment. Randomisation, data collection and management was performed by the Netherlands Comprehensive Cancer Organization. The study was approved by the institutional Medical Ethics Committee (NTR3540).

In short, patients were included within a week after start of systemic therapy and subsequently randomized in a 1:1 ratio to either the intervention group or the control group. Only patients assigned to the intervention group were invited to complete the DT and PL prior to their scheduled outpatient visit. Dependent on the DT-score, type of problems identified, and/or patient's referral wish, responses were discussed with a nurse practitioner specialized in psychosocial issues. Patients were subsequently offered referral to an appropriate and licensed professional (e.g. a psychologist, social worker, physical therapist, or a dietician). Patients assigned to the control group were not routinely screened for distress and did not complete the DT and PL. They received care as usual as determined by the treating clinician. The primary outcome was the mean change in the EORTC-QLQ-C30 global QoL-score between 1 and 25 weeks.

2.2. Study population

Between 1 January 2010 and 30 June 2013, 223 patients were enrolled in the trial (response rate 66%). All patients had received a histological diagnosis of any type of lung cancer (stage Ib through IV), had an Eastern Cooperative Oncology Group (ECOG) performance scale of 0, 1 or 2, had to start a form of systemic treatment, were without cognitive impairment, and were able to complete questionnaires in Dutch. Systemic treatment was defined as treatment with chemotherapy, adjuvant chemotherapy, chemo-radiotherapy, or treatment with biologicals. Of the patients included, 110 were randomized to the intervention arm. These patients were asked to complete the DT and were therefore included in the current analyses.

2.3. Patient characteristics and survival

Sociodemographic characteristics were obtained from the hospital's electronic health record at study entry as were clinical characteristics

detailing on histological tumour type, performance status, recurrent versus new diagnosis, disease stage, initial type of treatment, and the Charlson age-adjusted co-morbidity index were also derived from the electronic health record [23]. Date of death was recorded from the electronic health record up to one year after randomisation.

2.4. Distress thermometer, quality of life, and mood

The DT is an extensively validated measure to screen for distress [19,24,25]. It consists of a single-item, visual analogue scale with a score ranging from 0 (no distress) to 10 (extreme distress) and is to be completed by the patient to quantify the level of distress experience in the past week. A score on the DT below either four or five, depending on the country and setting, has been propagated as optimal cut-off to rule out significant distress in patients with cancer [19,26]. An optimal cut-off value of five was observed among Dutch patients with cancer and therefore used in the current study. We did not use data obtained through the Problem List in these analyses.

All patients also completed the EORTC-QLQ-C30 [27] to assess health-related QoL and the Hospital Anxiety and Depression Scale (HADS) [28] to assess mood. Scores on the EORTC-QLQ-C30 may range from 0 to 100 with higher scores reflecting better QoL. We only used the global QoL subscale in the current study as a best approximation to generic QoL. The HADS assesses symptoms of anxiety and depression over the past week with scores ranging from 0 (not at all) to 3 (very much). It consists of 14 questions and scores may vary from 0 to 21 with higher scores indicating more symptoms of anxiety or depression. All PROMs were completed after patients were randomised but within a week after the start of systemic therapy.

2.5. Selection of clinical predictors

Candidate predictors for one-year survival were selected based on the literature as well as expert opinion and availability of such predictors in clinical settings [29–33]. We selected the following five clinical or demographic predictors to be included in the model: 1) gender; 2) performance status (dichotomized as 0 or 1 versus 2);3) disease stage (dichotomized as non-metastasized: stage I, II and IIIa versus metastasized: stage IIIb and IV); 4) the Charlson age-adjusted comorbidity index (entered as a continuous variable) and; 5) tumour histology (dichotomized as non-small cell lung carcinoma versus small-cell lung carcinoma).

2.6. Statistical analyses

To characterize the study population, descriptive statistics were used to evaluate the frequencies, mean, and standard deviations for all sociodemographic and clinical characteristics as well as other study measures at study entry. Patients with significant distress (DT-score ≥ 5) were compared to those without significant distress (DT-score < 5) using independent T-tests and Chi-square tests [26]. The one-year survival of patients with and without significant distress was compared with the log-rank test and illustrated with a Kaplan-Meier curve. Statistical tests were performed with two-sided alternatives and considered significant if $P \leq 0.05$, using SPSS software version 25 and STATA/IC version 13.

2.7. Model building

Univariable Cox proportional hazard models were used to determine the association of these predictors separately with one-year survival. We examined the proportional hazards assumption using log-minus-log plots. Regardless of statistical significance, all selected predictors were subsequently entered together simultaneously into a Cox proportional hazard model. This constituted the basic model. Hereafter, we separately added three sets of PROMs to the basic model: 1) the DT-

score; 2) the EORTC-QLQ-C30 global QoL score; and 3) the HADS total score. We report on the added value of these PROMS to the basic model by evaluating the change in -2 log likelihood (-2LL), the statistical significance, and Harrell's C-statistic with a 95% CI [34]. The -2LL is a measure of accuracy or overall performance of the model whereas the C-statistic demonstrates the difference in discriminatory value of a model comparable to the area under the receiver operating characteristic curve [34,35].

2.8. Reclassification of high-risk patients

To provide better clinical insight regarding the added value of the DT, we constructed a reclassification table including all patients who completed the DT. This table depicts the shift in classification of cases of mortality and non-cases separately for the basic model and the model after addition of the DT-score. To obtain this table, the individual survival risk was calculated for each patient using the baseline survival and the regression coefficients of the selected predictors. We then defined two risk groups (normal risk vs. high risk) primarily based on the net one-year survival date of patients with lung cancer. We defined the high risk group as patients having a one-year mortality risk as ≥85 percent [36,37]. This reclassification was not performed for models that included the EORTC-QLQ-C30 global QoL score or the HADS total score.

3. Results

3.1. Study population

Relevant demographic and clinical characteristics of the included patients are displayed in Table 1. Approximately half of these patients was female (46%), 65% was diagnosed with stage IV lung cancer, and 81% was initially treated with a chemotherapy or chemo-radiotherapy regimen. A total of 97 patients (88%) accurately completed the DT. Patients not completing the DT (N = 13) were comparable in all sociodemographic as well as clinical characteristics to patients who completed the DT (all p-values ≥0.10; data not shown).

3.2. Comparison of patients with and without significant distress

Of the 97 patients who accurately completed the DT, 51 had a DT score > 5 and 46 had a score < 5. Patients with and without significant distress were comparable in terms of sociodemographic and illness-related characteristics (Table 1; all p-values ≥0.10). Patients with clinically relevant distress reported a significantly lower global QoL (p < 0.001), and depicted higher scores on the depression and anxiety subscales of the HADS as well as the total HADS score (p = 0.004; p = 0.004; and p = 0.001; respectively). Median one-year survival time among patients with clinically relevant distress was significantly shorter: 7.6 months (95% CI: 6.5–8.7) versus 10.0 months (95% CI: 9.1–11.0; P = 0.02).

3.3. Univariable analyses and performance of multivariable models

Table 2 displays the univariable relationships between the five selected predictors and the three sets of PROMS with one-year survival. Performance status, disease stage, and the Charlson age-adjusted comorbidity index were all found to be significant predictors. Of the included PROMs, the global QoL-score and the DT-score were identified as significant predictors, but not the HADS.

Table 3 depicts the performance of the multivariable model as well as the performance of subsequent multivariable models when combined separately with the three sets of PROMs. The -2LL, i.e. the accuracy of

the model, significantly improved after addition of the global QoL-score (491.4 to 431.9; P < 0.001), addition of the HADS total score (491.4 to 410.0; P < 0.001), and addition of the DT-score (491.4 to 397.5; P < 0.001). The C-statistic, i.e. the discriminatory value, improved slightly from 0.69 (95% CI: 0.63 – 0.76) in the model with clinical predictors to 0.71 (95% CI: 0.64 – 0.77) after addition of the DT-score. Addition of the global QoL-score and the HADS total score led to a C-statistic of 0.69 (95% CI: 0.62 – 0.77) and 0.67 (95% CI: 0.60 – 0.75), respectively.

3.4. Improved reclassification of high risk patients

The reclassification model of the 97 patients of whom 50 died within one year is shown in Table 4. The proportion of correctly classified high-risk patients who died within one year increased from 8 percent to 28 percent (10 additional patients) after addition of the DT-score to the basic model. Moreover, addition of the DT-score did not considerably increase the proportion of patients incorrectly classified as high risk (Table 4; increase from 3% to 5%).

4. Discussion

To our knowledge, this is the first study to show that addition of a patient-reported distress score, as measured by DT, to selected clinical predictors may hold prognostic value when estimating one-year survival. Similar results were obtained when combining the selected predictors with QoL and symptoms of anxiety or depression. Further, patients with clinically relevant distress had a significantly shorter median one-year survival time when compared to patients without clinically relevant distress, whilst being comparable in terms of clinical and sociodemographic characteristics. This finding was also supported by the improvement in the classification of patients with a high risk of death (≥85%) after combining the DT-score with selected predictors. This suggests that addition of a patient-centered outcome that can be rapidly interpreted may allow clinicians to more accurately determine which patients are at risk for a poor prognosis and possibly personalize care accordingly.

When viewed in the light of current clinical practice, these findings are important for several reasons. First, we specifically opted to study the prognostic value of the DT since prognosis of patients with lung cancer is often poor and the overall one-year net survival is only 30 percent [36,38]. The DT was originally developed as a rapid screening and diagnostic tool to rule out clinically relevant distress in patients with cancer [14,25]. Studying the prognostic value of the DT may thus move this tool beyond the originally intended purpose. Yet, other PROMs such as QoL, anxiety, and depression have previously been identified as important prognostic indicators in multiple, large-scale studies [8–11]. More importantly perhaps, these outcomes are associated with distress [39,40]. Having a fast and efficient tool available that screens for distress, and simultaneously conveys prognostic information, is therefore a promising finding in this patient population.

Second, numerous studies conducted across different care settings have provided clear evidence to support the earlier integration of palliative care, sometimes even delivered concurrently with (curative) treatment [41,42]. This has led to an increased interest with regards to the earlier integration as well as official endorsement by clinical guidelines [43]. Yet, many patients with advanced (lung) cancer either receive such care at a late stage and the quality of such care may not be optimal [44,45]. Although the use of a short screening tool cannot substitute careful clinical assessment and management, routine use of the DT may aid clinicians in identifying those patients at risk for poor outcomes and provide a vantage point from which to earlier engage patients and caregivers in patient-centered conversations about

Table 1
Description of total study population at study entry and comparison of groups with and without significant distress according to the Distress Thermometer.

Characteristic	Total study population (N = 110)	DT-score < 5 (N = 46)[a]	DT-score ≥ 5 (N = 51)[a]
Age (mean ± SD)	60.6 ± 10.5	59.8 ± 10.5	61.3 ± 10.7
Female sex (N [%])	50 (46)	20 (43)	24 (47)
Performance status			
(N [%])	46 (42)	22 (48)	21 (41)
0	56 (51)	21 (46)	27 (53)
1	8 (7)	3 (6)	3 (6)
2			
Recurrent disease, yes (N [%])	29 (26)	9 (20)	16 (31)
Disease stage (N [%])	10 (9)	5 (11)	5 (10)
Stage 1 or 2	29 (26)	14 (30)	12 (23)
Stage 3 Stage 4	71 (65)	27 (59)	34 (67)
Smoking status (N [%])	48 (44)	16 (35)	28 (55)
Yes	51 (46)	25 (54)	17 (33)
Quit	11 (10)	5 (11)	6 (12)
Never			
Charlson age-adjusted comorbidity index (mean ± SD)	8.3 ± 2.4	7.9 ± 2.4	8.6 ± 2.5
Histology (N [%])	64 (58)	25 (54)	31 (61)
Adenocarcinoma	19 (17)	8 (18)	9 (18)
Squamous cell	5 (5)	2 (4)	2 (4)
carcinoma Large cell	20 (18)	10 (22)	8 (16)
n.o.s.	2 (2)	1 (2)	1 (1)
Small-cell carcinoma			
Other			
Initial type of treatment (N [%])	60 (55)	22 (48)	32 (63)
Chemotherapy	29 (26)	15 (33)	11 (22)
Chemo-radiotherapy	21 (19)	9 (19)	8 (16)
Biological			

Characteristic	Total study population (N = 110)	DT-score < 5 (N = 46)[a]	DT-score ≥ 5Please change to the symbol used abose (N = 51)[a]
EORTC-QLQ-C30 score[b,d] (mean ± SD) Global quality of life (N = 94)	59.2 ± 20.8	69.4 ± 19.1	51.5 ± 17.3***
HADS score (mean ± SD)[c,d] Anxiety subscale (N = 93)	6.4 ± 4.1	5.1 ± 3.6	7.5 ± 4.2**
Depression subscale (N = 93)	6.2 ± 3.9	4.9 ± 3.7	7.2 ± 3.6**
Total score (N = 92)	12.6 ± 7.2	10.0 ± 6.3	14.6 ± 7.0**
Distress Thermometer (N = 97) Score (median; range)	5.0 (0 – 10)	–	–
Score ≥5 (%)	46	–	–

Abbreviations: DT: Distress Thermometer, SD: Standard Deviation.

*p < 0.05, ** p < 0.01, ***P < 0.001, otherwise not significant (p > 0.10).

[a] Patients below the DT-score cutoff and DT-score above cutoff were compared. The remaining 13 patients did not accurately complete the DT and could not be included in this analysis.

[b] The 30-item EORTC-QLQ-C30 assesses QOL. Scores can range from 0 to 100 with higher scores reflecting better functioning.

[c] The 14-item Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depression levels over the last week in two subscales each consisting of seven items. Scores vary from 0 to 21 with higher scores indicating greater anxiety or depression.

[d] Number of respondents vary and are denoted per questionnaire or subscale.

advance care planning and palliative care options.

In contrast to our findings, one previously conducted study (N = 113) did not identify the prognostic value of the DT in patients with stage III lung cancer treated with chemotherapy containing carboplatin [21]. Notably, the observed median DT-score in that study was lower compared to the current study and the majority of patients refused to complete the DT and the associated Problem List. As described by the authors, this selection bias may account for the contrasting findings. Previous studies, although conducted among different cohorts of patients with advanced cancer, have shown that screening for distress has positive effects on the experienced of physical as well as psychosocial problems [46,47]. Moreover, these studies also observed that distress measures may convey important prognostic information in terms of survival.

A recent systematic review concluded that more effort is needed towards ensuring patients' adherence when completing PROMs and that routine completion should be supplemented by clear guidelines to support clinicians when discussing responses with patients [12]. Other PROMs such as QoL and anxiety or depression have been found to convey important prognostic information in patients with cancer [9,11,16,48]. Yet, these instruments are often lengthy and require additional training and time investment. Also, healthcare professionals have cited practical concerns related to the length of questionnaires and required time investment, disruption of workflow, costs, and a lack of training for accurate interpretation [49]. In contrast to this, the DT allows for rapid assessment and may therefore be easier to integrate in clinical settings.

Our findings should be viewed in light of certain limitations. The

Table 2
Univariable associations of selected clinical predictors with one-year survival.

Clinical predictors	Coefficient	HR (95% CI)	P-value
Gender	–	–	–
Male[a]	−1.95	0.82 (0.49 – 1.38)	0.46
Female			
Performance status at inclusion	–	–	–
0, 1[a]	1.43	4.18 (1.9 – 9.35)	0.001
2			
Disease stage	–	–	–
Stage Ib, II, IIIa[a]	0.92	2.51 (1.14 – 5.53)	0.02
Stage IIIb, IV			
Charlson age-adjusted comorbidity index	0.23	1.26 (1.12 – 1.42)***	< 0.001
Histology	–	–	–
Non-small cell lung carcinoma[a]	− 0.25	0.78 (0.39 – 1.54)	0.47
Small-cell carcinoma			
Patient-reported outcome measures			
EORTC-QLQ-C30 score	− 0.15	0.99 (0.97 – 1.0)	0.02
Global quality of life scale			
Hospital Anxiety and Depression scale	0.013	1.01 (0.98 – 1.05)	0.32
Total score			
Distress Thermometer	0.21	1.24 (1.09 – 1.40)	0.001
Total score			

a: Reference category The Hazard Ratio is displayed per unit of the score for continuous variables.

current study represents a secondary analysis of a previously conducted RCT at a single, academic institution and our sample size was small. Further, although we did include patients with any histological subtype of lung cancer and all patients started a form of systemic treatment, only patients with an ECOG performance status between 0 and 2 were eligible for inclusion in the trial (the full score ranges from 0 to 5). These observations limit the generalizability of our findings. Third, the current patient population does not include patients treated with immunotherapy. This recent treatment modality is likely to markedly shift the prognosis of patients with advanced lung cancer in the near future. It would therefore be interesting to investigate whether patients with increased levels of distress are also at risk of a poor prognosis among those patients treated with immunotherapy.

Next, we used the -2LL and the C-statistic as a best approximation to general performance of the different multivariable models. The -2LL did show significant improvements after addition of the different PROMs but we did not observe similar findings using the C-statistic (all values between 0.67 and 0.71). The C-statistic, however, has been criticized for a lack of sensitivity with regards to recognizing the added value of a risk marker. It has therefore been recommended to additionally construct and report on a reclassification table since this conveys important

Table 4
Improved predicted one-year mortality risk classification with addition of the Distress Thermometer score to selected predictors among 97 patients with lung cancer.

Predicted risk of mortality within one year	Yes, N (%)	No, N (%)	Total
Selected predictors			
Normal risk < 85%	46 (92)	46 (97)	92
High risk ≥85%	4 (8)	1 (3)	5
Total risk group	50 (100)	47 (100)	97
Selected clinical predictors + Distress Thermometer score			
Normal risk < 85%	36 (72)	45 (95)	81
High risk ≥85%	14 (28)	2 (5)	16
Total risk group	50 (100)	47 (100)	97

The five selected predictors: 1) gender, 2) performance status at inclusion, 3) disease stage, 4) Charlson age-adjusted comorbidity score, 5) histology.

complementary information [50]. In line with this, we decided to use a cutoff of 85 percent to define patients at high risk of dying within one year [36,37]. We specifically decided not to include the EORTC-QLQ-C30 or the HADS in this reclassification table. Instead, we contrasted the performance of these PROMs in the outlined multivariable models to demonstrate similar performance of the DT when compared to other PROMs.

Further, although this cutoff likely represents the futility of further tumor-targeted treatment in this patient population, it was arbitrarily chosen and should be further validated in future studies. Last, the response rate in the original trial was relatively low (66%). This was most likely because of the high symptom burden these patients already face and was also stated as the most common reason for participation refusal (41% of objectors). This should be taken into consideration when interpreting our current findings.

4.1. Conclusions

In conclusion, this is the first study to provide evidence for added prognostic value of the DT-score in patients with lung cancer. The possible relationship between the DT-score and survival should be evaluated further in prospective, longitudinal studies across different settings and institutions [9]. Yet, our findings are promising and may allow clinicians to identify those patients at risk for poor outcomes and prevent discordance between care received and personal patient preferences near the end of life. This may further improve the timely delivery of high quality, patient-centered care among patients with lung cancer.

Fig. 1. Kaplan-Meier overall one-year survival curve stratified by significantly elevated elevated distress as evaluated by the Distress Thermometer (cutoff score of 5). Survival data was calculated from the date of randomization and date of death was recorded up to one year later.
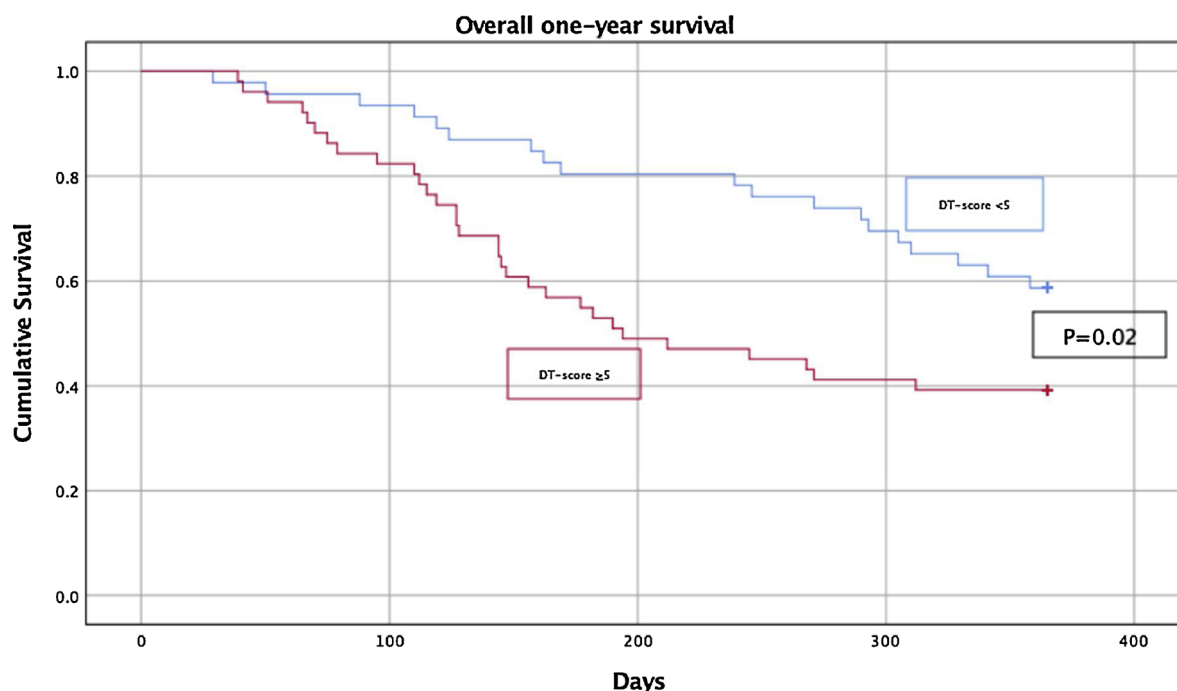
Table 3
Different multivariable models of selected predictors when combined with various patient-reported outcome measures.

Variables included in model	− 2 LL	P-value	C-statistic (95% CI)
Selected predictors (N = 110)	491.4	–	0.69 (0.63 – 0.76)
Selected predictors + global Quality of Life (N = 99)	431.9	< 0.001	0.69 (0.62 – 0.77)
Selected predictors + symptoms of anxiety and depression (N = 96)	410.0	< 0.001	0.67 (0.60 – 0.75)
Selected predictors + Distress Thermometer score (N = 97)	397.5	< 0.001	0.71 (0.64 – 0.77)

P-value calculated (Chi-square two-sided test) versus model with selected predictors only.
Abbreviations: -2 LL: -2 Log Likelihood. C-statistic: Harrel's C concordance statistic The five selected predictors1) gender, 2) performance status at inclusion, 3) disease stage, 4) Charlson age-adjusted comorbidity score, 5) histology.; Global Quality of Life was measured using the global QoL subscale of the EORTC-QLQ-C30. Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale total score.

Fig. 1. Kaplan-Meier overall one-year survival curve stratified by significantly elevated elevated distress as evaluated by the Distress Thermometer (cutoff score of 5). Survival data was calculated from the date of randomization and date of death was recorded up to one year later.

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