

**Original Article**

# Mild to Moderate Cognitive Impairment Does Not Affect the Ability to Self-Report Important Symptoms in Patients With Cancer: A Prospective Longitudinal Multinational Study (EPCCS)



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## Abstract

**Context.** Patients with advanced cancer commonly suffer from both distressing symptoms and cognitive impairment, but the effect of cognitive impairment on the reliability and validity of symptom self-report is unknown.

**Objectives.** To evaluate the reliability and validity of symptom self-report in cancer outpatients with and without mild to moderate cognitive impairment.

**Methods.** This was an analysis of the longitudinal European Palliative Care Cancer Symptom study of adults with incurable cancer in specialized palliative care (30 centers across 12 countries). Patients who could not comply with the study because of severe cognitive impairment were excluded. Cognitive status on the Mini-Mental State Examination short version and nine symptoms (pain, tiredness, drowsiness, nausea, appetite, breathlessness, depression, anxiety, and well-being) using the revised Edmonton Symptom Assessment System were self-reported at baseline and one-month follow-up. Reliability was analyzed using intraclass correlation coefficients and validity using regression of each symptom with health-related quality of life (HrQoL) measured with European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 for Palliative Care.

**Results.** A total of 1047 patients were included: mean age of 62.9 years; 54.4% women; main cancer types were of digestive organs (26.6%), breast (21.6%), and lungs (21.2%). Cognitive impairment was present in 181 (17.3%) at baseline and associated with worse self-reported tiredness, drowsiness, appetite, and depression. Reliability (intraclass correlation coefficient) and validity (associations with HrQoL) were similar between people with/without cognitive impairment across the nine symptoms, except breathlessness, which showed a weaker relation to HrQoL in patients with cognitive impairment. Findings were robust in sensitivity analyses and after controlling for potential confounders.

**Conclusion.** In advanced cancer, self-report of nine major symptoms was reliable and valid also in people with mild-to-moderate cognitive impairment.

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### Key Words

*Dyspnea, cognitive impairment, patient-reported outcomes, reliability, validity*

### Key Message

In this longitudinal cohort study of 1047 cancer outpatients, mild-to-moderate cognitive impairment was common (17%). Self-report of nine major symptoms was reliable and valid also in patients with mild-to-moderate cognitive impairment, but proxy report may be needed for some patients with advanced cancer who are unable to self-report.

### Introduction

Symptom assessment is essential for clinical evaluation and care in people with cancer for improved health-related quality of life (HrQoL) and reduced patient suffering. Symptoms should be assessed using validated instruments, which have established reliability and enable valid interpretation and comparison, such as a 0–10 Numerical Rating Scale (NRS).<sup>1,2</sup> Although important throughout the disease trajectory, symptom assessment becomes even more important in advanced cancer with worsening symptom burden. At this stage, self-reported symptom measures might be influenced by clinical factors including cognitive impairment.

Cognitive impairment is common in cancer, affecting up to 30% before chemotherapy<sup>3</sup> and up to 75% during or after chemotherapy.<sup>4</sup> The impairment is often global, affecting, for example, memory, attention, and executive functions.<sup>5</sup> The cause is multifactorial and can be related to cancer therapy (especially chemotherapy),<sup>6</sup> pain and other symptoms,<sup>7</sup> medications, the cancer itself,<sup>4</sup> or secondary symptoms, such as insomnia, pain, fatigue, and depression.<sup>8,9</sup> Many cancer-related symptoms, such as pain, are underreported (if not actively assessed) in cognitively impaired compared with cognitively unimpaired individuals.<sup>3</sup> This leads to poorer pain management among cognitively impaired<sup>3,10–13</sup> and highlights the need to actively administer and thoroughly evaluate self-reported symptom scales in vulnerable patients to assess and document symptoms and optimize treatment.

However, cognitive impairment may affect the ability to self-assess symptoms on, for example, the NRS measures. Because these are popular tools both in clinical settings and drug trials of patients with cancer, incorrect self-reporting, on, for example, the NRS,

could result in poorer symptom management and affect trial outcomes. There are previous studies that evaluated the properties of the NRS to assess pain in elderly and cognitive impaired patients;<sup>14–19</sup> however, to our knowledge, the systematic assessment of the effect of cognitive impairment on symptom scoring using an NRS in patients with cancer is unknown. An issue when evaluating the accuracy of symptom report is the lack of an objective gold standard for the experienced sensations other than self-report. As a way to address this issue, studies have examined the effect of cognition on the symptom scores' test-retest reliability,<sup>14,16,20</sup> which informs on the amount of variability or random error. By comparing with the reliability in people without cognitive impairment, one can evaluate whether people with cognitive impairment self-rate in a less reliable and more varying manner. In addition, the association between the symptom scores with other relevant scales such as HrQoL (concurrent validity) can be evaluated, which informs on the systematic error, or to what degree the measure assesses the right thing and in a similar way between groups.<sup>21,22</sup>

The aims of the present study were to examine if individuals with advanced cancer and cognitive impairment had lower test-retest reliability in self-reported measures of pain, tiredness, drowsiness, nausea, lack of appetite, breathlessness, depression, anxiety, and well-being; poorer association between these ratings and global HrQoL; and higher rates of missing data, compared with patients with cancer without cognitive impairment.

### Material and Methods

#### *Study Design and Population*

This was a prospective longitudinal analysis of the European Palliative Care Cancer Symptom (EPCCS) study, the largest prospective longitudinal study to date of adults with incurable cancer enrolled in a palliative care program, with data from 30 palliative care centers across Europe, Australia, and Canada (12 countries).<sup>23</sup> The study was performed according to the Declaration of Helsinki and was registered in the [ClinicalTrials.gov](https://clinicaltrials.gov) database (NCT01362816). This article is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology framework for observational studies.<sup>24</sup>

Inclusion criteria for the present analysis were available data on cognition (Mini-Mental State Examination [MMSE] short version) and all nine symptom scores at baseline. Exclusion criteria for the EPCCS study included inability to participate because of psychotic disorders, severe cognitive impairment, or language problems.<sup>23</sup>

### Assessments

We included data from the first clinical assessment (baseline) and the first follow-up appointment after approximately four weeks.<sup>23</sup> Data from subsequent appointments were not included because of high rates of missing data. At baseline, assessments included demographics; time from cancer diagnosis; diagnosed comorbidities (chronic obstructive pulmonary disease [COPD], heart disease, liver disease, and renal disease); marital status; and highest education. At each study assessment, data were collected on height and weight; change in weight during the previous two and six months; cancer diagnosis, cancer stage, metastases to bone, central nervous system (CNS), lung, lymph nodes, other; medications, including glucocorticoids, opioids, other analgesics, and sedatives/anxiolytics; Karnofsky Performance Scale;<sup>25</sup> severity of nine symptoms (the revised Edmonton Symptom Assessment System; ESAS-r);<sup>26</sup> and whether data were patient or proxy reported. Data on medication preparation or doses were unavailable. Cognitive status was assessed using the four-item short version of the MMSE.<sup>27,28</sup> In this short version, the following MMSE items are included: 1) recalling present year (0–1 p), 2) recalling present date (0–1 p), 3) backward spelling of WORLD (0–5 p; 1 p for each correct letter), and 4) copying of two interlocking pentagons (0–1 p). This instrument screens for cognitive impairment in memory, attention/executive, and visuospatial domains. Cognitive impairment was defined as 0 p for year (i.e., incorrect year) or <3 p on spelling WORLD backward or 0 p on pentagon copying at baseline (i.e., incorrect pentagon copying).<sup>29</sup> Date was not included in the definition of cognitive impairment because even cognitively unimpaired individuals can have difficulties recalling the exact present date. Severity of symptoms was scored on an NRS between 0 (no) and 10 (worst possible) using the wording of the ESAS-r: “Please circle the number that best describes how you feel now.”<sup>26</sup> HrQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 for Palliative Care questionnaire.<sup>30</sup>

### Statistical Analyses

Baseline patient characteristics were summarized using mean with SD and median with range or interquartile range for continuous variables with normal and skewed distribution, respectively. Categorical

variables were expressed as frequencies and percentages. Data from the first two assessments were used because of high rates of patients with missing data at the third assessment on symptoms or cognition ( $n = 716$ ; 45.4%). Only data by patient self-report were included in the analyses. ESAS-r symptom scores, their reliability, and concurrent validity (association with HrQoL) were compared between patients with and without cognitive impairment. Reliability between baseline and the second visit was analyzed using the intraclass correlation coefficient using multilevel linear regression, accounting for repeated measurements. Associations (concurrent validity) for symptoms with HrQoL at baseline were analyzed using linear regression. Analyses were adjusted for the potential confounders: age, sex, level of education, opioid treatment, and treatment with sedatives/anxiolytics. Whether the associations differed by cognitive impairment was tested using an interaction term in the fully adjusted model. *P*-values of interactions were calculated using likelihood ratio test.

A sensitivity analysis was conducted, where all analyses were compared between patients who had cognitive impairment at both baseline and follow-up and patients who did not have cognitive impairment at any of these assessments. The group with cognitive impairment at both assessments was relatively small ( $n = 52$ ); it was not the primary study population but was analyzed as a sensitivity analyses.

Estimates were reported with 95% CIs. Statistical significance was defined as two-sided *P*-value <0.05. Statistical analyses were conducted using the software packages Stata, Version 14.2 (StataCorp LP, College Station, TX).

## Results

### Patient Characteristics

A total of 1047 patients were included in the analysis after excluding patients with missing baseline data on cognition ( $n = 56$ ) or missing ESAS-r symptom scores ( $n = 107$ ) and patients with data reported by proxy ( $n = 529$ ). The included 1047 patients had a mean age of 62.9 (SD 12.1) years, 54.4% were women, and the most common cancer types were cancer of the digestive organs (26.6%), breast cancer (21.6%), and lung cancer (21.2%) (Table 1). Most patients were ambulatory (not bedbound), with 69.7% having a functional status on Karnofsky Performance Scale of 70 or higher.

### Cognitive Impairment and Follow-Up

Cognitive impairment was present in 181 (17.3%) patients at baseline. The distributions of MMSE scores stratified by cognitive status are shown in Appendix

Table 1  
Patient Baseline Characteristics by the Presence of Cognitive Impairment

Factor	With Cognitive Impairment, <i>n</i> (%)	Without Cognitive Impairment, <i>n</i> (%)	<i>P</i>
<i>N</i>	181	866	
MMSE short version total score; median (IQR)	5.00 (4.00, 7.00)	8.00 (8.00, 8.00)	<0.001
Age; mean (SD)	68.55 (11.52)	61.71 (11.87)	<0.001
Women	83 (45.9)	487 (56.2)	0.011
Highest completed education			<0.001
Less than nine years of schooling	95 (52.5)	194 (22.4)	
10–12 yrs of schooling	65 (35.9)	394 (45.5)	
College or university less than four years	10 (5.5)	169 (19.5)	
College or university four years and greater	11 (6.1)	102 (11.8)	
Missing	0 (0.0)	7 (0.8)	
Days since diagnosis; median (IQR)	391 (195, 1114)	634 (246, 1627)	0.006
Principal cancer diagnosis			0.021
Cancer of the head	8 (4.4)	28 (3.2)	
Cancer of the digestive organs	43 (23.8)	235 (27.1)	
Cancer of the respiratory organs	45 (24.9)	177 (20.4)	
Malignant bone tumors	0 (0.0)	8 (0.9)	
Skin cancer incl. malignant melanoma	3 (1.7)	18 (2.1)	
Malignant connective and soft tissue tumors	3 (1.7)	21 (2.4)	
Breast cancer	23 (12.7)	203 (23.4)	
Gynecological cancer	18 (9.9)	45 (5.2)	
Cancer of the male genital organs	13 (7.2)	56 (6.5)	
Urinary cancer	8 (4.4)	30 (3.5)	
Tumors of the CNS	4 (2.2)	6 (0.7)	
Malignant endocrine tumors	1 (0.6)	4 (0.5)	
Secondary and ill-defined malignant tumors and unspecified	4 (2.2)	8 (0.9)	
Leukemias and lymphomas	7 (3.9)	24 (2.8)	
Missing	1 (0.6)	3 (0.3)	
Stage of nonsolid cancer			0.46
Localized	4 (2.2)	8 (0.9)	
Disseminated	5 (2.8)	18 (2.1)	
Stage of solid cancer			
Localized	8 (4.8)	34 (4.2)	0.74
Metastatic	135 (76.7)	732 (86.3)	0.001
Metastasis to lung	51 (28.3)	256 (29.6)	0.74
Metastasis to liver	46 (25.6)	265 (30.6)	0.18
Metastasis to CNS	17 (9.4)	65 (7.5)	0.38
Metastasis to bone	66 (36.7)	356 (41.1)	0.27
COPD	14 (7.7)	79 (9.1)	0.55
Heart disease	68 (37.6)	212 (24.5)	<0.001
Liver disease	10 (5.5)	20 (2.3)	0.018
Renal disease	7 (3.9)	28 (3.2)	0.67
Karnofsky Performance Status; mean (SD)	63.28 (14.94)	72.94 (14.00)	<0.001
Body mass index; mean (SD)	24.36 (5.00)	24.61 (4.93)	0.56
Oral corticosteroids	79 (43.6)	379 (43.8)	0.88
Opioids	118 (65.2)	479 (55.3)	0.005
Nonopioid analgesics	81 (44.8)	383 (44.2)	0.72
Sedatives/anxiolytics	71 (39.2)	209 (24.1)	<0.001
Antidepressants	34 (18.8)	118 (13.6)	0.061
Follow-up visit with self-reported data	86 (47.5)	590 (68.1)	<0.001

MMSE = Mini-Mental State Examination; IQR = interquartile range; CNS = central nervous system; COPD = chronic obstructive pulmonary disease. Data presented as frequency (%) or mean (SD) unless otherwise stated.

Fig. 1. Characteristics in patients with and without cognitive impairment are shown in Table 1. The cognitively impaired group had higher prevalence of men,

lower level of education, lower functional status, more recent cancer diagnosis, more often in treatment with opioids, sedatives/anxiolytics and



**Table 2**  
Symptom Scores by Cognitive Status at Baseline

Symptom	With Cognitive Impairment (N = 181)	Without Cognitive Impairment (N = 866)	P
Pain	2.30 (2.51)	2.07 (2.38)	0.25
Tiredness	4.77 (3.13)	3.98 (2.79)	<0.001
Drowsiness	3.27 (2.88)	2.82 (2.74)	0.048
Nausea	0.76 (1.79)	1.04 (1.97)	0.081
Appetite	3.45 (3.41)	2.58 (2.97)	<0.001
Breathlessness	1.69 (2.29)	1.66 (2.34)	0.89
Depression	3.17 (3.00)	2.27 (2.76)	<0.001
Anxiety	2.46 (2.71)	2.21 (2.58)	0.24
Well-being	3.70 (2.64)	3.39 (2.67)	0.15

Data presented as mean (SD). P-values were calculated using t-tests.

antidepressants, and were older than patients without cognitive impairment. Characteristics were similar between groups in terms of cancer types (except slightly less breast cancer among cognitively impaired), cancer stage, rate of CNS cancer, and CNS metastases (9.4% vs. 7.5% in patients without cognitive impairment).

The follow-up assessment was attended by 810 (77.4%) patients after a median of 29 days (interquartile range 27–35; range 14–162). Fewer patients with cognitive impairment attended the follow-up assessment (125 of 181 [69.1%] vs. 685 of 866 [79.1%];  $P = 0.003$ ), and fewer of those attending follow-up had self-reported data (86 of 125 [68.8%] vs. 590 of 685 [86.1%];  $P < 0.001$ ). Cognitive status (MMSE) by self-report at follow-up was available for 47.5% of patients with cognitive impairment at baseline, compared with 68.1% of patients without baseline cognitive impairment (Appendix Table 1). For symptom data, patients with cognitive impairment at baseline had higher rates of missing data at follow-up, which was consistent across the different symptoms (Appendix Table 2).

#### Reliability of Symptom Ratings in Cognitively Impaired and Unimpaired

Cognitive impairment was associated with worse self-reported tiredness, drowsiness, appetite, and perceived depression at baseline (Table 2). There were no differences by cognitive status for levels of pain, nausea, breathlessness, anxiety, or overall well-being.

Reliability (variability between the baseline and the follow-up assessment) was similar, with no consistent systematic difference (similar estimates with overlapping 95% CIs) between patients with and without cognitive impairment overall across the nine symptoms (Table 3). There were trends of differences for a few symptoms; patients with cognitive impairment tended to have somewhat lower reliability for anxiety and depression and slightly higher for nausea, but differences were generally small.

**Table 3**  
Reliability of Symptom Self-Ratings by Cognitive Status at Baseline

Symptom	With Cognitive Impairment	Without Cognitive Impairment
	ICC (95% CI)	
Pain	0.51 (0.41–0.62)	0.53 (0.49–0.57)
Tiredness	0.53 (0.43–0.63)	0.54 (0.51–0.58)
Drowsiness	0.50 (0.39–0.60)	0.51 (0.47–0.55)
Nausea	0.55 (0.45–0.65)	0.42 (0.37–0.46)
Appetite	0.56 (0.46–0.66)	0.50 (0.46–0.54)
Breathlessness	0.54 (0.44–0.64)	0.58 (0.54–0.62)
Depression	0.44 (0.33–0.55)	0.60 (0.56–0.63)
Anxiety	0.40 (0.29–0.52)	0.56 (0.52–0.60)
Well-being	0.59 (0.49–0.68)	0.52 (0.48–0.56)

ICC = intraclass correlation coefficient.

Reliability of symptom scores (on the revised Edmonton Symptom Assessment System) was measured using the ICC based on the baseline and first follow-up visit. Estimates are presented with 95% CIs.

#### Cognition and Concurrent Validity of Symptoms With HrQoL

The association of each symptom score with the perceived overall HrQoL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 for Palliative Care) was compared between people with and without cognitive impairment, as shown in Table 4. Associations were adjusted for age, sex, level of education, and treatment with opioids and sedatives/anxiolytics. Worse symptom scores in both groups were associated with worse HrQoL. There were no statistically significant group differences in the associations between symptoms and HrQoL (interaction group  $\times$  symptom score), except for breathlessness where the association between breathlessness and worse HrQoL was smaller in patients with cognitive impairment ( $P = 0.016$  for interaction; Table 4).

#### Sensitivity Analyses

As cognitive status changed in some patients between baseline and follow-up, all analyses were also conducted in patients with cognitive status defined as the presence/absence of cognitive impairment both at baseline and follow-up. Of 641 patients included in this analysis, 52 (8.1%) had cognitive impairment at both baseline and follow-up, and 589 (91.9%) did not have cognitive impairment at any of the assessments. Symptom scores were overall similar between groups (Appendix Table 3), with cognitive impairment associated with worse scores for tiredness, appetite, and depression but with lower levels of nausea and breathlessness, which was not seen in the main analysis of the larger patient cohort. Reliability estimates showed lower precision (because of the smaller sample size), but the pattern of estimates was similar to the main analysis (Appendix Table 4). There was no evidence of lower reliability in people with

cognitive impairment. Associations of symptoms with HrQoL showed a similar pattern as in the main analysis.

In addition, because of non-normality of symptom scores, we ran all analyses using the logarithm instead of raw symptom scores, which yielded similar findings.

## Discussion

In this large, multinational, prospective, and longitudinal study of 1047 participants with advanced cancer, we examined the relation between mild-to-moderate cognitive impairment and the ability to self-report a range of important symptoms: pain, tiredness, drowsiness, nausea, lack of appetite, breathlessness, depression, anxiety, and overall well-being. Compared with cognitively unimpaired, patients with cognitive impairment had similar test-retest reliability and similar associations with overall QoL for the symptom scores. Patients with cognitive impairment had more severe disease and were less likely to attend follow-up and to self-report. The main finding is that among people with cancer and cognitive impairment who were able to self-report, symptom ratings were still reliable and valid compared with people without cognitive impairment.

This is the largest study, to our knowledge, that evaluates the relation between cognitive impairment and symptom report and also the broadest study in terms of the range of evaluated symptoms (nine items), covering the major symptoms that affect people with cancer. Most previous studies evaluated self-report of pain and report that the ability seems intact in mild-to-moderate cognitive impairment,<sup>16–19</sup> in agreement with the present study, and that self-assessed and staff-assessed pain scores agree down to MMSE scores of 10 out of 30 points (severe cognitive impairment).

Although the concurrent validity with other scales seem to diminish in severe dementia,<sup>14</sup> at least one study has shown a high reliability (intraclass correlation coefficient) between three self-reported pain scales (0.88–0.98), reflected also in correlation with observational pain ratings ( $r = 0.25–0.63$ ).<sup>15</sup>

In the present study, we found that worse symptom scores were related to cognitive impairment for tiredness, drowsiness, appetite, and perceived depression, which is in line with previous reports.<sup>31–33</sup> Cognitive status was, however, not associated with ratings for any other symptoms, which is in agreement with previous studies on anxiety<sup>34,35</sup> and pain.<sup>36</sup> To the authors' knowledge, there are no comparable studies on cognition and reported breathlessness. Experimentally induced acute breathlessness was reported to affect cognitive control of locomotion in healthy people.<sup>37</sup> In COPD, cognitive impairment on the MMSE was associated with having more severe symptoms and a larger difference between experienced and recalled breathlessness ( $n = 30$ ).<sup>38</sup> In contrast, another study of 183 patients with COPD found similar characteristics, symptoms, and QoL between patients with and without cognitive impairment.<sup>39</sup>

In the present study, symptom scores had similar associations with perceived HrQoL between patients with and without cognitive impairment, except for breathlessness, where a similar increase in the symptom score (worse breathlessness) was associated with a smaller reduction in HrQoL in patients with cognitive impairment than in patients without cognitive impairment. As this was the only statistically significant difference, it should be interpreted with caution as it not only might reflect a random fluctuation but also could indicate that other things may be more influential on HrQoL in cognitive impairment.

A limitation of the present study is that the definition of cognitive impairment was based on a brief cognitive

Table 4  
Associations of Self-Rated Symptoms With Global Quality of Life by Cognitive Status

Symptom	Patients With Cognitive Impairment		Patients Without Cognitive Impairment		Difference in Association (Interaction) Between the Groups <i>P</i>
	Coefficient	95% CI	Coefficient	95% CI	
Pain	-3.17	-4.76 to -1.58	-2.48	-3.21 to -1.76	0.56
Tiredness	-3.93	-5.01 to -2.84	-3.11	-3.67 to -2.54	0.29
Drowsiness	-3.45	-4.72 to -2.18	-2.50	-3.10 to -1.90	0.71
Nausea	-3.63	-5.80 to -1.46	-2.68	-3.50 to -1.86	0.41
Appetite	-2.51	-3.60 to -1.43	-3.02	-3.55 to -2.48	0.40
Breathlessness	-0.18	-1.90 to 1.55	-2.07	-2.77 to -1.38	0.016
Depression	-4.05	-5.26 to -2.84	-2.76	-3.36 to -2.17	0.067
Anxiety	-2.64	-4.12 to -1.15	-2.60	-3.24 to -1.97	0.94
Well-being	-5.03	-6.31 to -3.75	-3.93	-4.51 to -3.35	0.190

Linear regression of the association for each symptom (assessed using the revised Edmonton Symptom Assessment System instrument) with global health-related quality of life (HrQoL) measured using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 for Palliative Care, adjusted for age, sex, level of education, and treatment with opioids and anxiolytics/sedatives. Difference in the associations between groups (interaction) was tested using likelihood ratio test. Higher HrQoL scores (outcome variable) reflect better HrQoL, whereas higher symptom scores (revised Edmonton Symptom Assessment System instrument; the predictors) reflect more severe symptoms. A negative association is interpreted as that higher symptom scores are associated with worse HrQoL.

screening test, which might not detect more subtle cognitive impairment and made it difficult to further stratify the participants in different stages of cognitive impairment. However, this present short version of the MMSE has shown very high agreement with the full-length version; it had 96% sensitivity and 91% specificity to identify cognitive impairment defined as <24 points on the full-length MMSE.<sup>27</sup> A further support for using this short version was that the prevalence of cognitive impaired in the present study (17%) was similar to previous studies on cognitive impairment in patients with cancer (15%–25%).<sup>40,41</sup> Nonetheless, to provide a more robust measure of cognitive status, we ran a sensitivity analysis requiring the cognitive status to remain stable from baseline to the follow-up visit (either cognitively impaired at both visits or cognitively unimpaired at both visits), which yielded similar results. As inability to comply with the study for reasons including severe cognitive impairment was an exclusion criterion (as in most trials), the present findings pertain to mild-to-moderate cognitive impairment. Another possible limitation includes the concurrent validity analysis using self-rated HrQoL. In a scenario, where the cognitively impaired participants do not remember recent symptoms (scores falsely low) and overrate their HrQoL, the association would incorrectly be similar to the cognitively unimpaired group. However, previous studies support the validity and hence the use of self-rated HrQoL scales also in cognitively impaired participants,<sup>42,43</sup> although it has been questioned in advanced dementia.<sup>44</sup> Nonetheless, we acknowledge that future studies should also include observational-based ratings for the concurrent validity analyses. Finally, there were more missing data for symptom ratings at follow-up for cognitively impaired participants (about 32% vs. about 23% for cognitively intact; [Appendix Table 2](#)). This may have caused a slight survival bias, and it also identifies a shortcoming of self-reported measures in people who are cognitively impaired compared with third-party observational assessments.

The present findings have important implications as they support the use of self-reported symptom measures also in patients with advanced cancer and mild-to-moderate cognitive impairment but also highlight that staff-assessed measures might be necessary to avoid under-reporting of symptoms as many patients with cancer may not be able to self-report using questionnaires.<sup>36</sup> This informs on the use of self-ratings in this population both in clinical practice and therapeutic trials.<sup>45</sup>

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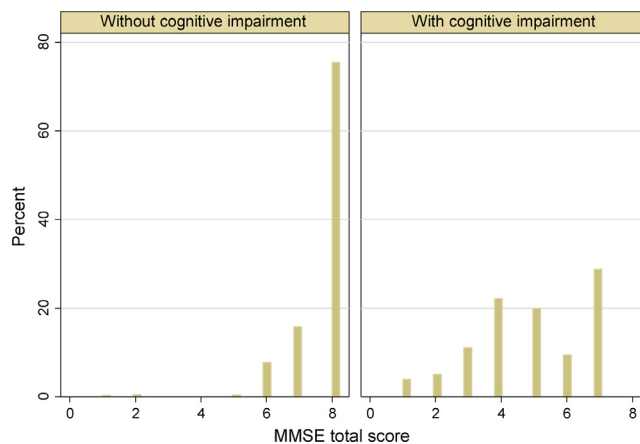
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Appendix



Appendix Fig. 1. Distribution of scores from the short version of MMSE at baseline stratified by the presence of cognitive impairment. The total score was 8 p (0–1 p for date, 0–1 p for year, 0–1 p for pentagon copying, and 0–5 for spelling WORLD backward). MMSE = Mini-Mental State Examination.

Appendix Table 1  
Cognitive Status at Follow-Up by Cognitive Status at Baseline

	Follow-Up		
	With Cognitive Impairment	Without Cognitive Impairment	Missing Data
Baseline			
Without cognitive impairment	49 (8.3)	525 (89.2)	15 (2.5)
With cognitive impairment	30 (34.9)	53 (61.3)	3 (3.5)

Cognitive impairment was defined according to the four-item short version of Mini-Mental State Examination, where 0 p on present year or <3 p on spelling WORLD backward or 0 p on pentagon copying was classified as cognitive impairment.

Appendix Table 2  
Rates of Missing Values for Self-Rated Symptom Scores at Follow-Up

	With Cognitive Impairment	Without Cognitive Impairment	P
	Missing Values, %		
Pain	32.0	22.5	0.006
Tiredness	32.0	22.2	0.005
Drowsiness	32.0	22.9	0.009
Nausea	32.6	22.5	0.004
Appetite	31.5	22.2	0.007
Breathlessness	32.0	22.6	0.007
Depression	32.0	22.5	0.006
Anxiety	31.5	22.5	0.010
Well-being	32.0	23.1	0.011

P-values were analyzed using Chi-squared tests.

Appendix Table 3

**Sensitivity Analysis of Symptom Scores in Patients With and Without Cognitive Impairment Both at Baseline and Follow-Up ( $n = 641$ )**

Symptom	With Cognitive Impairment Both at Baseline and Follow-Up ( $n = 52$ )	Without Cognitive Impairment Both at Baseline and Follow-Up ( $n = 589$ )	<i>P</i>
Pain	1.88 (2.30)	1.87 (2.22)	0.97
Tiredness	4.37 (3.40)	3.67 (2.76)	0.087
Drowsiness	2.65 (2.95)	2.48 (2.61)	0.64
Nausea	0.33 (0.96)	0.96 (1.91)	0.018
Appetite	3.10 (3.39)	2.20 (2.81)	0.032
Breathlessness	0.67 (1.28)	1.39 (2.19)	0.021
Depression	3.02 (2.91)	2.06 (2.66)	0.014
Anxiety	2.58 (2.70)	2.02 (2.47)	0.12
Well-being	3.15 (2.41)	2.99 (2.57)	0.66

Data presented as mean (SD). *P*-values were calculated using t-tests.

Appendix Table 4

**Sensitivity Analysis of Reliability of the Symptom Scores in Patients With and Without Cognitive Impairment Both at Baseline and Follow-Up ( $n = 641$ )**

Symptom	Cognitive Impairment at Baseline and Follow-Up	Without Cognitive Impairment at Baseline and Follow-Up
	ICC (95% CI)	
Pain	0.71 (0.56–0.82)	0.51 (0.47–0.55)
Tiredness	0.63 (0.46–0.77)	0.53 (0.49–0.57)
Drowsiness	0.53 (0.36–0.70)	0.50 (0.46–0.54)
Nausea	N/A	0.40 (0.36–0.44)
Appetite	0.68 (0.52–0.81)	0.49 (0.45–0.54)
Breathlessness	0.58 (0.41–0.73)	0.59 (0.55–0.63)
Depression	0.51 (0.33–0.68)	0.58 (0.54–0.62)
Anxiety	0.50 (0.33–0.67)	0.55 (0.51–0.59)
Well-being	0.59 (0.43–0.74)	0.51 (0.47–0.55)

ICC = intraclass correlation coefficient; N/A = not available. Sensitivity analysis performed in patients with cognitive impairment both at baseline and follow-up ( $n = 52$ ) and patients without cognitive impairment at any of these assessments ( $n = 589$ ). Nausea in cognitively impaired could not be analyzed because of few cases.