Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients

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Abstract

Purpose: Clinical observations indicate that patients with advanced cancer and depression report higher symptom burden than non-depressed patients. This is rarely examined empirically. Study aim was to investigate the association between self-reported depression disorder (DD) and symptoms in patients with advanced cancer controlled for prognostic factors.

Methods: The sample included 935 patients, mean age 62, 52% males, from an international multicentre observational study (EPCRC-CSA). DD was assessed by the PHQ-9 and scored with DSM-5 algorithm for major depressive disorder, excluding somatic symptoms. Symptom burden was assessed by summing scores on somatic ESAS symptoms, excluding depression, anxiety and well-being. Item-by-item scores and symptom burden of those with and without DD were compared using non-parametric Mann-Whitney U tests. The relative importance of socio-demographic, medical, and prognostic factors and DD in predicting symptom burden was assessed by hierarchical, multiple regression analyses.

Results: Patients with DD reported significantly higher scores on ESAS items and a twofold higher symptom burden compared to those without. Factors associated with higher symptom burden were: Diagnosis; lung (β=0.15, p<0.001) or breast cancer (β=0.08, p<0.05), poorer prognosis; high CRP (β=0.08, p<0.05), lower KPS (β=-0.14, p<0.001) and greater weight loss (β=-0.15, p<0.001), taking opioids (β=0.11, p<0.01), and having DD (β=0.23, p<0.001). The full model explained 18% of the variance in symptom burden. DD explained 4.4% over and above that explained by all the other variables.

Conclusions: Depression in patients with advanced cancer is associated with higher symptom burden. These results encourage improved routines for identifying and treating those suffering from depression.

Introduction

The main goal of supportive and palliative care for patients living with or affected by cancer is to improve their quality of life [1], which implies a clear obligation to ensure optimal symptom management.[2] Patients with advanced cancer generally report a range of somatic symptoms that for most patients increase in intensity with disease progression.[3] The negative impact of these symptoms on patients' functional status and quality of life is well known,[4] yet there is evidence that many symptoms are left unrecognized.[5]

Depression in patients with advanced cancer is relatively common, with average prevalence rate estimates around 15% using structured clinical interviews or patient-reported measures that include the diagnostic criteria of a depressive disorder.[6, 7] Nevertheless, depression in patients with advanced cancer is often not detected in the clinic, hampering adequate treatment.[8, 9] Depression is associated with reduced functional status, lower treatment compliance, prolonged hospitalizations and desire for hastened death.[10, 11] In clinical practice it is often assumed that depression affects both the presence and intensity of somatic symptoms,[12] and that patients who are depressed may have physical symptoms that are difficult to manage.[13]

A symptom is defined as any subjective evidence of disease or unusual state, and accordingly can only be perceived by the individual affected.[14] Recent research from non-cancer medical populations suggests that an interaction between medical and psychological factors contributes to the experience and reporting of somatic symptoms.[15] In line with this, numerous studies also from non-cancer populations consistently report associations between depression and increased levels of somatic symptoms [15, 16] , albeit sparsely studied in cancer settings.[17] Most studies in cancer settings to date have explored this in mixed populations, focusing on specific somatic symptoms, primarily pain and fatigue.[18, 19] Indeed, depressive symptoms are found to co-occur with pain and fatigue among cancer patients with mixed diagnoses.[18, 20] It could be that psychological factors play a role in the experience and reporting of a *range* of somatic symptoms, not only pain and fatigue.[15] Besides, the relationship between depression and somatic symptoms may vary through the disease trajectory. A handful of small-sized studies on patients with advanced cancer have explored the relationship between depression and a number of symptoms. The findings are equivocal, as studies both support[21], reject[22], or report mixed findings[23], regarding such a relationship. Despite consistent reports that poor prognosis is related to both increased somatic symptom burden[3] and depression,[24] the potential effect of disease-related factors on

symptom burden was considered in only one of these studies.[21] Finally, assessment of depression in cancer populations is challenging, primarily due to the overlap of depressive symptoms and cancer- and treatment-related symptoms, and of functional impairments and depression.[25] Studies of depression in patients with advanced cancer have used a range of different assessment instruments,[25] and few differentiate between depressive symptoms and an established *depressive disorder*, as defined by diagnostic criteria and recommended by ASCO.[26] Given these methodological issues, the inconsistent results of the few studies to date are perhaps not surprising.[20, 21, 27] Hence, it remains unclear whether depression is associated with, and thus may contribute to increased somatic symptom burden among patients with advanced cancer *irrespective of* prognostic factors.

Therefore, the aim of the present study was to compare the intensity of somatic symptoms as reported by patients meeting the criteria for depressive disorder with that of patients not meeting these criteria. Based on clinical experience, we hypothesized that patients with depression report a higher symptom burden than those without. Results in support of this hypothesis serve as a strong incentive to increase the focus on detecting and treating co-morbid depression in the clinic also as a means to improve symptom management. Moreover, we wanted to explore the relative contribution of demographic, medical and prognostic factors, medication use and depression to increased symptom burden.

Methods

Study design and patients

Data were collected through a large international cross-sectional study from the EU-funded EPCRC project.[28] From 2008 to 2009, 1051 patients with advanced cancer were recruited from 17 centres in eight countries, including in- and out-patient units, hospices/inpatient palliative care beds, general oncology and medical wards. Inclusion criteria were: incurable metastatic or locally advanced cancers; and age 18 years or above.[29] Of the 1051 patients, 969 completed the symptom (ESAS) and depression (PHQ-9) assessments. Of these, patients with a likely moderate or severe cognitive impairment (sum-score < 18, Mini-Mental State Exam (MMSE), N=12)[30] or those with missing MMSE-scores (N=22) were excluded, leaving a final sample of N=935 in this paper.

Study measurements

Socio-demographic and medical data were collected by health care providers (HCPs), while participants completed a range of patient-reported instruments directly on touch-sensitive tablet computers.[29]

Medical status: Medical status included the primary cancer diagnosis and current disease status: loco-regionally advanced or metastatic (Table 1).

Prognostic factors: Medical information was retrieved from patient records and HCP registrations, including Karnofsky Performance Status scores (KPS);[31] dichotomous registration of co-morbidities (heart disease, arthritis, COPD, renal, liver disease and "other") and CRP-values if obtained within three days of study-inclusion. High CRP was defined as CRP>10mg/L. Weight change past six months was calculated as self-reported weight in kilograms six months ago minus current self-reported weight.

Medication use: Current use of opioids and antidepressants (ADs) not as adjuvant for pain was dichotomized (use vs. not use).

Depression: Depression was assessed using the PHQ-9, a self-report questionnaire commonly used in medically ill samples, including patients with cancer.[7],[32] The PHQ-9 items correspond to the DSM-5 diagnostic criteria for major depressive disorder (MDD) and assess the frequency at which the corresponding symptoms have been bothersome during the past two weeks: 0="*not at all*", 1="*several days*", 2="*more than half the days*" and 3="*nearly every day*". To avoid artificially inflating potential relationships between depression and symptom burden in this paper, we used an exclusive scoring-method based on the DSM-5 scoring algorithm.[7] This scoring method excludes four somatic symptoms likely to reflect the cancer disease (sleep problems, fatigue, change of weight or appetite, and psychomotor retardation/agitation) and requires three out of the remaining five criteria to be present, including anhedonia or depressed mood.[33] Although the PHQ-9 is not a diagnostic tool, patients meeting the criteria for exclusive DD were categorized as depressed in this study.

Symptom burden: Symptom burden was measured using the original Edmonton Symptom Assessment Scale (ESAS)[34] scored on 11-point numerical rating scales with 0 as "*no symptom at all"* and 10 as "*worst possible symptom*". In the multivariate model, the sum-score of the six somatic ESAS symptoms was calculated, excluding

depression, anxiety and feeling of well-being due to content overlap with depression. A higher sum-score (range 0-60) indicates higher symptom burden.

Statistical methods

Variables to be included in the multivariate models were determined using bivariate regression models with statistical significance set at $p<0.10$. Candidate variables were: medical status variables; prognostic factors; medication use; and DD. Demographic variables were controlled for in the multivariate models. Multivariate, hierarchical regression was used to explore the relationships between the above-mentioned variables and the sum-score of the somatic ESAS symptoms. This method allowed us to estimate the unique variance in the ESAS sum-score accounted for by the groups of variables. *P*-values<0.05 were considered statistically significant. Statistical analyses were done using IBM-SPSS 22 (Armonk, NY: IBM Corp.).

Ethical considerations

The study was performed according to the Helsinki declaration. Ethical approval was obtained at each site before study start. All participants gave written informed consent.

Results

Sample characteristics

Characteristics of the sample are provided in Table 1. In brief, the sample consisted of 48% female patients and the mean age was 62.1 years. The most common site of the primary cancer was the gastrointestinal tract (27%) and 85% had metastatic disease. Of the 935 patients, 801 (85.7%) were not depressed and 134 (14.3%) scored at or above the cut-off for being depressed.) Anti-depressants not as an adjuvant to pain medication were used by 92 (11.5%) patients in the non-depressed group and by 32 (23.9%) patients in the depressed group.

Insert Table 1 about here

Group comparisons of individual ESAS symptoms

For the purpose of exploring symptom load in terms of individual somatic ESAS symptoms for those depressed or not, we divided the sample into four groups: 1) not depressed and not taking ADs (n=709), 2) not depressed and taking ADs (n=92), 3) depressed and not taking ADs (n=102), and 4) depressed and taking ADs (n=32). Non-parametric Mann-Whitney U tests showed no significant differences between the two non-depressed groups not

using or using ADs, or between the two depressed groups not using or using ADs. For the purpose of further analyses we therefore collapsed the four groups into two: not-depressed (n=801) and depressed (n=144). The depressed patients scored significantly higher on all somatic ESAS symptoms compared to the non-depressed (all *ps*< 0.001).

Determinants of ESAS sum-score

The univariate and multivariate models predicting sum-score of the ESAS somatic symptoms are presented in Table 2. The following variables were significantly associated with a higher sum-score in the univariate analysis; diagnosed with breast cancer (β=0.10, p=0.006) or lung cancer (β=0.12, p=0.002), prognostic factors including high CRP (β=0.17, p<0.001), lower Karnofsky performance score (β= -0.30, p<.001) and greater self-reported weight loss the past 6 months (β= -0.21, p<.001); taking opioids (β= 0.27, p<.001) and meeting the criteria for MDD (β= -0.30, p<.001). The multivariate model accounted for 18% of the variance in the ESAS sum scores. Of this, Step 1, the demographic variables accounted for 0.2%; Step 2, medical status 9.8%; Step 3, prognostic factors 2.4%; Step 4, medication use 1% and Step 5, DD 4.6% of the variance over and above the variance accounted for by the previous steps in the model. In the fifth and final step of the model, higher symptom burden was associated most strongly with depression (β= -0.23, p<.001) after controlling for the effects of all other variables, followed by greater weight loss over the past 6 months (β= -0.15, p<.001), being diagnosed with lung cancer (β= 0.15, p<.001), lower performance status (β= -0.14, p<.001), and taking opioids (β= -0.11, p<.001).

Insert Table 2 about here

Discussion

To the best of our knowledge, the present study is the first to examine the relationship between depression according to diagnostic criteria, and self-reported somatic symptom burden in a large sample of patients with advanced cancer while also considering disease-related factors. In line with our main hypothesis, being categorized as depressed was significantly associated with higher somatic symptom burden.

It is known that depressed individuals' negative and pessimistic way of thinking promotes a negative view of their health and results in heightened awareness of unpleasant experiences.[36] Although these mechanisms primarily have been suggested to play a role in illnesses characterized by medically unexplained symptoms,[15] recent

research has proposed that disease specific symptoms, e.g. dyspnoea in pulmonary disorders or chest pain in cardiac disease, may be partly accounted for by comorbid depression which adds to the physical severity of the underlying medical disorder.[16] Similarly, it is likely that medical and psychological factors interplay in the experience and reporting of physical symptoms of cancer disease and treatment as well. Our finding that depression is independently associated with a range of somatic symptoms, rather than just a few specific ones, is consistent with this assertion. Longitudinal studies, however, are needed to clarify the potential reciprocity in the interplay between medical and psychological factors. Somatic disease may indeed have an aetiological role in the genesis of depression, supported by studies that have identified physical distress as a risk factor for the development of depression.[24]

The emotional, interpersonal and health economical costs of depression are considerable. [10],[11] Even though pharmacological and psychosocial interventions are documented to effectively reduce depression in patients with advanced cancer,[37] nurses and doctors frequently fail to detect it. Many health care personnel believe they do not have the skills to assess and recognize depression.[38] Complicating this further is the common misconception among patients and health care personnel that the other party should initiate discussions about psychological issues.[39] Consequently, a considerable under-treatment in this patient group has been documented.[8, 9]

One limitation of the present study is its cross-sectional design, which prohibits us from drawing conclusions on directionality. Thus, answering the question of possible bidirectional effects between depression and symptoms necessitates longitudinal investigations. In addition, the use of self-report to measure both depression and symptom severity may have caused conflated associations between variables, i.e. common method variance. We believe, however, that this problem was reduced by excluding the somatic symptoms from our depression measure and including objectively assessed indicators of prognosis such as KPS and CRP measures. We lack information about patients who were not invited or declined participation. However, the most severely affected patients are not likely to have been included due to gate-keeping by the recruiting health care workers. Also of note is the use of self-report to assess depression rather than the gold standard, i.e. a structured psychiatric interview. Nevertheless, the PHQ-9 corresponds to the criteria used in the SCID-MDD interview[40], hence the main difference is the mode of administration, not the content. Indeed, the PHQ-9 is the screening tool recommended for assessment of depression by ASCO.[26]

The main strength of this study is the large, international sample of patients with advanced cancer characterized on a broad range of symptoms, functioning and medical status. Further, we not only controlled for disease- and treatment related factors, but also for objective measures of prognosis.

Conclusions and implications

In this large and well-characterized sample of patients with advanced cancer, depression was associated with an increased somatic symptom burden when controlled for disease, treatment status and prognosis. Our findings are in line with the suggestion that psychological as well as organic factors impact on the experience of somatic symptoms in patients with advanced cancer. Future research should investigate prospectively whether improvement of depression, assessed by validated means, results in reduction of somatic symptom burden. When clinicians are assessing and managing symptoms among patients for whom cure is no longer feasible and the aim of care is best possible quality of life, they should consider the potential for a co-morbid depression. Given that depression in patients can be treated effectively even in the last few weeks of life,[41] patients presenting with a high intensity across a wide array of symptoms should make clinicians especially attentive to such co-morbidity.

Conclusively, the results of the present study clearly support the argument in the Institute of Medicine's report, namely that cancer care can be improved by attending not only to the patient's biomedical needs, but to all aspects of the patient's situation.[42]

Declaration of conflict of interest. None of the authors have declared any conflict of interest.

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Table 1. Characteristics of the 935 patients included in the analysis.

Continuous variables	Mean	SD	Range
Age	62.1	12.39	18-89
MMSE[1]	28.0	2.39	18-30
KPS	71.2	16.12	20-100
Total number co-morbidities[2]	0.7	0.87	0-6
ESAS sum-score somatic symptoms[3]	15.5	9.78	0-48
Categorical variables	n[4]		%
Gender			
Female	452		48%
Male	483		52%
Education			
< 10 years	319		34%
10-12 years	331		35%
> 12 years	285		31%
Marital status[5]			
Spouse	613		66%
No spouse	322		34%
Nationality			
Norwegian	476		51%
Not Norwegian	459		49%
CRP[6]			
Normal	303		45%
High >10	367		55%
Setting			
In-patient	527		56%
Out-patient	408		44%
Site of primary cancer			
Gastrointestinal tract	249		27%
Lungs	154		16%
Breast	164		18%
Prostate & male genital organs	100		11%
Other[7]	267		29%
Current disease status			
Metastatic[8]	794		85%
Loco-regionally advanced	141		15%
Use of opioids			

Yes	529	57%
No	406	43%
Use of antidepressants[9]		
Yes	124	13%
No	881	87%
Depression		
Yes	134	14%
No	801	86%

Notes: KPS = Karnofsky Performance Status score, where 100=normal functioning and 0=dead.

[1]MMSE =Mini Mental State Exam.

[2]Co-morbidities: Heart disease, arthritis, COPD, renal and liver disease and other.

[3]Sum-score of the six somatic symptoms on the ESAS, excluding depression, anxiety and feeling of well-being. Possible range: 0-60, where a higher score indicates higher symptom burden.

[4]Number of patients for each variable may not add up to 935 due to missing cases.

[5]Spouse denotes co-habiting with a partner, married or unmarried.

[6]CRP: normal = CRP≤10 mg/L, high = CRP>10 mg/L.

[7]Other cancers include: urinary tract cancers (5.6%), skin cancers incl. malignant melanomas (4.0%), leukaemia/lymphoma (4.6%), secondary/ill-defined malignant tumours (2.6%), malignant connective / soft tissue tumours (3.3%), head and neck (3.0%), gynaecological (2.6%), tumours of the CNS (1.5%), malignant endocrine tumours (0.7%), multiple primary cancers (0.4%).

[8]Metastatic disease includes one or more metastases in the following locations; bone, brain, liver, lungs, lymph nodes, or other.[1]

[9]Antidepressants not taken as an adjuvant for pain.

Group comparisons of individual ESAS symptoms

For the purpose of exploring symptom load in terms of individual somatic ESAS symptoms for those depressed or not, we divided the sample into four groups: 1) not depressed and not taking ADs (n=709), 2) not depressed and taking ADs (n=92), 3) depressed and not taking ADs (n=102), and 4) depressed and taking ADs (n=32). Non-parametric Mann-Whitney U tests showed no significant differences between the two non-depressed groups not using or using ADs, or between the two depressed groups not using or using ADs. For the purpose of further analyses we therefore collapsed the four groups into two: not-depressed (n=801) and depressed (n=144). The depressed patients scored significantly higher on all somatic ESAS symptoms compared to the non-depressed (all *ps*< 0.001).

Table 2. Univariate and hierarchical multivariate regression models predicting the sum-scores of the ESAS somatic symptoms**.** Univariate predictors with $p<0.10$ were included in the multivariate regression model. Standardized beta values are shown.

		Univariate	Multivariate				
	Model Steps		**1**	**2**	**3**	**4**	**5**
1	**Demographics:**						
	Gender[1]	0.01	-0.02	-0.03	-0.02	-0.03	-0.04
	Age[2]	-0.01	-0.05	-0.05	-0.05	-0.05	-0.04
	Education						
	High school	-0.08[#]	-0.06	-0.05	-0.04	-0.04	-0.04
	University	-0.08[#]	-0.03	-0.01	0.02	0.02	0.03
	Marital status[3]	0.02					
2	**Medical Status:**						
	Diagnosis[4]						
	Breast cancer	0.10**		0.06	0.10*	0.09*	0.09*
	Lung cancers	0.12**		0.16**	0.13**	0.14**	0.15***
	GI cancers	0.03		0.06	0.07	0.08	0.08
	Male genital cancers	-0.02		0.03	0.02	0.01	0.02
	Total comorbidities	0.04					
3	**Prognostic factors:[5]**						
	CRP (high)	0.17***			0.12**	0.10*	0.08*
	KPS	-0.30***			-0.22***	-0.18***	-0.14***
	Weight change (last 6mths)	-0.21***			-0.19***	-0.18***	-0.15***
4	**Medication use**						
	ADs	0.06[#]				0.01	0.01
	Opioids	0.27***				0.12**	0.11**
5	**Depression (DD) [6]**	0.30***					0.23***
	$R^2_{adj.}$		**0.002**	**0.010***	**0.124*****	**0.134****	**0.180*****

Note. In Step 5: N=623. Significance levels indicated by: [#]<0.10, *<0.05, **<0.01, ***<0.001.

[1]Male (vs female).

[2]Age categorised in decades: 18-27, 28-37, 38-47, 48-57, 58-67, 68-77, 78-87, 88-100.

[3]Married/de facto vs. not married/divorced/single.

[4]Diagnoses: Reference category = all other diagnoses

[5]CRP: reference category = normal = CRP≤10 mg/L, KPS – Karnofsky Performance Status, Weight change: (self-reported weight six months ago) – (current self-reported weight)

[6]Depression (DD): Reference category = no DD. DD = meeting the criteria for a depression disorder using the DSM-5 scoring algorithm excluding the somatic symptoms.