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Symptom severity and distress in advanced cancer

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Abstract

We determined the relationship between symptom severity and distress for multiple cancer symptoms, and examined patient demographic influences on severity and distress in advanced cancer. A Cochran–Armitage trend test determined whether symptom distress increased with severity. Chi-square, Fisher's exact test and logistic regression analysis examined moderate/severe ('clinically important') and distressful symptoms by age ($\leq$65 versus $>$65), gender, primary site group, and ECOG performance status. Forty-six symptoms were analyzed in 181 individuals. More than 50% of individuals with clinically important symptoms rated them as distressful. The median percentage of individuals with mild but still distressful symptoms was 25%, with a range of 0% (bad dreams) to 73% (sore mouth). In both univariate and multivariate analysis, younger ($\leq$65 years) patients, females, and those with poor performance status had more clinically important and a higher prevalence of distressful symptoms (only anxiety was more frequently distressful to older individuals). Clinically important symptoms and two of those considered distressful varied by primary site group. After control for severity, symptom distress did not differ by primary site group. The prevalence of distress increased with greater symptom severity. Younger individuals, those with poor performance status, and females had greater symptom severity and distress. Mild symptoms were often distressful. After adjustment for severity, age, gender, and performance status all influenced symptom distress.

Keywords

age, distress, gender, performance status, severity, symptom

Introduction

Symptoms are subjective, and severity is often graded to assist in establishing treatment and research priorities. For example, the WHO analgesic ladder recommends pain management based on pain severity.[1] Symptom characteristics, other than severity (chronicity, distress, duration, frequency) may also contribute to our understanding of suffering, and might influence treatment. Prevalence, severity, and frequency are most often assessed as separate symptom characteristics; distress is rarely included.[2–5]

Screening in routine outpatient practice for overall distress (spiritual, physical, emotional, and family problems) using the Distress Thermometer has been recommended by the National Comprehensive Cancer Network (NCCN).[6] Distress, from somatic or

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psychological symptoms, is associated with poor quality of life (QoL).[7–9] We lack a universally accepted definition of distress. One is 'discomfort severe enough to warrant treatment toward its relief'.[10] Symptom distress (from physical or mental symptoms) may also be differentiated from psychological distress (anxiety, depression).[11] Symptom distress has also been associated with the existential meaning of symptoms.[12]

Distress has been a variable construct with conflicting conclusions about its content and value. This has resulted in inconsistent assessment.[13] Distress concepts, and symptom domains that reflect it, differ between instruments.[2,5,14,15] Distress has been included in symptom assessment as either a single domain, or alternatively the proxy sum of several domains (presence, severity, frequency, and symptom interference with life) termed 'symptom burden'.[2,14,16] The degree to which these characteristics contribute to overall distress is unclear. For instance, chronicity (rarely included in symptom assessment) might contribute to distress more than frequency. No instrument directly assesses the existential meaning of symptoms as a component of distress.

Data about the relationship between symptom severity and distress in palliative medicine is limited. A moderate correlation was reported between overall cancer symptom severity and distress,[4] but in individual assessments this appeared highly variable (severity was rated higher or lower than distress).[17] In addition the study was conducted in a limited range of primary sites. We had also noted in a prior report that demographic characteristics (including age and gender) appeared to influence symptom prevalence and severity. We report the relationship of distress and severity for multiple symptoms from data obtained in a previously published prospective study, which originally compared patient symptom reports to systematic assessment.[18] The aim of this secondary analysis was to determine the relationship of distress measured by a single question (symptom bothersome or not) with self-assessed symptom severity measured by a categorical scale (mild, moderate, severe) in a heterogeneous group of cancer primary sites. A secondary aim was to determine whether symptom prevalence or distress was influenced by any demographic characteristics.[19]

Methods

A total of 218 advanced cancer patients were enrolled and screened; 37 were excluded most often because of delirium or poor performance status. One hundred and eighty one consecutive patients were assessed at initial consultation by our palliative medicine program.[18] They included both inpatients and outpatients. They were all referred by their attending physician for evaluation and/or continuing care. The majority would have discontinued chemotherapy or radiation therapy recently or subsequent to the palliative medicine consultation. We did not collect information about those or other recent treatments, or subsequent survival. After first volunteering any distressful symptoms, patients were systematically assessed by an empirically derived 48 question checklist of symptoms categorically graded for severity as 'none, mild, moderate and severe', and graded for distress as bothersome/distressful or not. Weight loss since the onset of illness was self-reported by individuals. Auditory hallucinations and blackouts were excluded from analysis, since both occurred in only one patient.

Symptom prevalence is described as the percentage of patients with each symptom (mild, moderate, or severe); symptom distress is described as the percentage of patients who indicated the symptom was distressful among those who had the symptom. Percentages are rounded to the nearest whole number. In the text and tables, symptoms are listed from highest to lowest prevalence. For descriptive purposes, symptom prevalence was arbitrarily defined as common (>25% prevalence) or infrequent (<25%). Moderate or severe symptoms are referred to as 'clinically important'.

Among patients with each symptom, the Cochran–Armitage trend test[20] was used to determine whether distress increased with greater symptom severity. For the remainder of the analyses, symptoms were analyzed as moderate or severe (clinically important) versus mild or none. Either the Chi-square test or Fisher's exact test was used to assess the association of clinically important prevalence and distress with four patient characteristics: age, gender, Eastern Cooperative Oncology Group (ECOG)[19] performance status (PS), and primary site group (PSG). For this analysis, age was analyzed as $\leq$65 versus >65 years; ECOG was analyzed as PS 1 versus PS 2 versus PS 3–4. Primary sites were combined into nine PSGs (Table 1). Logistic regression analysis was used to determine whether distress remained associated with patient characteristics after adjusting for symptom severity; logistic regression results are summarized as the odds ratio and corresponding 95% confidence interval.

Data were analyzed using SAS® software (SAS Institute, Inc., Cary, NC, USA). With the exception of the trend test, all statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Patient demographics and symptom assessment have been reported in detail elsewhere.[18] Briefly, the mean age of the 181 persons was 64 years (±13), and the median ECOG PS was 2 (range 1–4). Twenty six

Table 1. Cancer primary sites and groups

Primary site	Number of patients	
Lung		43
Lung	40	
Mesothelioma	3	
Hepato-biliary		25
Pancreas	18	
Liver	4	
Cholangio Ca	3	
GI		28
Colorectal	15	
Esophagus	10	
Gastric	3	
Hematologic		17
Lymphoma	4	
NHL lymphoma	4	
Multiple myeloma	3	
Myeloma	2	
Leukemia	2	
Myelodysplasia	2	
Breast		11
GU		20
Cervix	7	
Kidney	5	
Prostate	4	
Bladder	2	
Ovarian	2	
Head & neck		9
Cancer Unknown Primary		9
Other		20
Brain	1	
Sarcoma	7	
Carcinoid	2	
Miscellaneous	10	
Total	181	181

primary cancer sites were combined into nine PSGs for this analysis (Table 1). Median symptom prevalence was 23%, with a range of 2% (fecal incontinence) to 72% (fatigue). All 46 symptoms were rated by at least one person as distressful. The median prevalence of symptom distress was 54%, with a range of 30% (wheezing) to 86% (pain) (Table 2).

Greater severity was associated with more distress for most symptoms. The exceptions were vision problems, sore mouth, urine incontinence, fever, visual hallucinations, and fecal incontinence. Infrequent symptoms (overall prevalence <25%) had a similar relationship between severity and distress as did more common symptoms. Except fecal incontinence, more than half of those who had clinically important symptoms rated them distressful (Figure 1). The median prevalence of distress for clinically important symptoms was 83%, with a range of 33% (fecal incontinence) to 100% (dizziness, dysphagia, nausea). The median prevalence of distress for mild symptoms was 25%, with a range of 0% (bad dreams) to 73% (sore mouth) (Figure 2).

Age and gender influenced the prevalence of clinically important symptoms more than distress. Eight of the 46 gastrointestinal (GI) and neuropsychological symptoms varied in prevalence by age, and six in distress by age (Tables 3 and 4). Younger patients had a higher prevalence of clinically important symptoms than older people (Table 3). Except for anxiety, younger patients also had a higher prevalence of distress than older patients. Females had more clinically important neuropsychological symptoms than males, and itch was more distressful to them (Tables 3 and 4).

Some clinically important and distressful symptoms differed with performance status. Patients were divided by into three groups by ECOG PS (64 PS 3–4; 41 PS 2; 76 PS 1). Those with the worst PS (ECOG 3–4) had more clinically important dyspnea (34% versus 17% versus 18%; $p = 0.045$); depression (23% versus 24% versus 8%; $p = 0.019$); confusion (20% versus 12% versus 5%; $p = 0.025$), dysphagia (13% versus 10% versus 0%; $p = 0.002$), and myoclonus (8% versus 5% versus 0%; $p = 0.027$). Those with the worst PS also had more distressful dry mouth (64% versus 41% versus 39%; $p = 0.042$), and hoarseness (60% versus 42% versus 14%; $p = 0.029$).

Clinically important edema, itching, skin problems, heartburn, dysphagia, vomiting, myoclonus, and urine incontinence varied by PSG. Compared with the entire group clinically important symptoms were more common in head and neck, breast cancer, and cancer of unknown primary (CUP). Distressful belching ($p = 0.005$) and urine incontinence ($p = 0.044$) varied by PSG.

After adjustment for symptom severity, only sore mouth remained more distressful to younger patients (Table 5). Anxiety, depression, and sweats were more distressful to females. Hoarseness was more distressful to individuals with poor ECOG PS (Table 5). Symptom distress did not differ by tumor PSG when severity was controlled.

We analyzed several multivariate logistic regression models of the effect of age, gender, and ECOG PS on symptom severity and distress. In the severity model, clinically important pain ($p = 0.021$), anorexia ($p = 0.024$), early satiety ($p = 0.001$), sleep problems ($p = 0.035$), numbness ($p = 0.009$), and urine incontinence ($p = 0.039$) remained more prevalent in younger

Table 2. Symptom prevalence and distress

Symptom	Prevalence *N* (%)[a]	Distressful *N* (%)[b]	Symptom	Prevalence *N* (%)[a]	Distressful *N* (%)[b]
Fatigue	130 (72)	100 (77)	Tremors	39 (22)	16 (41)
Pain	122 (67)	105 (86)	Itching	36 (20)	20 (56)
Dry mouth	119 (66)	59 (50)	Vision problems*	33 (18)	19 (58)
Anorexia	111 (61)	84 (76)	Hiccup	31 (17)	12 (39)
Weight loss	101 (56)	52 (51)	Skin problems	30 (17)	15 (50)
Early satiety	90 (50)	60 (67)	Sweats	30 (17)	21 (70)
Sleep problems	82 (45)	53 (65)	Wheezing	30 (17)	9 (30)
Dyspnea	78 (43)	53 (68)	Heartburn	28 (16)	14 (50)
Drowsiness	73 (40)	31 (42)	Hearing problems	26 (14)	15 (58)
Cough	72 (40)	35 (49)	Dizziness	24 (13)	14 (58)
Constipation	72 (40)	50 (69)	Dysphagia	24 (13)	15 (63)
Depression	64 (35)	34 (53)	Sore mouth*	24 (13)	18 (75)
Belching	61 (34)	21 (34)	Indigestion	23 (13)	10 (43)
Taste change	59 (33)	41 (69)	Chills	22 (12)	15 (68)
Bloating	56 (31)	33 (59)	Vomiting	22 (12)	18 (82)
Edema	55 (30)	24 (44)	Diarrhea	18 (10)	11 (61)
Anxiety	54 (30)	34 (63)	Headache	17 (9)	8 (47)
Memory problems	53 (29)	26 (49)	Myoclonus	15 (8)	8 (53)
Nausea	50 (28)	36 (72)	Urine incontinence*	14 (8)	8 (57)
Agitation	47 (26)	22 (47)	Bad dreams	12 (7)	5 (42)
Confusion	47 (26)	25 (53)	Fever*	12 (7)	7 (58)
Hoarseness	46 (25)	19 (41)	Visual hallucinations*	8 (4)	3 (38)
Numbness/tingling	44 (24)	15 (34)	Fecal incontinence*	3 (2)	1 (33)

[a]Percentage of 181 patients.
[b]Percentage of those with the symptom.
*No significant correlation was found between severity and distress.

individuals. Clinically important anxiety ($p = 0.038$), vision problems ($p = 0.034$), and headache ($p = 0.045$) were consistently more common in females. Clinically important dyspnea ($p = 0.035$), depression ($p = 0.015$), dysphagia ($p = 0.009$), confusion ($p = 0.010$), myoclonus ($p = 0.04$), fatigue ($p = 0.019$), and hoarseness ($p = 0.028$) were associated with poor PS. In the symptom distress model, early satiety ($p = 0.017$), sleep problems ($p = 0.006$), and sore mouth ($p = 0.047$) remained more frequently distressful in those $\leq$65 years, whereas anxiety ($p = 0.022$) had a higher prevalence of distress in older individuals.

In the multivariate analysis of distress, additional symptoms were influenced by ECOG PS and gender. In addition to itch ($p = 0.014$), sleep problems ($p = 0.04$) and anxiety ($p = 0.035$) were more distressful to females. In addition to dry mouth ($p = 0.029$) and hoarseness ($p = 0.013$), fatigue ($p = 0.022$), depression ($p = 0.045$), bloating ($p = 0.047$), and urine incontinence ($p = 0.048$) were more often distressful in those with better PS. After symptom data were adjusted for severity level, symptom distribution resembled that from the univariate analysis: depression ($p = 0.040$), anxiety ($p = 0.022$), and sweats ($p = 0.040$) were more commonly distressful in females; hoarseness ($p = 0.034$) had a higher prevalence in those with poor ECOG PS. Unlike the univariate model, sore mouth was uninfluenced by age ($p =$ NS).

Discussion

We previously reported that only certain distressful symptoms were volunteered by patients if they were not assessed in a systematic fashion.[18] This current analysis revealed that mild (both common and infrequent) symptoms can also often be distressful. More than 50% of individuals with a given symptom rated it distressful. In general, the more severe symptoms were also more distressful. Importantly, one third of those with mild symptoms also considered them distressful. Symptoms may be ignored by caregivers when rated as mild if distress is not also assessed separately.

Demographic features influenced both symptom distress and severity consistently in both univariate and

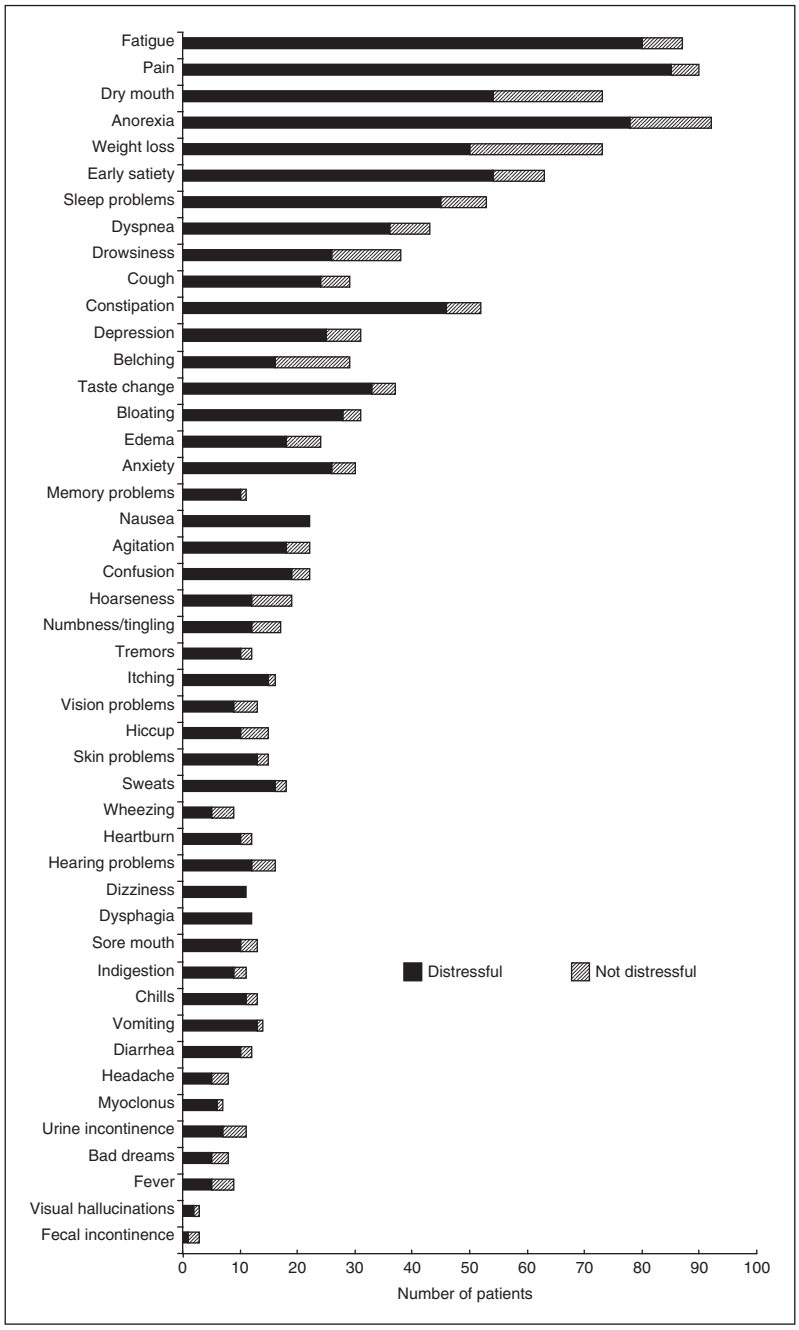

Figure 1. Overall prevalence and symptom distress of clinically important (moderate/severe) symptoms.

multivariate analysis. Younger patients and those with poor ECOG PS were more likely to have both clinically important and distressful symptoms. Individuals with head and neck, breast cancer, and CUP had more clinically important symptoms than other PSG.

In the initial analysis, demographic influences were apparent on the prevalence of severe symptoms. However, their influence on distress was reduced after adjustment for symptom severity. Distress increased with symptom severity, but severity was not the only factor that predicted distress. After control for severity, the effect of age and ECOG PS on distress decreased, i.e. fewer symptoms varied with age and PS. Distress was influenced by gender, but not PSG. Females had a nearly five-fold higher prevalence of distress with both anxiety and depression than males with similar degrees

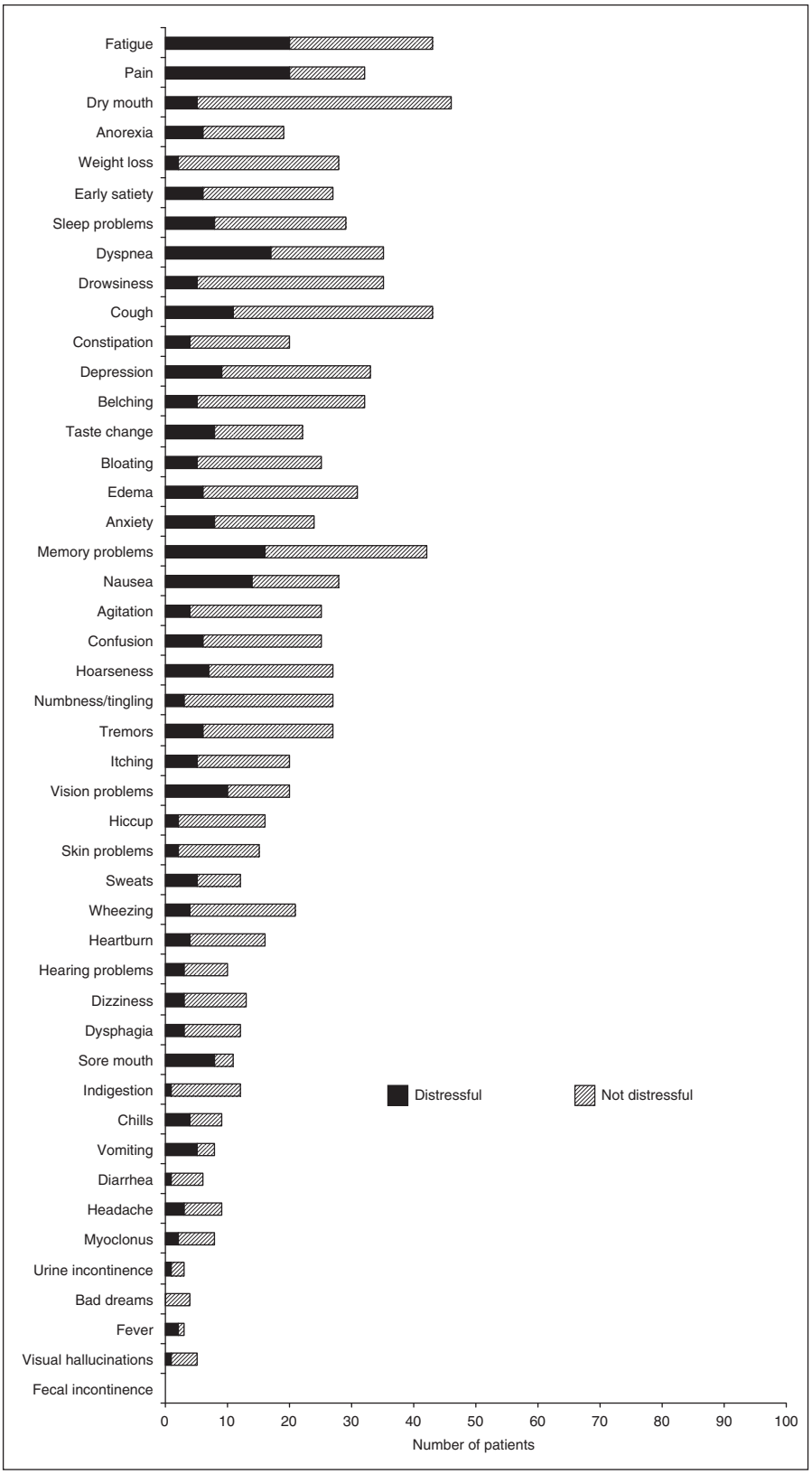

Figure 2. Overall prevalence and symptom distress of the mild symptoms.

of severity for these symptoms. In our study, anxiety and depression were usually reported as distressful regardless of their severity. Others have found greater symptom distress with decreased PS, female gender, lower age, and in more advanced disease.[21–23] Factors like gender, personality traits, existential meaning, coping skills, resilience and behavioral interventions may also influence distress independent of symptom severity.[23,24] This may explain why primary site, and ECOG PS and age influenced mostly symptom severity. Distress (from physical and psychological symptoms), suffering, spirituality, and symptom burden have a complex inter-relationship in advanced disease, which requires further research.[25,26] Higher distress in lung cancer may predict shorter survival.[21–23] We did not have survival data available. It would be important to consider distress and severity as prognostic factors in future studies.

Some report that the 'most troublesome' symptoms are also the 'most severe' symptoms.[27] For certain common (nausea) and uncommon (diarrhea) symptoms this relationship may not hold.[27] Forty-five percent of older community-dwelling adults with chronic diseases rate fatigue severity one level higher or lower than distress, 15% rate it two levels higher or lower.[17] In addition, physical and psychological symptoms may contribute differently to perceived distress based on their pathophysiology and symptom domain (in our data, mild fever was as distressful as mild pain, whereas mild fatigue, anxiety and depression were less often distressful). Fatigue, anxiety, and depression involve complex endocrine, neurohumoral, neurotransmitter and inflammatory factors, which may influence symptom distress, but perhaps also have a different relationship with perceived severity.[28] Pain severity, psychological symptom distress, and QoL scores may be influenced differently by cancer pain management.[29] Symptom relief (which possibly has greater clinical relevance) reports can be at variance with those of reduced severity.[30,31] The relationship between distress and severity in symptom relief needs to be explored further.

The distress dimension may explain some of the variability in symptom severity observed between visual analogue (VAS), verbal and numerical rating (NRS) scales.[32,33] Pain researchers have defined clinically

Table 3. Univariate analysis of clinically important (moderate/severe) symptoms that differed by age or gender

	%		
Symptom	Age ≤ 65 ($n = 101$)	Age > 65 ($n = 80$)	p value
Anorexia	58	41	0.022
Pain	57	40	0.02
Early satiety	46	21	<0.001
Sleep problems	36	21	0.035
Numbness/tingling	16	1	<0.001
Heartburn	10	2	0.047
Dysphagia	10	2	0.047
Urine incontinence	10	1	0.024
	Female ($n = 84$)	Male ($n = 97$)	
Anxiety	23	11	0.042
Vision problems	12	3	0.022
Headache	8	1	0.026

Table 4. Univariate analysis of distressful symptoms that differed by age or gender

	%		
Symptom	Age ≤ 65	Age > 65	p value
Sore mouth	88	43	0.038
Fever	78	0	0.046
Sleep problems	77	47	0.005
Early satiety	76	51	0.014
Anxiety	53	88	0.015
Numbness	44	8	0.035
	Female	Male	
Itching	80	38	0.013

Table 5. Univariate analysis of distress across age, gender, and ECOG after adjusting for symptom severity

Parameter	Symptom	OR	CI	p
≤ 65 versus > 65	Sore mouth	9.73	1.14–83.2	0.038
Female versus male	Anxiety	4.69	1.01–21.9	0.049
	Depression	4.45	1.01–21.9	0.037
	Sweats	14.4	1.08–192.2	0.044
ECOG 2 versus ECOG 1	Hoarseness	7.33	0.75–71.6	0.09
ECOG 3–4 versus ECOG 1	Hoarseness	10.2	1.25–83.1	0.030

OR: odds ratio, CI: confidence interval.

important changes in VAS severity scores. Pain intensity >30 mm, but <50 mm on VAS is rated as moderate by some, and by others as a 'little bit of distress'.[34,35] Perceptions of severity and distress can differ, particularly for mild anxiety, drowsiness and dyspnea;[35] a significant number of our patients rated them distressful, despite only mild or moderate severity. The relation between quantitatively mild but qualitatively distressful symptoms (and factors that modulate severity and distress) suggests that the two symptom domains are indeed distinct. Distress has been proposed as a sixth vital sign.[36]

A limitation to our study was the cross-sectional design. In a longitudinal study, distressful symptoms in lung cancer had a similar rank order at each assessment point, but severity changed over time, which suggested a complex relationship between the two symptom domains.[37] Assessment timeframes may also have influenced this observation. Distressful symptoms were ranked by patients without a timeframe, while only symptoms 'at the present time' were assessed for severity.[37] In our study, in contrast, we used a similar timeframe ('today') for both severity and distress. We used a non-validated instrument, and were unable to correlate symptoms or distress to cancer stage. The grouping by primary tumor site assumed that the patients within these groups were similar, and this could have influenced some conclusions. Distress was measured dichotomously, which prevented any comparison of severity of distress and severity. The order of questions may have influenced the results, since we always assessed distress after severity. Lastly prior or current therapy may have influenced severity and/or distress.

The clinical importance of our findings is that distress or severity alone is inadequate to guide treatment or response to symptom management. Most symptoms were rated as distressful by someone. Distress likely adds important clinical information to that of symptom severity. Changes in distress may theoretically have more impact on symptom treatment outcomes than severity changes.[38] It is noteworthy that infrequent symptoms were often distressful. This also suggests that only a comprehensive symptom assessment can capture the total burden experienced by an individual. This also argues against a selective reductionist approach to symptom assessment.

Our study supports other observations[4,17,27,35] that distress adds clinical value to severity for symptom assessment. Our study is the only one that has examined the relationship of categorical assessment of severity with distress separately for multiple symptoms in a large group of consecutive cancer patients. We believe this gives important new information. Symptom distress may have a different clinical meaning to the individual at different severity levels.[26,27] It is important to remember that patient expectations may change with PS and indirectly influence perceptions of severity and/or distress. Our data also suggest that mild symptoms can often be distressful. They may remain untreated if only assessed for severity. Demographic characteristics, particularly gender, and to a lesser extent age, and performance status (but not tumor primary site) seemed to influence the perception of distress, regardless of symptom severity.

Future research[39] should focus on quantitative comparisons between different levels of symptom relief, severity, and distress. Variations in symptom perception by severity and distress at assessment time points should be determined. Qualitative research on characteristics that determine distress, and the association between distress, personality, coping skills (resilience), and family dynamics is also needed.

Conclusions

There was a strong relationship between symptom severity and symptom distress in advanced cancer; the more severe (clinically important) symptoms were usually distressful. Importantly, however, one third of individuals with mild symptoms also considered them distressful. Severity did not appear to be a proxy for distress. The clinical importance of symptoms cannot be judged by severity alone. Anxiety and depression, which are markers of psychological disturbance, were distressful regardless of severity. Measurement of both severity and distress will likely better gauge the need for treatment and assess outcomes. The severity of certain clinically important symptoms was influenced by demographic features (age, gender, primary site, and performance status). Younger people and those with poor performance status were more likely to have both clinically important and distressful symptoms. After control for symptom severity, distress was influenced by gender, but less so by performance status and age, and not at all by primary site. The prevalence of distress in anxiety and depression was nearly five times higher in females than males for similar degrees of symptom severity. The relationship between, severity, distress, prognosis, and symptom relief needs to be explored further. Longitudinal research on characteristics that determine distress, associated with demographic factors, personality, and coping skills (resilience) should help us better understand symptom distress and its individual meaning.

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