Factors Associated With Pain Among Ambulatory Patients With Cancer With Advanced Disease at a Comprehensive Cancer Center

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Abstract

Purpose: The prevalence and severity of pain have not been well described among oncology patients in ambulatory care. To better understand the burden of pain among patients with advanced cancer, we examined the prevalence of pain reported during office and treatment visits.

Methods: A retrospective study of 4,014 patients with advanced disease (stage 4 at diagnosis or metastatic progression) who completed an ambulatory visit between 2004 and 2006 was conducted at a comprehensive cancer center in Boston, Massachusetts.

Results: At their first visit during the study period, 74% of patients reported no pain (0 score); 12%, low pain (1 to 3 score); 9%, moderate pain (4 to 6 score); and 5%, severe pain (7 to 10

score). The prevalence of pain was highest among patients who were younger than 60 years of age, were nonwhite, did not speak English as their primary language, or were covered by Medicaid, received free care, or paid their own health care costs. Patients with thoracic, breast, and head and neck cancers had higher pain scores than those with other diseases. Pain was reported more frequently among patients whose diagnosis or metastatic progression occurred less than 3 months before the reported pain score. In multivariable regression analysis, age, race, cancer type, and time since diagnosis/progression were identified as important factors associated with severe pain.

Conclusion: Younger age, minority race, and recent onset of advanced disease are associated with severe pain among patients with cancer. Recognizing these high-risk groups could inform targeted interventions to address pain care in ambulatory patients with advanced cancer.

Introduction

Although pain is a common and serious complication of cancer, the prevalence and severity of pain have not been well described among oncology patients, particularly those in the outpatient setting. The occurrence of pain in patients with cancer is quite variable.^{1,2} Several studies have reported the prevalence of pain to be 30% to 60% of patients,¹⁻⁶ although frequencies as low as 14%⁷ and as high as 100%⁸ have also been observed. The variability in findings likely reflects the heterogeneity of the populations surveyed with respect to patient setting, cancer type, and disease stage.

A number of studies have compared pain prevalence among patients with different types of cancer. In some, the frequency of pain has been observed to be higher among patients with head and neck tumors⁹⁻¹² and those with lung cancer.^{9,11-14} However, a higher prevalence of pain has also been reported in patients with prostate,^{7,10,15} breast,^{7,14} gynecologic,^{10,15} colorectal,¹³ and pancreatic¹² cancers. In general, patients with metastatic malignancies have more severe pain than those with nonmetastatic disease, affecting as many as 70% to 90% of those with advanced disease.^{1,2,5,10,12,15,16}

The existing literature offers conflicting information about factors associated with cancer pain. Female sex has been associated with greater pain in a few studies,^{16,17} although other studies have not found a significant difference by sex.^{3,9,11,13,15} Similarly, more severe pain has been reported for younger pa-

tients in some^{9,15,17} but not all studies.^{3,11,16} With respect to race and ethnicity, minorities with cancer tend to report higher levels of pain and to receive inadequate treatment for their pain.^{16,18,19}

Few studies have examined pain experienced by patients with advanced disease during ambulatory cancer treatment and follow-up. To better understand the burden of pain among ambulatory patients with advanced cancer, we retrospectively examined the prevalence of pain reported during office and treatment visits at a comprehensive cancer center between 2004 and 2006. We evaluated the distribution of reported pain scores in this large cohort of patients according to their sociodemographic and disease characteristics.

Methods

Study Patients

All adult patients seen for an ambulatory visit at Dana-Farber Cancer Institute (DFCI), a Boston-based comprehensive cancer center, between January 1, 2004, and December 31, 2006, were potentially eligible for this study. The analytic cohort was assembled retrospectively by identifying patients with at least one assessment of pain during this interval and either stage 4 disease at diagnosis ($n = 2,003$) or documented metastases after initial diagnosis at an earlier stage ($n = 2,011$). Information on stage at diagnosis was derived from the institutional tumor reg-

istry, and presence of metastases was obtained from the DFCI Clinical Research Information System (CRIS). CRIS contains detailed longitudinal sociodemographic and clinical data abstracted from the medical records of consenting patients receiving care at DFCI. During the study period, CRIS data were available for more than 80% of DFCI patients with breast, prostate, thoracic, and GI cancers. In the present study, 2,222 patients with progressive disease were included from CRIS, of whom 2,011 had an available pain score after metastatic progression in 2004 to 2006. Thus, the total size of the cohort of patients with advanced disease was 4,014. The study protocol was approved in advance by the institutional review board of Dana-Farber/Harvard Cancer Center.

Data Collection

Patients' pain scores were obtained retrospectively from the electronic medical record for all ambulatory visits from January 1, 2004, to December 31, 2006. Clinic assistants routinely solicit patients' pain intensity on a 0-to-10 numeric and/or visual analog scale at each outpatient visit using a standard script in which "0 is no pain, and 10 is the worst you can imagine" and record the result in the electronic medical record.²⁰ In a review of more than 150,000 appointments at DFCI during 2004, we found that clinic assistants recorded pain scores in the electronic medical record for 96% of visits to the cancer center (unpublished data).

Information from DFCI and Brigham and Women's Hospital tumor registries was used to determine type of cancer and date of diagnosis. Patients were grouped into the following solid tumor categories based on International Classification of Diseases for Oncology codes in the tumor registries: breast, thoracic, GI (esophagus, stomach, liver and intrahepatic bile ducts, colon/rectum, pancreas), urogenital (cervix, uterus, ovary, prostate, testis, kidney, bladder), head and neck (oral cavity and pharynx, thyroid, larynx), and other (brain and other nervous system, melanoma, sarcoma). In the tumor registry, the diagnosis date is the date of cancer diagnosis first reported by the medical practitioner, regardless of where the diagnosis was made or whether the diagnosis was histologically confirmed. For patients with metastases after treatment for earlier stage disease, CRIS documents the first date on which metastatic disease was identified clinically or pathologically.

Basic demographic data, including date of birth, sex, race, and primary language as well as primary insurance, were drawn from the DFCI patient registration system. Information on race is obtained by direct query of patients. For the analysis, we categorized race as white or nonwhite and medical insurance type as Medicare, private, or Medicaid/free care/self-pay.

Data Analysis

The prevalence of pain was examined at patients' first (index) ambulatory visit during the study period, according to their demographic and clinical characteristics. If a patient had more than one visit on a given date, the pain score from the first visit for that day was used. The index pain scores were categorized as no pain (0 score), low pain (1 to 3 score), moderate pain (4 to 6

score), or severe pain (7 to 10 score) and compared across patient characteristic groups using the χ^2 statistic. Time since diagnosis or progression was the interval between the date of initial diagnosis for patients with advanced disease at diagnosis or the date of metastatic progression for patients with progressive disease, respectively, and the date of the index pain score.

In addition, logistic regression modeling was performed to identify factors associated with severe pain at the index visit. Variables associated at $P < .10$ in bivariate analysis were then entered into a multivariable model; this significance level was used to increase the sensitivity of the analysis to detect factors associated with severe pain. Using a stepwise backward elimination strategy, covariates with $P < .10$ were retained in the final model of factors independently related to severe pain. Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Patient characteristics are listed in Table 1. The mean age at the index visit during the study period was 61.2 years (standard deviation, ± 12.4 years). Fifty-seven percent of the patients were men, and more than 90% were white and spoke English as their primary language. Almost all of the patients had either private medical insurance (56%) or Medicare (39%).

The distribution of cancer diagnoses is also provided in Table 1, with urogenital and GI malignancies being the most represented groups. The mean interval between initial diagnosis of advanced disease or metastatic progression and pain score was 1.3 years, although for half of the patients, this interval was 3 months or less.

Prevalence of Pain

The overall mean pain score at the index visit was 1.1 (standard deviation, ± 2.2), with 74% reporting no pain (0 score); 12%, low pain (1 to 3 score); 9%, moderate pain (4 to 6 score); and 5%, severe pain (7 to 10 score; Table 1). Table 2 lists the prevalence of the pain score groups by patient characteristics. Patients who were younger than 60 years of age were more likely to report any pain compared with older patients (32% *v* 21%); the prevalence of severe pain was highest among those age 18 to 39 years (9%). Women had a somewhat higher frequency of any pain compared with men (29% *v* 24%). Patients who were nonwhite (33% *v* 25%) or who did not speak English as their primary language (37% *v* 26%) were also more likely to be experiencing pain at the index ambulatory visit. In addition, the prevalence of reported pain, particularly at moderate or severe levels, was higher for patients who were covered by Medicaid, received free care, or self-paid.

Pain scores differed across disease groups (Table 2). Although 20% to 30% of patients reported some pain, the prevalence of moderate or severe pain was highest among patients with thoracic (18%), breast (18%), and head and neck (17%) cancers. The prevalence of pain was lowest among patients with urogenital cancer, with only 2.4% reporting a severe pain score

Table 1. Patient Demographics and Clinical Characteristics (N = 4,014)

Characteristic	No.	%
Age, years		
18-39	197	4.9
40-49	554	13.8
50-59	1,102	27.5
60-69	1,104	27.5
70-79	821	20.5
≥ 80	236	5.9
Mean		61.2
SD		12.4
Sex		
Male	2,289	57.0
Female	1,725	43.0
Race		
White	3,739	93.3
Nonwhite	296	6.7
Missing	6	
Primary language		
English	3,797	95.9
Non-English	164	4.1
Missing	53	
Primary insurance		
Medicare	1,576	39.4
Medicaid/free care/self-pay	203	5.1
Private	2,218	55.5
Missing	17	
Cancer type		
Breast	611	15.2
Thoracic	721	18.0
GI	957	23.8
Urogenital	1,191	29.7
Head and neck	307	7.7
Other	227	5.7
Cancer stage		
Stage IV at diagnosis	2,003	49.9
Metastatic progression	2,011	50.1
Time since diagnosis/progression		
≤ 3 months	2,012	50.7
3 months to 1 year	630	15.9
1 to 5 years	1,015	25.6
> 5 years	314	7.9
Missing	43	
Mean years		1.3
SD		2.2
Pain score at index visit		
0	2,977	74.2
1-3	472	11.8
4-6	379	9.4
7-10	186	4.6
Mean		1.1
SD		2.2

Abbreviation: SD, standard deviation.

at their index visit during the study period. Reported pain was higher for patients with stage IV cancer at diagnosis compared with those with progressive metastatic disease (30% *v* 23%) and for those whose diagnosis or metastatic progression occurred less than 3 months before the time of the reported pain score compared with more than 1 year (32% *v* 18%).

Factors Associated With Severe Pain

In the unadjusted bivariate logistic regression analysis (Table 3), the likelihood of reporting severe pain was higher for patients who were female, were of nonwhite race, or did not speak English as their primary language. Greater odds of severe pain were also found for patients whose primary form of insurance was Medicaid/free care/self-pay or private. Patients who were 40 years of age or older were less likely to report severe pain, with odds ratios ranging from 0.67 for those age 40 to 49 years to 0.33 for those older than 70 years. Compared with patients with urogenital cancer, those with breast, thoracic, GI, and head and neck cancers had increased odds of experiencing severe pain. The probability of severe pain was elevated approximately two-fold if the pain score was reported within 1 year of diagnosis/progression.

In the multivariable logistic regression model, only age, race, cancer type, and time from diagnosis/progression remained as important independent factors associated with reported severe pain (Table 3). In this model, the odds of severe pain was more than two-fold for patients of nonwhite race and those with breast, thoracic, and head and neck cancers. A more than 70% increased likelihood of reporting severe pain was observed for patients with an advanced disease diagnosis or metastatic progression that occurred within 1 year. Patients who were 70 years of age or older had half the odds of experiencing severe pain as compared with those who were younger than 40 years, after accounting for other patient characteristics. In a secondary analysis, we examined whether the observed associations differed between patients with advanced disease at diagnosis and those with metastatic progression. Similar adjusted odds ratio estimates were found for both groups (data not shown).

Discussion

Pain was common in this large cohort of ambulatory patients with advanced cancer. On the basis of reported pain scores, 26% of patients were experiencing some pain; for 9%, the level was of moderate intensity, and for 5%, the level was severe. The prevalence of any pain at the index ambulatory visit was highest among patients who were younger than 60 years of age, were of nonwhite race, did not speak English as their primary language, or were covered by Medicaid, received free care, or paid for their own health care costs. Patients with thoracic, breast, and head and neck cancers had higher pain scores than those in other disease groups. Pain also was experienced more frequently among patients whose advanced disease diagnosis or metastatic progression had occurred less than 3 months before the time of the reported pain score. In a multivariable model, age, race, cancer type, and time from diagnosis/progression were identified as important factors associated with reported severe pain.

Table 2. Prevalence of Pain Score at Index Visit by Patient Characteristics

Characteristic	Pain Score								P
	None (0)		Low (1-3)		Moderate (4-6)		Severe (7-10)		
	No.	%	No.	%	No.	%	No.	%	
Age, years									< .001
18-39	126	64.0	35	17.8	19	9.6	17	8.6	
40-49	363	65.5	93	16.8	65	11.7	33	6.0	
50-59	778	70.6	157	14.3	110	10.0	57	5.2	
60-69	851	77.1	109	9.9	97	8.8	47	4.3	
70-79	658	80.2	57	6.9	76	9.3	30	3.7	
≥ 80	201	85.2	21	8.9	12	5.1	2	0.9	
Sex									< .001
Male	1,749	76.4	249	10.9	210	9.2	81	3.5	
Female	1,228	71.2	223	12.9	169	9.8	105	6.1	
Race									< .001
White	2,791	74.7	445	11.9	344	9.2	159	4.3	
Nonwhite	181	67.3	27	10.0	34	12.6	27	10.0	
Primary language									.007
English	2,828	74.5	446	11.8	352	9.3	171	4.5	
Non-English	104	63.4	24	14.6	22	13.4	14	8.5	
Primary insurance									< .001
Medicare	1,262	80.1	134	8.5	124	7.9	56	3.6	
Medicaid/free care/self-pay	124	61.1	27	13.3	31	15.3	21	10.3	
Private	1,577	71.1	311	14.0	223	10.1	107	4.8	
Cancer type									< .001
Breast	425	69.6	77	12.6	64	10.5	45	7.4	
Thoracic	496	68.8	92	12.8	89	12.3	44	6.1	
GI	708	74.0	128	13.4	80	8.4	41	4.3	
Urogenital	966	81.1	103	8.7	93	7.8	29	2.4	
Head and neck	219	71.3	35	11.4	34	11.1	19	6.2	
Other	163	71.8	37	16.3	19	8.4	8	3.5	
Cancer stage									< .001
Stage IV at diagnosis	1,430	71.4	270	13.5	207	10.3	96	4.8	
Metastatic progression	1,547	76.9	202	10.0	172	8.6	90	4.5	
Time since diagnosis/progression									< .001
≤ 3 months	1,361	67.6	312	15.5	223	11.1	116	5.8	
3 months to 1 year	485	77.0	54	8.6	59	9.4	32	5.1	
1 year to 5 years	834	82.2	80	7.9	68	6.7	33	3.3	
> 5 years	260	82.8	20	6.4	29	9.2	5	1.6	

These findings suggest that younger and minority race patients with recent onset of advanced disease are at increased probability of experiencing severe pain.

The prevalence of pain found in the present study is lower than has been observed in other studies of patients with advanced cancer, in which frequencies of greater than 50% and often higher than 70% have been reported.^{1,2,5,10,13,16,21-23} However, many of those studies involved patients who were hospitalized,^{5,13,21} receiving palliative care,^{5,10,23} or in the terminal stage of disease.²¹ Such patients would be expected to have higher pain scores than patients in the present study. In addition, in some studies, the occurrence of pain was based on

receipt of analgesics²¹ or assessed over the previous week,^{13,16,22} in contrast to our patients, in whom pain information was based on reported pain scores routinely collected at the time of an ambulatory visit.

With respect to the occurrence of pain across cancer disease groups, the findings in literature have been variable. In a study of patients with metastatic breast, colorectal, prostate, and gynecologic cancers seen at a comprehensive cancer center, patients with prostate or breast cancer had a higher prevalence of pain.⁷ The prevalence of moderate to severe pain was among the highest for patients with head and neck cancer in a study of patients with advanced cancer in hospice centers in Europe, the

Table 3. Factors Associated with Severe Pain

Variable	Bivariate			Multivariable*		
	OR	95% CI	P	OR	95% CI	P
Age, years						
18-39	1.0		—	1.0		—
40-49	0.67	0.37 to 1.23	.20	0.72	0.39 to 1.33	.29
50-59	0.58	0.33 to 1.02	.056	0.68	0.38 to 1.20	.18
60-69	0.47	0.26 to 0.84	.010	0.63	0.34 to 1.14	.12
≥ 70	0.33	0.18 to 0.61	< .001	0.48	0.25 to 0.90	.022
Sex						
Male	1.0					
Female	1.77	1.31 to 2.38	< .001			
Race						
White	1.0		—	1.0		—
Nonwhite	2.51	1.64 to 3.86	< .001	2.38	1.54 to 3.40	< .001
Primary language						
English	1.0		—			
Non-English	1.98	1.12 to 3.50	.019			
Primary insurance						
Medicare		1.0	—			
Medicaid/free care/self-pay	1.38	0.99 to 1.91	.058			
Private	1.60	1.15 to 2.24	< .001			
Cancer type						
Urogenital	1.0		—	1.0		—
Breast	3.19	1.98 to 5.14	< .001	2.47	1.49 to 4.10	< .001
Thoracic	2.60	1.61 to 4.21	< .001	2.03	1.23 to 3.35	.0056
GI	1.79	1.11 to 2.91	.018	1.44	0.87 to 2.37	.15
Head and neck	2.64	1.46 to 4.78	.0013	2.25	1.22 to 4.14	.0091
Other	1.46	0.66 to 3.24	.35	1.04	0.46 to 2.34	.93
Cancer stage						
Stage IV at diagnosis	1.0		—			
Metastatic progression	0.93	0.69 to 1.25	.63			
Time since diagnosis/progression						
≤ 3 months	2.08	1.43 to 3.02	< .001	1.75	1.19 to 2.59	.0048
3 months to 1 year	1.82	1.13 to 2.94	.015	1.72	1.06 to 2.81	.029
> 1 year	1.0		—	1.0		—

Abbreviation: OR, odds ratio.

* Final logistic regression model of factors related to severe pain at $P < .10$.

United States, and Australia but was lower among those with lung and breast cancers.¹⁰ In a multicenter study in France of patients with metastatic and nonmetastatic disease, those with GI or lung cancer had a somewhat higher frequency of moderate or severe levels of pain than did patients with head and neck or breast cancer.⁹ In contrast to the present study, the presence of severe pain was not found to be significantly higher for patients with breast, lung, or head and neck cancer in two studies of patients with advanced cancer in the United States.^{15,16} In the study of outpatients treated at sites affiliated with the Eastern Cooperative Oncology Group, Cleeland et al¹⁶ observed similar high levels of pain across all disease sites. The variability across studies with respect to the relative prevalence by disease type likely reflects differences in the patient populations studied

(eg, inpatient *v* outpatient) as well as the disease groups created (eg, gynecologic malignancies included genitourinary cancers).

Of interest was our observation that onset of advanced disease within the previous year, whether newly diagnosed or related to metastatic progression, was associated with a higher prevalence of severe pain. Although advanced disease has been associated with increased cancer pain, these results suggest that the onset of advanced disease or metastatic lesions poses a particularly vulnerable time and one in which symptom assessment and mitigation require heightened attention. Although treatment of the underlying malignancy is often a key objective in this setting, symptom management is a critical component of care. Thus, psychologic distress related to new or worsening disease can contribute to the higher pain levels experienced by

these patients,²⁴ and higher pain may also produce greater anxiety, depression, and psychologic distress.^{25,26} Of note, a recent clinical trial found that early palliative care resulted in improved quality of life and longer survival for patients with newly diagnosed metastatic non-small-cell lung cancer.²⁷

With respect to the relationship between sociodemographic factors and severe pain, our findings support those from previous studies. Some studies have found younger age to be associated with the occurrence of severe pain among patients with advanced cancer.^{15,28,29} However, other studies have reported no association of age with severe pain in this patient group.^{3,23,30} Despite the potential undertreatment of pain among older patients with cancer,^{16,17} pain may be harder to control in younger patients, who may be more likely to report pain and pain interference.^{29,30} Although in the present study women seemed to be more likely to experience severe pain in the unadjusted analysis, sex did not remain as a risk factor in the multivariable model. The lack of an association between sex and pain severity has been observed in most studies of patients with cancer,^{3,11,28,29,31-34} with a few studies reporting a slightly higher occurrence of pain among women.^{16,17,23,35}

Pain and severe levels of pain were more likely to be reported by patients with cancer of minority race in nearly all studies that examined this factor.^{18,19,30-32,36,37} A relatively strong association between nonwhite race and severe pain was found in the present study of ambulatory patients with advanced disease, independent of age, cancer type, and time since diagnosis or progression. Although non-English speaking patients were more likely to report severe pain in the unadjusted analysis, the association was no longer apparent in a multivariable model that included race. Lack of adequate pain treatment may account for the increased pain experienced by minority patients with cancer.^{16,32,36} Issues related to access to care and insurance coverage likely contribute to racial disparities in pain care.^{18,19,32,38} It also has been suggested that cultural differences with respect to perceptions about pain tolerance and pain medication could affect patient-physician communication and treatment decisions concerning pain management.^{19,32,38,39} In addition, variations in psychosocial stressors across social, demographic, and ethnic groups may play a role in pain response.³⁸

Several limitations of the study should be noted. Only one measure of pain intensity was used, and as such, it does not reflect the complex and multidimensional experience of pain or its impact on quality of life. Nonetheless, this pain assessment method is well validated and widely used among cancer centers for pain screening.²⁰ Our study also lacked information on

cancer treatment and use of analgesics, which would affect reported pain. Unfortunately, the data on treatment regimens and pain medications were only available for a subset of patients and were not of sufficient detail to allow evaluation. The retrospective conduct of the study could represent a potential limitation. However, because inclusion in the study was based on having a pain score in the electronic medical record, which was found to be recorded for 96% of visits, no bias likely was introduced. Last, because the study involved patients from a single comprehensive cancer center, the generalizability of the findings may be somewhat limited. The prevalence of pain and characteristics of patients who report severe pain may be different in other health care settings.

In conclusion, we found that pain is a prevalent symptom among ambulatory patients with advanced cancer across multiple malignancy types. Severe pain was associated with younger age, minority race, and recent onset of advanced disease. Early identification of patients at increased risk of experiencing high levels of pain could facilitate targeted pain and palliative care assessment and the implementation of a comprehensive treatment plan to reduce the most severe and persistent symptoms.

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