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Habberstad, R, Hjermstad, MJ, Brunelli, C et al. (4 more authors) (2019) Which factors can aid clinicians to identify a risk of pain during the following month in patients with bone metastases? A longitudinal analyses. Supportive Care in Cancer, 27 (4). pp. 1335-1343. ISSN 0941-4355

https://doi.org/10.1007/s00520-018-4405-9

Which factors can aid clinicians to identify a risk of pain during the following month in patients with bone metastases? -A longitudinal analyses.

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Research funding:
This work was supported by the Central Norway Regional Health Authority (grant no. 46055100), the Cancer Foundation St Olavs Hospital, Trondheim University Hospital (grant no. 6070), the Liaison Committee for Education, Research and Innovation in Central Norway and an unrestricted grant from the Helsinn Group, Switzerland.

Conflicts of interest:
Kaasa S. hold stocks in EIR Solutions A/S. The other authors have no conflicts of interest.

Trial registration in clinicaltrials.gov: NCT01362816

ABSTRACT

Purpose: Explore clinical factors associated with higher pain intensity and future pain in patients with bone metastases to identify patients who can benefit from closer follow-up or pain-modifying interventions.

Methods: This is a secondary analysis of 606 patients with bone metastases included in a multi-center longitudinal study. The dependent variables were "average pain" and "worst pain" in the last 24 hours (0-10 NRS). Twenty independent variables with potential association to pain intensity were selected based on previous literature. Cross-sectional analyses were performed with multiple linear regression to explore factors associated with pain intensity at baseline. Longitudinal data were analyzed with a generalized equation models to explore current factors associated with pain intensity at the next visit in one month.

Results: Current pain intensity ($p < 0.001$), sleep disturbances (p 0.01 and 0.006), drowsiness (p 0.003 and 0.033) and male gender (p 0.045 and 0.001) were associated with higher average and worst pain intensity in one month. In addition, breakthrough pain was related to higher worst pain intensity (p 0.003) in one month. The same variables were also associated with higher average pain intensity at baseline.

Conclusion: Higher current pain intensity, sleep disturbances, drowsiness, male gender and breakthrough pain are factors associated with higher pain intensity in patients with bone metastases at the next follow-up in one month. These factors should be assessed in clinical practice and may aid clinicians to identify patients that can benefit from closer follow-up or medical interventions to prevent lack of future pain control.

Key words: cancer, pain, bone metastases, cancer-induced bone pain, associations

Introduction

Pain is an important cause of reduced quality of life in cancer patients, and more than 60% of advanced cancer patients experience pain.[7, 45] Bone metastases, which may cause cancer-induced bone pain (CIBP), are the most frequent causes of pain in cancer patients.[30]

The occurrence of bone metastases is highest in patients with multiple myeloma (70-95%), breast cancer (65-75%), prostate cancer (65-75%), lung cancer (30-40%), bladder cancer (40%) and malignant melanoma (14-45%).[6, 22] The development of bone metastases results from a close interaction between bone cells, tumor cells and their microenvironment. Cytokines in the bone microenvironment modulate genes expressed in cancer cells, and disrupt normal bone homeostasis.[43] These mechanisms, important in development of bone metastases, are essential mediators of CIBP.[43] The intensity of CIBP is related not only to the size and location of metastases but also to biological factors in the bone microenvironment, including factors that activate osteoclasts and sensitize primary afferent neurons.[27, 28, 35]

A number of preclinical studies have investigated the pathophysiological mechanisms of CIBP, but few studies have specifically described the clinical presentation of pain in patients with bone metastases.[4, 6, 25, 30, 44, 46] Laird et al reported that 75% of patients with CIBP had breakthrough pain usually with less than five minutes from the start of the pain escalation until maximum pain. The duration of a breakthrough pain episode was less than 15 minutes.[25] CIBP is also associated with neuropathic pain, with an incidence of approximately 25%.[26] Both breakthrough pain episodes and the presence of neuropathic pain are related to more severe pain in cancer patients.[20, 24, 25]

CIBP can be difficult to treat with analgesic medications, according to the WHO pain ladder. [8, 25, 42, 47] More specific treatment options are bone-targeting agents such as bisphosphonates and RANK ligand inhibitors, anti-cancer treatments such as chemotherapy or hormonal treatments, surgical management of pathological fractures, radioisotope treatment or external beam radiation therapy. These treatment options improve pain control in many patients but have a slow onset.[19, 47] For example, the response after external beam radiotherapy to treat painful bone metastases is approximately 60%, and the median time to response is up to 4 weeks after treatment.[2, 3, 49]

Knowledge about the clinical predictors for CIBP can contribute to early intervention to avoid or delay increased pain. Current studies are mostly cross-sectional, reporting associations between clinical and demographic variables and pain at a given time point.[23] A longitudinal analysis on the clinical factors related to pain intensity in a heterogeneous cohort of cancer pain patients found that initial pain intensity, breakthrough pain, lung cancer and age were predictors of pain two weeks after the initial assessment.[23] We wanted to investigate if this model could be reproduced and further developed with a more robust study design using repeated measures in a well-defined cohort, namely, patients with bone metastases only. This group of patients will have more similar pathophysiology of pain and more uniform pain treatment options. Additionally, to the best of our knowledge, there are no studies examining the associations between the clinical symptoms observed at one particular time point and the risk for increased pain needing intervention within the next weeks in patients with bone metastases. Thus, we aim to explore which clinical factors are

associated with higher pain intensity in patients with bone metastases and which of the current factors that are associated with higher pain intensity in the following month.

METHODS

Study design

This paper is based on data from the European Palliative Care Cancer Symptom study (EPCCS), a prospective longitudinal multicenter study conducted from 2011 to 2013 in 12 countries across Europe, Australia and Canada.[15]

Patients

Adult cancer patients under palliative care were included in the EPCCS study.[15] Study inclusion criteria required that patients were eligible for at least one follow-up assessment. Patients receiving curative anti-cancer treatment, those with severe cognitive or psychiatric disorders, or those who were unable to complete registrations were not included. In the present analysis, only patients with bone metastases from solid cancers were included.

Assessments

Clinical data

Patients were followed approximately once every month from baseline, for at least 3 months or until death or withdrawal. If they were in the hospital, health care providers completed a registration form with clinical data, and patients filled in a questionnaire on symptoms and functioning. If the patients were not in the hospital, clinical data were extracted from electronic patient records and by phoning the client if necessary,

and the patient questionnaires were sent by postal mail. In the present study, the following data were used: demographics, the characteristics of the cancer disease (diagnosis, distribution of metastases, current oncological treatment), Karnofsky Performance Status (KPS)[10] for functional status, a brief 4-item version of the Mini-Mental State Examination (MMSE)[12] for cognitive function, the Edmonton Classification System for Cancer Pain (ECS-CP)[37] for neuropathic pain, and the use of analgesic medications (non-opioid analgesics and opioids).

Symptom registration by patients

Average and worst pain intensity in the last 24 hours were assessed by self-report using an 11-point numeric rating scale (NRS) anchored with 0 (no pain) to 10 (worst imaginable pain) from the Brief Pain Inventory (BPI).[5, 48] Breakthrough pain was self-reported using the introductory question of the Alberta Breakthrough Pain Questionnaire.[14] Other symptom intensities were registered using the Edmonton Symptom Assessment System-Revised (ESAS-R), with patient-reported symptoms on a 0-10 numerical rating scale (NRS) with 0=no symptoms and 10=worst possible symptoms.[1] Further, self-reported sleep disturbances and constipation from the EORTC QLQ-C15-PAL, scored on a four-point categorical scale (not at all, a little, quite a bit, very much), were used.[13]

Statistical methods

The baseline characteristics of patients with bone metastases are presented with descriptive statistics. Multivariable linear regression was used to analyze factors potentially associated with pain intensity at baseline. Factors examined were chosen based upon previous literature and clinical experience: age, sex, performance status

(KPS), cognitive function (MMSE), cancer diagnoses (gastrointestinal cancer including colorectal, esophageal, gastric and pancreatic cancers, lung cancer, prostate cancer, kidney and urothelial cancer, and cancer of other origin), cancer treatment (chemotherapy, radiotherapy and hormone therapy), neuropathic pain, breakthrough pain, drowsiness, nausea, depression, anxiety, trouble sleeping and constipation.[23-25, 33, 41, 44] A generalized estimating equation (GEE) model with robust standard error and exchangeable covariance structure was applied to analyze longitudinal data on which factors were associated with higher pain intensity in patients with bone metastases at the next study visit in one month. The exchangeable covariance structure was chosen over unstructured and order 1 autoregressive covariance structure based on the expectancy of the data output, the quasi-likelihood independence model criterion (QIC)[40] and the distribution of residuals.[18] The choice of an optimal covariance structure can be challenging, but the GEE model is known to be robust to misspecification of the covariance structure.[51] We created a lagged variable for pain at the next visit and used the lagged variable as the dependent variable in the GEE model. Longitudinal assessments in which the interval between the two visits was outside the range of 4 weeks (+/- 6 days) were excluded from the analysis. A maximum of 6 repeated observations per person were entered into the model to ensure a balanced influence from each patient. Complete case (list wise deletion) and available case analyses (pairwise deletion) were performed respectively in cross sectional and longitudinal regression analyses to account for missing data. The variables “sleep disturbances” and “constipation” from the EORCT-C15 were converted to a 0-10 scale to correspond with items on the ESAS-R in all of the analyses (“not at all” 0, “a little” 3.333, “quite a bit” 6.666, “very much” 10). We did not standardize any of the parameters, and the coefficients are therefore smaller for

the continuous variables than for the categorical variables. All regression models were adjusted by country and use of analgesic medications, and regression diagnostics were performed for all analyses. Interactions between gender and primary disease were also examined. Analyses were performed with STATA version 14.2 (Stata Corporation LP; College Station, TX, USA).

Ethical considerations

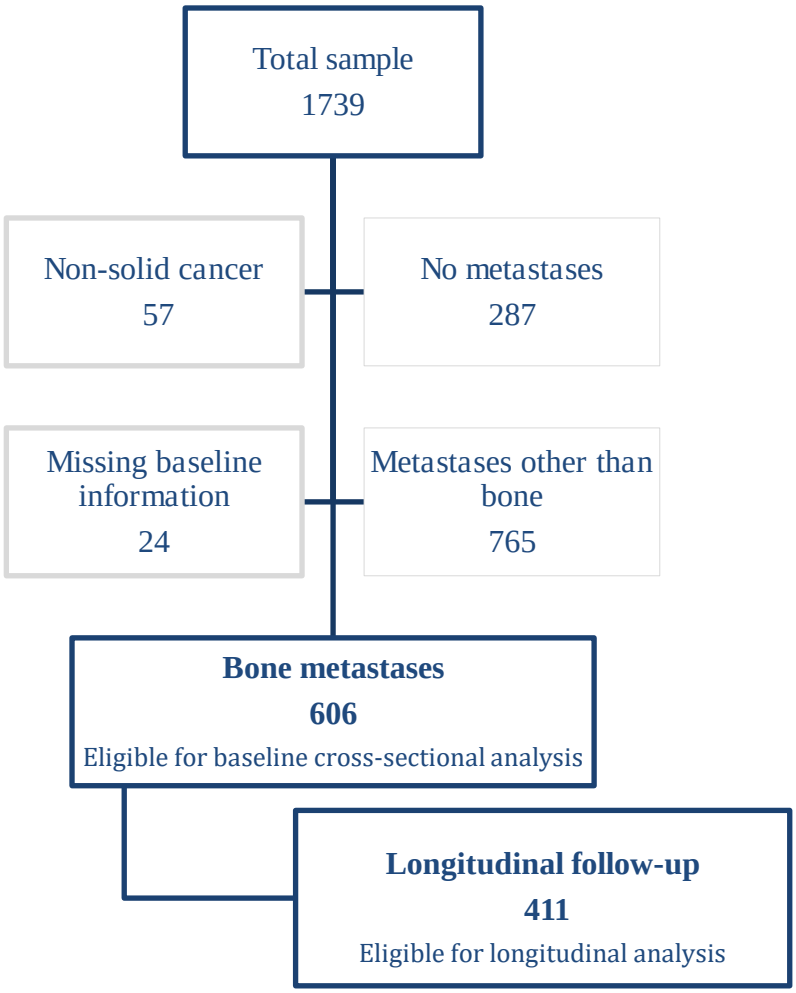
The study was registered in the clinicaltrials.gov database (NCT01362816). All patients provided written informed consent, and committees for medical research ethics in each country approved the study before initiation.

3. RESULTS

The total number of patients enrolled in the EPCCS study was 1739. We excluded patients with non-solid cancers, no metastases, and metastases at sites other than bone, as well as patients missing baseline information. A total of 606 patients with bone metastases were eligible in the baseline analyses.

411 patients were eligible in the longitudinal analyses as 146 patients had only one pain registration and 49 patients had a time interval between two subsequent visits outside the defined monthly interval (4 weeks +/- 6 days).

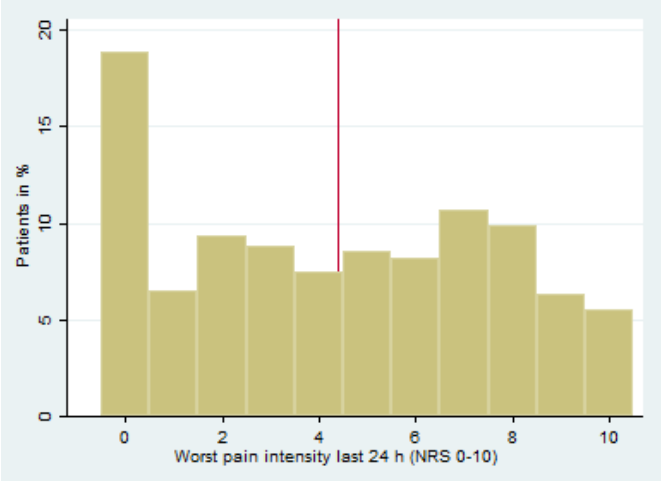
Figure 1. Sample size

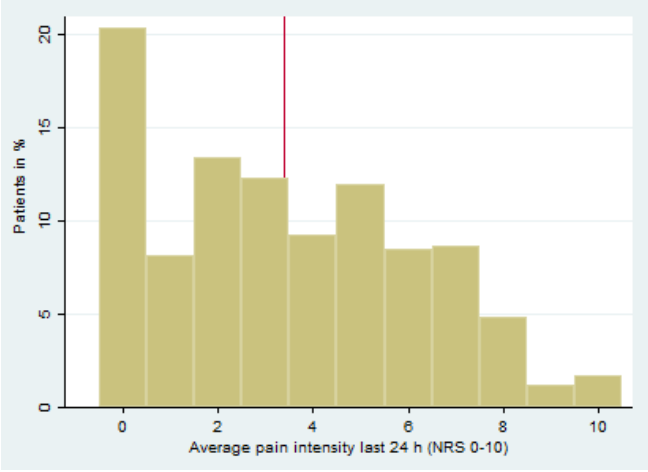


Descriptive analyses

Sample characteristics are presented in Table 1. The most common diagnoses were breast (34%), lung (22%) and prostate (18%) cancers. There was an even distribution between genders (53% female), and the mean age of the sample was 64 years (standard deviation (SD) 12.4). The average pain score in the last 24 hours at baseline was 3.4 (SD 2.7), and the worst pain in the last 24 hours was 4.4 (SD 3.2) (Table 1). The distribution of pain scores (NRS 0-10) at baseline is illustrated in Figure 2. Neuropathic pain was present in 24% of the patients, and 40% of the patients had breakthrough pain episodes. Sixty-eight percent of the patients were using opioid analgesics, and 49% were using non-opioid analgesics (Table 1).

Figure 2. Distribution of pain scores (NRS 0-10) at baseline





The vertical line represents mean pain scores.

Table 1. Patient characteristics at inclusion (N=606)

Characteristics	**Number** (%)	**Mean** (SD)	**Missing** [1]
Female sex	318 (52.5)		0
Age		64.3 (12.4)	0
Karnofsky Performance status		66.6 (15.9)	0
Abbreviated MMSE [2]		6.9 (1.7)	10
Cancer Diagnosis			3
Gastrointestinal	60 (10.0)		
Lung	133 (22.1)		
Breast	207 (34.3)		
Prostate	107 (17.7)		
Kidney and urothelial	26 (4.3)		
Other origin	70(11.6)		
Oncological treatment			
Chemotherapy	244 (40.3)		0
Radiotherapy	53 (8.8)		0
Hormone therapy	145 (23.9)		0
Analgesic Treatment			
Opioid analgesics	410 (68.3)		6
Non-opioid analgesics	293 (48.9)		7
Pain Characteristics			
Average pain in last 24 hours		3.4 (2.7)	2
Worst pain in last 24 h hours		4.4 (3.2)	6
Neuropathic pain [3]	143 (24.4)		19
Breakthrough pain [4]	238 (40.0)		11
Other Symptoms			
Drowsiness [5]		3.3 (2.9)	11
Nausea [5]		1.0 (2.0)	6
Feel depressed [5]		2.5 (2.8)	5
Anxiety [5]		2.4 (2.7)	5
Sleep disturbances [6]		3.2 (3.2)	4
Constipated [6]		2.8 (3.2)	7

(1) Number of patients with missing observations

(2) Abbreviated MMSE (maximum score 8) [12]

(3) Neuropathic pain from Edmonton Classifications System for Cancer Pain[38]

(4) Patient-reported flare-ups of breakthrough pain in the last 24 hours

(5) Edmonton Symptom Assessment System-Revised (ESAS-r)[1]

(6) EORTC QLQ-C15-PAL[13]

Factors associated with pain intensity in patients with bone metastases at baseline

Twenty variables with potential associations with CIBP were entered into one multivariable model for average pain and one multivariate model for the worst pain, and both models were adjusted for country and the use of analgesic medications (Table 2). Complete case analysis included respectively 541 (89%) and 538 (89%) patients at baseline for the average and worst pain models. Breakthrough pain, neuropathic pain and male gender were significantly associated with higher pain intensity in both the average and the worst pain model. Breakthrough pain had the strongest association with the worst pain intensity, with an increase of 2.49 (95% CI 2.00-2.97) if present. The presence of neuropathic pain influenced pain intensity in the both models (increase average pain 0.89 (95% CI 0.43-1.35), worst pain 0.82 (95% CI 0.29-1.36)). Age, drowsiness, nausea, anxiety and trouble sleeping were associated with a higher average pain intensity score but not worst pain at baseline. The explained variance (adjusted R^2) was 0.36 for the average pain model and 0.41 for the worst pain model (Table 2).

Table 2. Multivariate analysis of the associations with pain intensity by inclusion

	Average pain in last 24 h (n=541)				Worst pain in last 24 h (n=538)			
Independent	**Coef**	**95% CI**		**p**	**Coef**	**95% CI**		**p**
Constant	-0.18	-2.35	2.00	0.872	-0.48	-3.02	2.06	0.710
Age	0.02	0.00	0.04	**0.036**	0.02	-0.01	0.03	0.141
Sex (female gender)	-0.72	-1.29	-0.16	**0.012**	-0.90	-1.55	-0.25	**0.007**
KPS	0.01	-0.01	0.02	0.257	0.01	-0.01	0.02	0.456
MMS [1]	-0.03	-0.15	0.09	0.665	0.10	-0.04	0.24	0.154
Cancer diagnosis: [2]								
Gastrointestinal	0.24	-0.54	1.01	0.548	-0.10	-1.00	0.80	0.821
Lung	-0.39	-1.03	0.25	0.231	-0.40	-1.15	0.35	0.278
Prostate	-0.78	-1.57	0.01	0.053	-0.70	-1.61	0.23	0.139
Kidney and urothelial	-0.25	-1.39	0.88	0.659	-0.29	-1.61	1.03	0.663
Other origin	0.19	-0.52	0.91	0.596	0.13	-0.71	0.96	0.768
Oncological treatment:								
Chemotherapy	0.15	-0.32	0.61	0.531	-0.14	-0.68	0.40	0.616
Radiotherapy	-0.11	-0.79	0.56	0.738	0.21	-0.58	0.99	0.607
Hormone treatment	-0.23	-0.80	0.34	0.424	-0.36	-1.02	0.31	0.294
Pain characteristics:								
Neuropathic pain [3]	0.89	0.43	1.35	**<0.001**	0.82	0.29	1.36	**0.003**
Breakthrough pain [4]	1.45	1.03	1.87	**<0.001**	2.49	2.00	2.97	**<0.001**
Other symptoms:								
Drowsiness [5]	0.08	0.01	0.16	**0.033**	0.08	-0.01	0.17	0.066
Nausea [5]	0.14	0.04	0.24	**0.008**	0.10	-0.02	0.22	0.109
Depression [5]	0.03	-0.07	0.13	0.569	0.08	-0.04	0.20	0.183
Anxiety [5]	0.14	0.03	0.24	**0.013**	0.11	-0.01	0.24	0.080
Trouble sleeping [6]	0.09	0.03	0.16	**0.004**	0.07	-0.00	0.14	0.061
Constipation [6]	0.05	-0.01	0.12	0.091	0,05	-0.02	0.13	0.150
Adjusted R-square				**0.362**				**0.413**

Analyses were adjusted for country and analgesic medications

(1) Abbreviated MMSE (maximum score 8) [12]
(2) Reference category breast cancer
(3) Neuropathic pain from Edmonton Classification System for Cancer Pain[38]
(4) Patient reported flare-ups of breakthrough pain last 24 h
(5) Edmonton Symptom Assessment System-Revised (ESAS-R)[1]
(6) EORTC QLQ-C15-PAL[13]

Current factors associated with pain intensity in one month

The same variables included in the cross-sectional analyses were applied in the longitudinal analyses, with the lagged variable for "pain the next visit" as the dependent variable. Only visits with a monthly interval were included. Separate models were estimated for average and worst lagged pain intensity (table 3). Available case analysis included 396 (96%) and 392 (95%) patients for the average and worst pain models, respectively. Current pain intensity, drowsiness, trouble sleeping, and male gender were associated with more average and worst pain after one month. Each factor was associated with minor changes in pain intensity. Current pain had the strongest association to pain in one month, with a one-point increase in current pain intensity associated with a 0.41 (95% CI 0.34-0.48) increase in average pain intensity and a 0.34 (95% CI 0.26-0.42) increase in the worst pain intensity at the next visit. For the other symptoms, a one-point increase in sleep disturbances was associated with a 0.06 (95% CI 0.02-0.11) increase in average pain intensity and a 0.08 (95% CI 0.02-0.14) increase in worst pain intensity, while a one-point increase in drowsiness was associated with a 0.09 (95% CI 0.03-0.15) increase in average pain intensity and a 0.07 (95% CI 0.01-0.14) increase in worst pain intensity at the next visit. Breakthrough pain at the initial time point was only significantly associated with higher worst pain intensity at the next visit, with a 0.59 (95% CI 0.20-0.99) increase in worst pain intensity. Patients with prostate cancer had a lower risk of future pain (Table 3).

Table 3. Longitudinal analysis on factors associated with pain intensity at the next study visit in 2-6 weeks

	Average pain in last 24 h (n=396)				Worst pain in last 24 h (n=392)			
Independent	Coef	95% CI		p	Coef	95% CI		p
Constant	0.99	-0.64	2.62	0.235	0.32	-1.41	2.05	0.716
Age	0.00	-0.01	0.01	0.666	0.01	-0.00	0.02	0.130
Sex (female gender)	-0.46	-0.91	-0.01	**0.045**	-0.91	-1.45	-0.36	**0.001**
KPS	0.00	-0.01	0.01	0.690	0.00	-0.01	0.01	0.958
MMS (1)	-0.00	-0.08	0.08	0.992	0.04	-0.07	0.15	0.443
Cancer diagnosis: (2)								
Gastrointestinal	0.12	-0.46	0.57	0.710	0.14	-0.63	0.91	0.716
Lung	0.04	-0.43	0.52	0.861	-0.24	-0.82	0.34	0.419
Prostate	-0.66	-1.23	-0.09	**0.023**	-1.21	-1.92	-0.50	**0.001**
Kidney and urothelial	-0.54	-1.38	0.30	0.208	-0.90	-1.87	0.08	0.073
Other origin	0.05	-0.46	0.57	0.992	-0.05	-0.70	0.60	0.876
Oncological treatment:								
Chemotherapy	0.31	-0.02	0.64	0.069	0.35	-0.05	0.75	0.085
Radiotherapy	-0.17	-0.75	0.40	0.556	0.06	-0.52	0.65	0.830
Hormone treatment	0.25	-0.12	0.63	0.186	-0.04	-0.48	0.40	0.870
Pain characteristics:								
Current pain intensity	0.41	0.34	0.48	**<0.001**	0.34	0.26	0.42	**<0.001**
Neuropathic pain (3)	-0.05	-0.35	0.25	0.743	0.16	-0.22	0.55	0.410
Breakthrough pain (4)	0.19	-0.11	0.49	0.209	0.59	0.20	0.99	**0.003**
Other symptoms								
Drowsiness (5)	0.09	0.03	0.15	**0.003**	0.07	0.01	0.14	**0.033**
Nausea (5)	0.06	-0.01	0.14	0.103	0.02	-0.06	0.11	0.604
Depression (5)	-0.01	-0.09	0.06	0.747	0.05	-0.04	0.14	0.249
Anxiety (5)	0.02	-0.06	0.11	0.589	0.03	-0.05	0.12	0.427
Trouble sleeping (6)	0.06	0.02	0.11	**0.010**	0.08	0.02	0.14	**0.006**
Constipation (6)	0.03	-0.02	0.07	0.277	0.02	-0.04	0.07	0.587

Analyses were adjusted for country and analgesic medications

(1) Abbreviated MMSE (maximum score 8) [12]
(2) Reference category breast cancer
(3) Neuropathic pain form Edmonton Classification System for Cancer Pain[38]
(4) Patient reported flare-ups of breakthrough pain last 24 h
(5) Edmonton Symptom Assessment System-Revised (ESAS-R)[1]
(6) EORTC QLQ-C15-PAL[13]

Discussion

This study showed that high pain intensity, sleep disturbances, drowsiness and male gender at the initial time point were associated with higher average and worst pain intensity at the next study visit scheduled in one month in patients with bone metastases. Breakthrough pain were also associated with higher worst pain intensity in one month. The same factors were associated with pain intensity in the cross-sectional analyses. Although each factor in these analyses contributed to minor changes in pain intensity, they may prompt clinicians to recognize a risk for imminent lack of pain control to identify patients for closer follow-up or to consider the use of specific pain treatment modalities such as radiotherapy.

A noticeable finding in the longitudinal analyses was that patients with higher pain intensity at one time point were more prone to higher pain intensity at the next visit. This association can be partly due to correlation between repeated measurements. However, the results are also supported by previous studies showing that high pain intensity itself is associated with a complex pain situation and more difficulties obtaining adequate analgesic treatment response.[11] These results are similar to results from a longitudinal study by Knudsen et al[23] in a general cancer population, reporting that initial pain intensity was the most important factor for pain at the next consultation. Clinicians must be aware that patients who report higher pain intensity are in need of special attention, as they are also more likely to present with higher pain at the next study visit, regardless of the use of analgesic medication.

Similar to our study, several previous studies have demonstrated significant associations between sleep disturbances and cancer pain.[9, 23, 31, 50] Pain can induce a lack of sleep, but sleep disturbances themselves may also influence the patient's pain perception. In this

study, we have further demonstrated in a longitudinal multivariate model that sleep disturbances were associated with pain in the following weeks. The present study is not designed to evaluate causality, but the longitudinal relationship between sleep disturbances and pain intensity strengthens the hypothesis that sleep disturbances also may increase pain perception.

Drowsiness is a known adverse effect of opioid treatment.[33] In the longitudinal analyses, we found that drowsiness was associated with both higher average and worst pain at the next visit. Adverse effects may hinder adequate titration of analgesic therapy with opioids and can explain this relationship. Similar to the other symptoms associated with cancer pain, the regression coefficients were low.

The high incidence of breakthrough pain has been used to explain some of the treatment challenges of CIBP.[25, 32, 44] The breakthrough pain incidence was 40% in this group of patients and was strongly associated with pain intensity in the cross-sectional analysis. The worst pain intensity increased by 2.49 points in patients who reported breakthrough pain, which is consistent with findings from previous studies on cancer pain in general and CIBP.[16, 23, 25] In this study, we have further demonstrated that patients with current breakthrough pain have higher worst pain intensity at the next visit in one month. In the longitudinal model, the worst pain intensity increased by 0.59 if breakthrough pain was present at the previous time point. Knudsen et al[23] reported a significant association between the presence of breakthrough pain and higher average pain score after two weeks in a general cancer population, but they detected no significant association with the worst pain intensity. Thus, these findings emphasize the difficulties in treating breakthrough pain episodes.

Bone metastases can involve and damage nervous tissue directly due to tumor invasion but also by activating molecular mechanisms sensitizing primary efferent neurons.[27, 29] The pathophysiological processes of CIBP may result in neuropathic pain, and previous studies report the incidence of neuropathic pain among CIBP patients to be approximately 17-25%.[21, 26, 36] This is consistent in our study, with 24% of patients having neuropathic pain at baseline.[37] As in studies on general cancer pain, we found a clear association between the presence of neuropathic pain and pain intensity in patients with bone metastases in the cross-sectional analyses.[16, 39] However, in the longitudinal analyses, the presence of neuropathic pain were not associated with a future increase in pain.

In this cohort of patients with bone metastases, female patients reported lower pain intensity than men in the cross-sectional analyses, and male gender increased the risk of pain in the next visit scheduled in one month. Few studies have investigated differences in cancer pain between genders, and most studies report no gender differences in pain intensity.[34] To rule out a potentially different gender effect by cancer diagnosis, we tested the interactions between these two factors in all models, but none were statistically significant.

Several associations reported in other studies were not observed in this study. The assessment of psychological distress, including anxiety and depression, is included in the ECS-CP.[38] In this study, anxiety was only associated with average pain intensity at baseline, and there was no association between pain and anxiety or depression in the longitudinal model. In agreement with the longitudinal analysis on a general cancer population by Knudsen et al[23], current pain intensity and breakthrough pain were

associated with pain intensity at the next visit, but the other significant variables differed. Age and lung cancer were not associated with higher pain intensity in our model, while sleep disturbances, drowsiness and male gender were not associated with higher pain intensity at the next visit in a general cancer population. These differences may suggest that prediction models have to be developed and validated for specific cohorts of cancer pain patients.

The potential benefit from establishing characteristics for patients with a lack of pain control is that the clinicians can be alerted to give these patients special attention. This attention may include closer follow-up or consider bone-targeting interventions, such as radiotherapy, to prevent future increases in pain. Such factors may also be included in computer-based decision support systems,[17] prompting the clinicians to address pain treatment.

Strength and Limitations

Longitudinal analyses with repeated measures, as performed in the present study, increase the analytical strength of observations because the individual changes in pain and associated symptoms can be investigated. We chose to include the subgroup of patients with bone metastases only. This decision was made not only because CIBP can be classified as a unique entity of cancer pain based on pathophysiological features but also because this group of patients can receive treatment directly targeted to the bone metastases. The sample size, for a longitudinal study on palliative cancer patients, is large, and the number of missing variables is limited both in the cross-sectional and longitudinal analyses. We believe that results from this study will contribute useful information to clinicians treating patients with bone metastases with regard to a) the symptoms and patient

characteristics associated with higher pain intensity, and b) potential factors to identify patients that will develop a complex pain situation that is difficult to treat with conventional analgesics. As far as we know, this is the first study specifically addressing factors associated with higher pain intensity at the next consultation in patients with bone metastases.

We recognize that this study has some limitations. First, we included all patients with bone metastases, including those with no pain. This strategy may result in an overestimation of the correlation between pain intensity and breakthrough pain and neuropathic pain, which obviously are only present in patients with pain. However, this study analyzed patients with bone metastases in the risk for future pain, which also may arise in patients with no initial pain. Separate analyses were performed on patients with pain only and revealed the same significant associations among neuropathic pain, breakthrough pain and pain intensity (data not shown). Second, patients with pain in the included cohort are defined as patients with CIBP, although pain due to other reasons than bone metastases can occur. Third, the selection of independent variables was limited by available variables from the original study. The use of opioids and non-opioid medications was recorded, but dosages were not registered, nor was the use of bone-targeting agents such as bisphosphonates. Potentially important variables including information about site and distribution of bone metastases, pathological fractures or soft tissue expansion outside bone were not available.
Fourth, the study did not include all eligible patients consecutively, thus introducing a risk for selection bias. Finally, patients were included in the study at different time points in their disease trajectory. On the other hand, this reflects the clinical reality. There is no standardized “starting point” for pain development; thus, this has been and will remain a challenge in cancer pain studies.

In conclusion, this paper identifies higher current pain intensity, sleep disturbances, drowsiness, male gender and breakthrough pain to be associated with future pain in patients with bone metastases. These factors should be assessed in clinical practice and may aid clinicians to identify patients with bone metastases that can benefit from closer follow-up or preventive interventions for optimal pain control. For each of the significant variables the explained variance is low, and further research including a more detailed specter of independent variables is needed to develop predictive models for future pain in patients with bone metastases.

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