Characteristics and associations of pain intensity in patients referred to a specialist cancer pain clinic

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BACKGROUND: Uncontrolled cancer pain (CP) may impair quality of life. Given the multidimensional nature of CP, its poor control is often attributed to poor assessment and classification.

OBJECTIVES: To determine the characteristics and associations of pain intensity in a specialist CP clinic.

METHODS: Consecutive patients referred to the CP clinic of the Portuguese Cancer Institute (Lisbon, Portugal) had standardized initial assessments and status documentation of the following: Brief Pain Inventory ratings for ‘pain now’ as the outcome variable; initial pain intensity (iPI) on a 0 to 10 scale; pain mechanism (using the Douleur Neuropathique 4 tool to assess neuropathic pain); episodic pain; Eastern Cooperative Oncology Group rating; oral morphine equivalent daily dose (MEDD); Hospital Anxiety Depression Scale and Emotional Thermometer scores; and cancer diagnosis, metastases, treatment and pain duration. Univariable analyses were conducted to test the association of independent variables with iPI. Variables with P<0.1 were entered into a multivariable regression model, using backward elimination and a cut-off of P=0.2 for final model selection.

RESULTS: Of 371 participants, 285 (77%) had moderate (4 to 6) or severe (7 to 10) iPI. The initial median MEDD was relatively low (30 mg [range 20 mg to 60 mg]). In the multivariable model, higher income, Eastern Cooperative Oncology Group rating 3 to 4, cancer diagnosis (head and neck, genitourinary and gastrointestinal), adjuvant use and initial MEDD were associated with iPI (P<0.05). The model’s R² was 18.6, which explained only 19% of iPI variance.

CONCLUSIONS: The diversity of factors associated with pain intensity and their limited explanation of its variance underscore the biopsychosocial complexity of CP. Adequacy of CP management warrants further exploration.

Key Words: Assessment; Cancer pain; Opioids; Pain characteristics; Pain intensity; Pain mechanisms

Les caractéristiques et les associations de l’intensité de la douleur chez les patients dirigés vers une clinique spécialisée en douleurs cancéreuses

HISTORIQUE: La douleur cancéreuse (DC) non contrôlée peut nuire à la qualité de vie. Étant donné la nature multidimensionnelle de la DC, son piètre contrôle est souvent attribué à une évaluation et une classification médiocres.

OBJECTIFS: Déterminer les caractéristiques et les associations de l’intensité de la douleur dans une clinique spécialisée en DC.

MÉTHODOLOGIE: Des patients consécutifs dirigés vers la clinique de la DC de l’institut portugais du cancer (à Lisbonne, au Portugal) disposaient d’évaluations initiales normalisées et de notes sur leur état sous les formes suivantes: évaluations du bref inventaire de la douleur pour la « douleur maintenant » comme variable de résultat clinique, intensité de la douleur initiale (IDi) sur une échelle de 0 à 10, mécanisme de la douleur (au moyen de l’outil de douleur neuropathique 4), douleur épisodique, classement du groupe d’oncologie coopératif de l’Est, dose quotidienne équivalente de la morphine (DQÉM) par voie orale, échelle d’anxiété et scores de dépression en milieu hospitalier, thermomètre émotionnel et diagnostic de cancer, de même que les métastases, le traitement et la durée de la douleur. Les chercheurs ont réalisé des analyses univariantes pour comparer l’association des variables indépendantes avec l’IDi. Les variables au P<0.01 étaient saisies dans un modèle de régression multivariée, au moyen de l’élimination régressive et d’un seuil de P=0.2 pour la sélection du modèle final.

RÉSULTATS: Des 371 participants, 285 (77 %) présentaient une IDi modérée (4 à 6) à marquée (7 à 10). La DQÉM initiale médiane était relativement faible (30 mg [plage de 20 mg à 60 mg]). Dans le modèle multivariée, un revenu plus élevé, un classement de 3 à 4 du groupe d’oncologie coopératif de l’Est, le diagnostic de cancer (tête et cou, système génito-urinaire ou gastro-intestinal), le recours à des adjuvants et la DQÉM initiale s’associaient à l’IDi (P<0.05). Le R² du modèle était de 18.6, ce qui n’expliquait que 19 % de l’écart d’IDi.

CONCLUSIONS: La diversité des facteurs associés à l’intensité de la douleur et l’explication limitée des écarts font ressortir la complexité biopsychosociale de la DC. D’autres explorations s’imposent sur la pertinence de la prise en charge de la DC.

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that CP is, overall, inadequately treated. Although opioids are the
mainstay of CP management according to guidelines from the WHO
(12), the European Society for Medical Oncology (13) and the
European Association for Palliative Care (14), they are underused,
especially in elderly patients (15,16). Underuse is due to a mix of
patient, physician, and health system and cultural factors (9,17,18),
including ‘morphinophobia’, as determined in a regional Portuguese
study (19).

One of the most consistent reasons identified for poor CP manage-
ment is inadequate assessment and classification of pain (9,20,21). CP
is multidimensional in nature, varying in physical, psychosocial and
spiritual components. The patient’s expression of pain, reported as
pain intensity, is therefore complex (22). Younger age, neuropathic
features, incident pain, psychological distress and addiction history
have each been identified as predictors of longer time to achieve stable
analgesia (23,24). Pain intensity has been identified in some but not
all studies as a predictor of the time required to achieve stable pain
control (22,23,25).

Given projected global demographic changes (26), and the associ-
ated increase in the number of patients with cancer (27), there is a
compelling need to better understand the nature of CP and inform
evidence-based strategies for its assessment, classification and manage-
ment. The present study aimed to describe the characteristics of CP
and determine the correlates and predictors of initial pain intensity
(iPI) when patients were referred to a CP clinic in Portugal.

METHODS

Setting and design
The present study was conducted from June 1, 2009 to April 30, 2010
in the specialist CP clinic of the Portuguese Cancer Institute, a
national tertiary-level cancer centre in Lisbon, Portugal. The study
was cross-sectional in design, reflecting assessments that were con-
ducted at subjects’ first consultation in the CP clinic.

Study population and eligibility criteria
Consecutive new patient referrals to an outpatient CP clinic were
approached for consent to participate in both an initial cross-sectional
and a related longitudinal study of CP characteristics and manage-
ment. The following eligibility criteria were applied: adult patients (>18 years
of age) were included if they had a cancer diagnosis, provided informed
consent to study participation, and had the cognitive capacity to rate
their current pain on a numerical rating scale (0 meaning no pain,
10 meaning the worst pain imaginable); patients were excluded if they
had no evidence of active cancer or had non-cancer-related pain. CP
was defined as pain directly related to malignant involvement or pain
related to anticancer treatment, such as chemotherapy, radiotherapy or
surgery. Ethics approval for the present study was obtained from the
Research Ethics Board of the Portuguese Cancer Institute. The assem-
bling of an electronic study dataset with numerical identifiers was
approved by the Portuguese Data Protection Authority.

Assessment data and tools
Patients underwent standardized assessments and documentation of
clinical data. Translated Portuguese versions of standard tools that
were previously validated in English and also, in most cases, in
Portuguese, were used. For ease of reporting, the Portuguese socio-
economic groupings of 1, 2 and 3; 4, 5 and 6; 7 and 8; and 9 were
transformed in a similar descending order to groups 1, 2, 3 and 4,
respectively (28). Regarding education, primary referred to zero to four
years of education; secondary referred to five to 12 years; and tertiary
referred to university or >12 years. A history of chronic depression
referred to depression preceding the cancer diagnosis and requiring
ongoing antidepressant medication. In addition to a global clinical rat-
ing of functional dependency level (independent, partial or fully
dependent), functional status (0 to 4; 0, fully active and able to carry
on all predisease performance without restriction; 4, indicating that
the patient is unable to provide self-care and confined to bed or chair)
was rated using the Eastern Cooperative Oncology Group (ECOG)

scale (29). Scores of ≥2 on the CAGE alcohol questionnaire (30,31),
≥4 on a Portuguese-translated version (unpublished) of the original
Short Portable Mental Status Questionnaire (32), ≥7 on the anxiety
and depression subscales of the Hospital Anxiety and Depression Scale
(HADS) (33) and ≥4 on the Emotion Thermometer (ET) tool (34,35)
were used to screen for a history of alcohol abuse, cognitive impair-
ment, anxiety, depression, and emotional distress, respectively.

Documentation of palliative status (in relation to the goals of treat-
ment) was recorded when present. Cancer disease-modifying treatments
(cytotoxic chemotherapy, radiotherapy or surgery) ≤30 days before first
CP clinic consultation were recorded. Pain data included the Brief Pain
Inventory (BPI) pain intensity ratings (worst and average in the past
seven days) (36,37) ‘pain now,’ as the primary outcome variable,
labelled as iPI, on a 0 to 10 scale; and pain duration. CP pain mechan-
ism was classified according to both standard clinical assessment and a
DNA4 score of ≥4 to designate a neuropathic CP component (37,38);
other categories were visceral, bone and mixed. Episodic pain, defined as
a transitory exacerbation of pain that occurs in addition to otherwise
stable persistent pain (39), was recorded and subdivided into episodic
incident pain when a trigger or incident activity was identifiable and
episodic breakthrough pain when no trigger was identified. The oral
morphine equivalent daily dose (MEDD) was calculated according to
standard recommendations (40), and recorded along with the number of
current adjuvant (pharmacological) analgesic treatments (grouped as
none, and one or more).

Data analyses
SAS statistical software version 9.1 (SAS Institute Inc, USA) was
used for data analysis. Means are expressed with SDs, and medians are
expressed with the first to third quartile range (Q1 to Q3) unless
otherwise stated. The initial MEDD was highly skewed and underwent
logarithmic transformation for further analysis. With iPI as outcome,
univariable analyses were conducted using the t test, one-way
ANOVA and Pearson correlation (r), as appropriate for independent
categorical and continuous variables, respectively. Variables with
P<0.1 were entered into a multivariable regression model, using back-
ward elimination and a cut-point of P=0.2 for final model selection.
The coefficient of determination (R²) for the model was calculated
and adjusted. Statistical significance was set at P<0.05 for analyses.

RESULTS

Of 459 individual patient referrals to the CP clinic, 88 were excluded
because of non-cancer-related pain (n=69), nonactive cancer (n=16)
or failure to consent (n=3). Demographic, psychosocial and functional

status data and corresponding iPI ratings are summarized in Table 1. In
the final study sample (n=371), the mean age was 62.1±14.3 years;
199 (54%) were female. A mild cognitive deficit was detected in
46 (12.4%) of patients. Approximately one-half of the study sample
were classed as partially or fully dependent, and 62 (16.7%) had
ECOG scores of 3 or 4.

Cancer disease and pain characteristics with corresponding iPI rat-
ings are summarized in Table 2. Of 371 patients, 263 (71%) had meta-
static disease, and 176 (47%) had their treatment goal documented as
palliative. The majority of cancers were solid tumours and 18 (4.8%)
hematological malignancies accounted for the remainder. Lung cancer
accounted for 10 (2.7%) of the cancer diagnoses.

Most pain syndromes (246 [66%]) were mixed neuropathic and
nociceptive. Using pain intensity scores derived from the BPI, the
mean iPI (pain now), pain worst and pain average were mean (± SD)
 scores of 5.4±2.6, 7.4±2.6 and 4.9±1.9, respectively, and all were
highly correlated (r=0.8, P<0.0001). Categorizing iPI scores into con-
tentional verbal pain intensity ratings, 86 (23.2%), 152 (41%) and
133 (35.8%) of patients had mild (0 to 3), moderate (4 to 6) and
severe (7 to 10) pain, respectively. The median (Q1 to Q3) pain dur-
ation was three (two to six) months. The initial median MEDD was
30 mg (20 mg to 60 mg). Forty-two patients had a mean iPI of
2.55±2.33 and were not receiving any opioid.

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In the univariable analyses testing the association of iPI with categorical variables (Tables 1 and 2), a positive association was found in relation to higher income and upper socioeconomic groups (groups 1, 2 and 3); a history of drug or alcohol abuse; greater functional dependency; ‘palliative’ status designation; primary cancer diagnosis (the highest iPI groups were those with head and neck, gastrointestinal, and genitourinary cancer); recent radiotherapy treatment; the presence of neuropathic CP or mixed pain; presence of metastases; and use of ≥1 adjuvant analgesic medication (P<0.05).

In the univariable analyses testing the association of iPI with continuous variables (Table 3), the only significant association occurred in relation to the initial MEDD (P<0.05), which was positive in direction. The HADS depression and anxiety subscale scores were >10 in
239 (64.4%) and 215 (57.9%) of patients, respectively, indicating abnormal levels of depression and anxiety. The ET scores were 24 for distress, anxiety, depression, anger and help desired in 208 (56%), 271 (73%), 280 (75.5%), 216 (58.2%) and 209 (56.3%), respectively.

In the multivariable model (Table 4), nine variables were retained and five were positively associated with iPI: higher income, ECOG ratings 3 to 4, cancer type (head and neck, genitourinary and gastrointestinal); adjuvant use and initial MEDD (P<0.05). The adjusted R² for this model was 18.6; thus, the model explained <20% of the variance in iPI.

### DISCUSSION

Using iPI ratings recorded as ‘pain now’ at the first CP clinic consultation, our study showed a high correlation between this measure and those of ‘pain worst’ and ‘pain average’ over the preceding seven days, suggesting that ‘pain now’ has validity as a measure of patients’ overall experience of pain intensity in the week preceding their initial CP clinic consultation. Our study sample was comparatively unique in that it included patients with earlier stage cancer, in addition to 47% whose treatment goals were documented as palliative. However, we have no data to verify the consistency and accuracy of this latter designation, other than indirectly inferred evidence, given that 71% had metastatic disease. Compared with other studies of pain in predominantly inpatient palliative care or hospice based populations (7,24,37), our outpatient sample had a relatively high performance status; only 16.7% had ECOG scores of 3 or 4. Furthermore, because longitudinal studies of pain intensity may generate more robust data regarding its predictors, correlates and variability (15,38), this needs to be acknowledged when comparing our study findings with those of longitudinal studies (23,25).

There is substantial evidence of suboptimal CP management by medical oncologists in the United States (9). The situation in Portugal is probably no different: although 77% of our study sample had pain of either moderate or severe intensity, based on their iPI ratings, the initial median (Q1 to Q3) MEDD of our sample was 30 mg (20 mg to 60 mg), which is very low compared with other studies (41,42), and suggestive of opioid underuse. It supports the finding of a population-based survey of patients with chronic pain in Portugal, in which the reported prevalence rate of opioid use in those with chronic CP was 10.13% (43). This warrants further standardized evaluation using a tool such as the Pain Management Index (44).

Despite literature data supporting the association of psychosocial distress with pain intensity levels (23,24,41), and despite our sample’s HADS and ET scores reflecting a very high level of such distress, we surprisingly found no dimensional correlation between these and iPI. Recognizing that all of the patients in our sample had some level of CP, it is possible that an association between CP and psychological distress might be more readily detected on a categorical rather than a dimensional severity basis, if we had conducted a broader population study to determine psychological distress in relation to the categorical presence or absence of CP. Regarding assessment tools, we used versions of the BPI and HADS that were validated in Portuguese, as spoken in Portugal (33,37). We used versions of the CAGE and ET that were validated in Brazilian Portuguese (31,35) and, thus, we cannot exclude the possible contribution of interpretive error to the lack of correlation between ET scores and iPI. Other researchers have demonstrated the association between CP and psychological distress (23,24,41), and although there is some commonality in the biological pathways that subserve depression and pain (45), studies have not been designed to determine a causal relationship in either direction (46). An association between CP intensity and a history of drug or alcohol abuse has been demonstrated in some studies (23,24).

Although a drug or alcohol abuse history had a statistically significant association with iPI in our univariable analysis, an independent association was not evident in the multivariable analysis. Other studies have demonstrated an association between pain intensity and episodic incident pain (22,23,42); however, our study failed to demonstrate this. Although our cross-sectional study found that psychosocial distress, a history of drug or alcohol abuse, and episodic pain were not independently associated with initial pain intensity, a longitudinal analysis may be more sensitive in detecting such associations.

In our final multivariable model, the primary cancer diagnoses of head and neck, genitourinary and gastrointestinal were independent predictors of higher iPI. The relatively high prevalence (29.2%) of neuropathic pain in the head and neck group may explain their higher iPI. Among the demographic variables, both higher income and poorer performance status were independently associated with iPI. We can only surmise that those on lower incomes may be less well able to verbalise their iPI. Our finding that iPI was associated with poorer performance status is consistent with literature data (47). Unlike other studies (23,24), age was not associated with iPI in our current study. Adjuvant use was independently associated with iPI, possibly reflecting an evidence-based approach to neuropathic pain management. The strongest independent association with iPI occurred in relation to opioid dose at the point of referral, reflecting an approach that is generally consistent with current guidelines, albeit possibly inadequate in terms of actual opioid dosing.

Our study has some unique features: its knowledge synthesis contributed is significant, given the limited literature data regarding CP in a Portuguese setting; its approach involved a comprehensive combination of standardized assessments with validated tools. Our study also has significant limitations. First, the presence of a referral bias is very likely with a CP clinic, as reflected by 77% of patients having moderate or severe pain. The number of patients with lung cancer was

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**TABLE 3**

| Variable                              | Correlation (r) | P     |
|---------------------------------------|-----------------|-------|
| HADS anxiety score                    | 0.04            | 0.4   |
| HADS depression score                 | 0.06            | 0.3   |
| Emotional thermometer scores          |                 |       |
| Distress                              | 0.00            | 0.9   |
| Anxiety                               | 0.06            | 0.3   |
| Depression                            | 0.04            | 0.5   |
| Anger                                 | -0.00           | 0.9   |
| Help desired                          | 0.08            | 0.1   |
| Duration of pain, months              | 0.04            | 0.4   |
| Initial morphine equivalent daily dose* | 0.32            | <0.0001 |

*Log value. HADS Hospital Anxiety and Depression Scale

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**TABLE 4**

| Parameter                              | Estimate | Pr > t │
|----------------------------------------|----------|--------|
| Intercept                              | 1.775    | 0.0009 |
| Income >€485/month                     | 0.596    | 0.02   |
| Socioeconomic groups 1,2,3             | 0.483    | 0.10   |
| Eastern Cooperative Oncology Group: 3,4 | 0.782    | 0.03   |
| Palliative status documented: Yes      | 0.47     | 0.10   |
| Cancer diagnosis: head and neck        | 0.867    | 0.03   |
| Cancer diagnosis: lung                 | -0.087   | 0.92   |
| Cancer diagnosis: gastrointestinal      | 1.054    | 0.01   |
| Cancer diagnosis: breast               | 0.448    | 0.36   |
| Cancer diagnosis: genitourinary        | 0.994    | 0.01   |
| Neuropathic pain (DN4-positive) or clinically classed as mixed | 0.506    | 0.11   |
| Initial morphine equivalent daily dose† | 0.426    | <0.0001 |

*Adjusted R² of model = 18.6; †Log value
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CONCLUSION
Pain intensity is associated with a heterogeneous group of factors: higher incidence; poorer functional status; cancer type (head and neck, genitourinary and gastrointestinal); adjuvant use and initial opioid dose. The diversity of associations, and our study’s limited explanation of pain intensity variance (<20%), together underscore the biopsychosocial complexity of CP. The level of opioid dosing was likely suboptimal in patients referred to our CP clinic. Adequacy of CP treatment therefore warrants further exploration. Prospective longitudinal studies are particularly needed to better understand CP, such as the contribution of neuropathic and other challenging components, and thus inform its classification and management.

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