Original Article

Cancer-Related Pain: A Longitudinal Study of Time to Stable Pain Control and Its Clinicodemographic Predictors

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Abstract

Context. Multidimensional assessment is pivotal in managing cancer-related pain.

Objectives. The objectives of this study were to determine time to stable pain control (SPC) and identify its baseline clinicodemographic predictors in patients with cancer pain.

Methods. This is a prospective longitudinal study of patients attending a cancer pain clinic. Scheduled clinic attendances and weekly investigator-led phone calls enabled monitoring of patients' daily pain diary, opioid use, and other analgesic interventions. Baseline clinicodemographic variables were examined in survival analyses, which included the construction of accelerated failure time models with time ratios [TRs, (95% CIs)], based on time to SPC (pain intensity ≤3 and <3 breakthrough opioid doses over three consecutive days) for variable categories.

Results. Of 319 participants, 22 died before achieving SPC and were censored in the survival analysis. The median survival time (95% CI) to SPC was 22 (19–25) days. In multivariable analysis, compared to their respective reference categories, female sex ($P = 0.001$), substance abuse ($P < 0.001$), a neuropathic pain component ($P < 0.001$), and use of ≥1 adjuvant analgesic ($P = 0.022$) each had TRs > 1 (1.03–2.54), whereas soft tissue pain ($P < 0.001$) had a TR = 0.71 (0.62–0.82), reflecting longer and shorter time to SPC, respectively.

Conclusion. SPC is achievable for most patients with cancer pain. Recognition of strong predictors of time to SPC, such as substance abuse, a neuropathic pain component, soft tissue pain, and current use of adjuvant analgesia, may help to triage care services based on therapeutic need and guide analgesic interventions. J Pain Symptom Manage 2019;58:812–823.

Key Words

Cancer-related pain, pain assessment, pain classification, pain management, palliative care, quality of life

Introduction

Cancer-related pain encompasses pain related to sites of cancer involvement in addition to cancer treatment–related pain, particularly surgery, chemotherapy, and radiation. A meta-analysis study reported a pooled cancer pain (CP) prevalence of 55% in patients undergoing disease-modifying treatment and a prevalence of 64% in advanced metastatic

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disease.[1] The burden of CP is projected to increase further, mainly in association with population aging,[2,3] but also with longer patient survival and more prolonged treatment regimens.[4] Undertreatment of CP generates distress and impairs quality of life for patients.[5,6] Although evidence-based guidelines on therapeutic interventions exist,[7,8] data indicate that CP remains undertreated worldwide.[9,10] Inadequate assessment has been identified as a major contributor to undertreatment.[11]

A comprehensive assessment of CP entails multidimensional evaluation of specific pain characteristics, recent analgesic treatment modalities, and both psychosocial and coping dimensions of the patient with CP.[12] Poor recognition and inappropriate therapeutic targeting of CP domains may result in failure to achieve stable pain control (SPC).[13,14] Studies have reported longer time to achieve SPC to varying extent for neuropathic pain, incident pain, higher initial pain intensity, a history of addictive behavior, psychological distress, and younger age.[15–17] The Edmonton Classification System for Cancer Pain (ECS-CP)[18] encompasses most of these items and is arguably the most studied and validated among the formal CP classification tools.[19,20] However, there are conflicting reports regarding some classification features, particularly initial pain intensity in predicting time to reach SPC.[21,22] Furthermore, the operational definitions for various classification features of CP such as psychological distress and incident pain have presented interpretive challenges.[19,23] Consequently, further evaluation and clarification of the role of previously identified classification features of CP is necessary. Meanwhile, the outcome, time to achieve SPC, may be regarded as an index of complexity and challenge in CP management.[16,19,24]

To our knowledge, there are no published Portuguese data on time to achieve SPC in patients with CP. We conducted a prospective longitudinal study in a Portuguese cohort of patients with CP to primarily determine the time to achieve SPC and the association of baseline demographic and clinical classification features of CP with it. A secondary objective was to determine the relative change in both the frequency of nonopioid, therapeutic analgesic interventions used, and the level of opioid consumption between baseline and the time of achieving SPC.

Methods

Study Setting, Participants, and Design

The study was conducted from June 1, 2009, to April 30, 2010, in the specialist CP clinic of the Portuguese Cancer Institute in Lisbon, Portugal. Newly referred patients were approached for consent to participate in a prospective, longitudinal, observational cohort study. The study was approved by the local Research Ethics Board.

Study Eligibility Criteria

Adult patients (>18 years old) with a cancer diagnosis, those providing informed consent to study participation, and those cognitively capable of rating their pain on a numerical scale (0, no pain; 10, worst pain imaginable) were included. Patients without evidence of active cancer and those with solely non-CP were excluded. CP was defined as pain directly related to either regional cancer involvement or to anticancer treatments. Patients with SPC (both average pain and worst pain scores <4) in the week preceding their first CP clinic visit were also excluded.

General Baseline Assessment

Patients underwent standardized assessment using Portuguese versions of validated tools, and clinical data were routinely documented. A score ≥2 on the CAGE (Cut down, Annoy, Guilt, Eyeopener) alcohol questionnaire was used to screen for any history of alcohol abuse.[25,26] Functional performance status was rated using the Eastern Cooperative Oncology Group scale.[27] Scores ≥4 on the Short Portable Mental Status Questionnaire,[28] >7 on the Hospital Anxiety and Depression Scale (HADS) subscales,[29] and ≥4 on the Emotion Thermometer tool,[30,31] screened for cognitive impairment, anxiety, depression, and emotional distress, respectively. Primary cancer diagnosis, metastatic sites, documentation of palliative treatment intent, cancer treatments (cytotoxic and targeted chemotherapy, radiotherapy, or surgery) within the 30-day prestudy period were recorded.

Baseline Assessment of Cancer Pain

Baseline pain assessment included Brief Pain Inventory (BPI) ratings,[32] including pain "now" intensity on a 0–10 scale (ref) and pain duration in months. Pain "now" intensity was categorized into mild (0–3), moderate,[4–6] and severe[7–10] for further analyses. The Douleur Neuropathique 4,[33,34] neuropathic pain screening tool, used a positive cutoff score of ≥4. As previously reported,[35] the presence of a neuropathic pain component was based on both positive Douleur Neuropathique 4 screening and clinical classification of mixed pain. Episodic pain,[36] defined as a transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain, was recorded and subdivided into incident pain when a trigger or incident activity was identifiable, and breakthrough pain when no trigger was identified. Standard guidelines and tables were used to calculate the oral morphine equivalent daily dose (MEDD) in milligrams.[37] As previously reported,[10] patients with a negative Pain

Management Index (PMI),[38] reflecting opioid undertreatment, were identified. The type and number of current adjuvant analgesic treatments were also recorded.

Longitudinal Assessment of Cancer Pain

Once consented, participants and family or domestic caregivers were instructed during their first CP clinic attendance on maintaining a pain diary with their daily pain intensity score (0−10) and record of daily breakthrough opioid analgesic use. Participants could access a 24-hour telephone line if necessary to leave a recorded message. In addition to their first CP clinic visit (C1) at baseline (T0), further CP clinic visits (C2 and C3) at week 5 (T5) and week 10 (T10), respectively, were planned. At the intervening weekly time points (T1−T4 and T6−T9) between clinic visits, the principal study investigator contacted participants by telephone to record pain intensity scores and breakthrough analgesia use and recommended analgesic dose adjustments, according to standard guidelines.[7,39] Study participation ended primarily on reaching SPC, but also in the event of death, loss to follow-up, or reaching T10 (70 days) without any of these events occurring. Time to SPC, the study's primary outcome was defined as time (days) to rating pain intensity ≤3 for three consecutive days and using <3 breakthrough opioid analgesia doses daily for the same three days. For participants unable to rate their pain intensity, SPC was defined solely as having three consecutive days in which <3 breakthrough opioid analgesia doses were used daily.

Data Analyses

Means are expressed with SDs and medians with the interquartile range, unless otherwise stated. Time-to-event, survival analysis was used to examine the association of baseline (T0) clinicodemographic predictor variables with the primary outcome. Continuous variables such as age and MEDD were categorized using clinically meaningful cut points for survival analyses. In univariable survival analyses, differences in survival probabilities were examined using the Kaplan-Meier method and the log-rank test. Participants who died left the study or lost to follow-up were censored in the survival analyses.

Cox analyses revealed significant violation of the proportional hazards assumption and consequently, as recommended in this context,[40,41] alternative parametric survival analyses with accelerated failure time (AFT) distributions and models were examined, generating time ratios (TRs) with 95% CIs. A covariate predictor with a TR > 1 indicates a decelerating or prolongation effect regarding its association with time to event, whereas a TR < 1 indicates the opposite. The specification of independent variables for multivariable AFT analyses was based mainly on clinical relevance and otherwise having $P < 0.2$ in the univariable analyses. Selected variables were block entered into multivariable AFT models and backward elimination used in constructing a final parsimonious model, which was also guided by Cox-Snell and deviance residual plotting, and comparative goodness of fit, using Akaike's inclusion criteria.

Pearson's chi-square test was used to compare use of adjuvants and neural blockade interventions at T0 with their use within the study; similarly, initial (T0) and final MEDDs (on the day of reaching SPC) were compared using the Wilcoxon signed-rank test. The Kruskal-Wallis test was used to compare final MEDDs according to the presence or absence of those predictor variables identified in the final multivariable model. Data were analyzed using both SAS, version 9.3 and Stata/IC, V14.2 statistical software[42,43]; statistical significance was set at $P < 0.05$.

Results

Study Sample Selection and Attrition

Of 459 patients screened, 88 were excluded because of non-CP ($n = 69$), nonactive cancer ($n = 16$), failure to consent ($n = 3$), or prestudy presence of SPC ($n = 52$) (Fig. 1). Of the final study sample ($n = 319$), 72 (22.6%) died and 14 (4.4%) were lost to follow-up.

Demographic and Baseline Cancer Characteristics

Baseline clinicodemographic characteristics of the study sample are summarized in Table 1. The mean age was 62.4 ± 14.4 years and 163 (51.1%) were female. Metastatic disease was present in 240 (71%) participants; bone (37%) was the most common site. The most common cancer was head and neck, which occurred in 86 (27%) participants. A palliative treatment goal was documented for 52.7% of the participants and most (81.5%) had an Eastern Cooperative Oncology Group score in the 0−2 range. Of all participants, 32%, 46.7%, and 50.8% had received recent surgery, chemotherapy, and radiotherapy, respectively.

Baseline Pain and Psychological Characteristics

There was evidence of a neuropathic pain component in 120 (37.6%) participants (Table 2). Soft tissue pain, referring mainly to muscle, fat, or fibrous tissue, occurred in 193 (60.5%) participants. Episodic breakthrough and incident pain were present in 144 (45.1%) and 193 (60.5%) participants, respectively. Most participants (82.5%) had pain for ≥1 month and the most common sites were limb in 89 (24%) and head and neck in 83 (26%). The highest BPI pain interference ratings were 7.4 ± 2.5 and

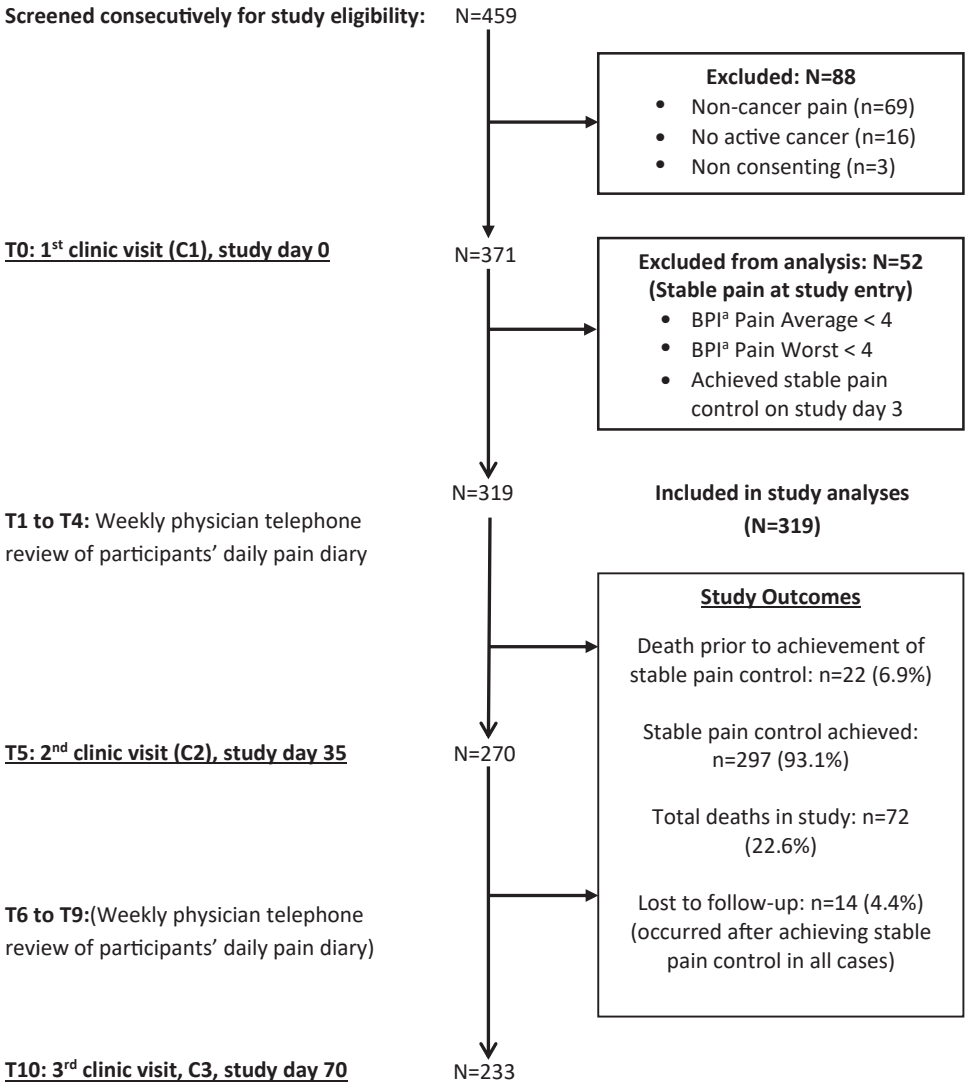

Fig. 1. Study flow diagram.

7.3 ± 2.4, in relation to mood and enjoyment of life, respectively. Cognitive screening detected a mild cognitive deficit in 43 (13.5%) participants. A history of drug or alcohol abuse was present in 82 (25.7%) participants. Regarding psychological distress, 223 (69.9%) and 243 (76.2%) screened positive on HADS anxiety and HADS depression assessments, respectively; the Emotion Thermometer distress screen was positive in 183 (57.4%) participants. In regard to pain management, the median MEDD at T0 was 30 mg (22.5–60); 77 (24.1%) participants had a negative PMI and 191 (59.9%) used ≥1 adjuvant analgesic.

Analyses of Time to SPC

SPC was achieved by 297 (93.1%) participants within 66 days; the median survival time (95% CI) was 22 (19–25) days. Twenty-two (6.9%) participants died before achieving SPC and were censored in the survival analyses. The designation of SPC was based solely on the number of breakthroughs used in 21 (7.1%) participants.

The Kaplan-Meier survival curves of the variables age group, sex, presence of a neuropathic pain component, presence of soft tissue pain, a history of drug or alcohol (substance) abuse, and use of adjuvant analgesics are presented in Fig. 2, labeled a–f, respectively. The log-rank test was highly significant ($P < 0.0001$) for the presence of a neuropathic pain component, a history of substance abuse, and the use of ≥1 adjuvant analgesic at T0; each category was associated with longer time to SPC. In addition, recent chemotherapy ($P = 0.013$) and HADS Anxiety

Table 1
Demographic and Clinical Characteristics of Study Sample

Characteristic	Total $n = 319$ (%)
Age, mean yrs ± SD	62.4 ± 14.4
Sex: female	163 (51.1)
Primary cancer diagnosis	
Lung	9 (2.8)
Head and neck	86 (27.0)
Gastrointestinal	74 (23.2)
Breast	35 (11.0)
Genitourinary	72 (22.6)
Other	43 (13.5)
Metastatic sites	
Bone	118 (37.0)
Lungs	50 (15.7)
Central nervous system	21 (6.6)
Liver	54 (16.9)
Nodal	54 (16.9)
Other	144 (45.1)
Palliative goals of care	168 (52.7)
Functional status (ECOG)[a]	
0	98 (30.7)
1	106 (33.2)
2	56 (17.6)
3	32 (10.0)
4	27 (8.5)
Surgery[b]	102 (32.0)
Chemotherapy[b]	149 (46.7)
Radiotherapy[b]	162 (50.8)

[a]Eastern Cooperative Oncology Group.
[b]Within the last 30 days.

score > 7 ($P = 0.018$) had statistically significant associations with longer and shorter time to SPC, respectively. Violation of the Cox proportional hazards assumption was determined statistically and graphically (Appendix Figs. 1 and 2: log-log plots demonstrate nonparallel status), and in subsequent AFT survival analyses, the lognormal distribution was selected as most appropriate.

The univariable AFT analyses with lognormal TRs for baseline clinicodemographic variables and pain and psychological variables are presented with the median (95% CI) time to SPC for each in Tables 3 and 4, respectively. The shorter median time to SPC of 19 (17−24) days for those aged ≥60 years was associated with a statistically significant ($P = 0.004$) TR of 0.76 (0.64−0.92). The longer median time to SPC of 26 (20−30) days for those with recent chemotherapy exposure was associated with a statistically significant ($P = 0.009$) TR of 1.27 (1.06−1.52). Recent radiotherapy was similarly associated with longer median time to SPC and a statistically significant ($P = 0.037$) TR of 1.21 (1.01−1.45). A neuropathic pain component, a history of substance abuse, and use of ≥1 adjuvant analgesic were associated with longer median times to SPC of 38 (32−41), 36 (31−40), and 26 (24−31) days and statistically significant ($P < 0.001$) TRs of 2.57 (2.2−3.0), 1.95 (1.61−2.36), and 1.48 (1.25−1.77), respectively. Soft tissue pain was associated with a shorter time to SPC of 18 (16−24) days and a TR of 0.78 (0.65−0.93) ($P = 0.007$).

Variables with a P value <0.2 in the univariable analyses (age, chemotherapy, radiotherapy, neuropathic pain, soft tissue pain, incident pain, pain duration, BPI pain now, drug or alcohol abuse history, and adjuvant analgesic use) were entered into a multivariable model along with variables of particular relevance (recent surgery, palliative treatment goal, HADS Anxiety score > 7, HADS Depression score > 7, initial MEDD, and PMI negative status), resulting in a total of 17 variables in the initial iteration of the model. The final model demonstrated an acceptable fit, based on graphing of Cox-Snell residuals versus survival (Appendix Fig. 3), deviance residuals (Appendix Fig. 4), and lowest Akaike's inclusion criteria value. Seven variables with $P < 0.2$ were retained in the final model (Table 5): age ($P = 0.077$) and soft tissue pain ($P < 0.001$) had time ratios of 0.88 and 0.71, respectively. Sex ($P = 0.001$), a history of substance abuse or a neuropathic pain component ($P < 0.0001$ for both), and use of ≥1 adjuvant analgesic ($P = 0.022$) had TRs of 1.27, 1.65, 2.19, and 1.18, reflecting longer time to SPC.

Pain Management

Comparing therapeutic interventions before study and within the study (Appendix Table 1), nonsteroidal anti-inflammatory medications, flupirtine, or neural blockade were not used before study but were used by 77.4%, 5.7%, and 2.4%−7.4% of participants, respectively, before achieving SPC. Meanwhile, during this time period, there was a statistically significant ($P < 0.001$) increase in use of other listed adjuvant analgesic medications, and a doubling in median MEDD to 60 mg (30−120) ($P < 0.0001$).

Comparing initial versus final MEDDs in relation to those predictor variables identified in the final multivariable model (Appendix Table 2), age < 60 years, presence of a neuropathic pain component, and use of adjuvant analgesics at baseline were associated with higher final MEDDs ($P = 0.0001$, $P = 0.0001$, and $P = 0.011$, respectively), whereas soft tissue pain was associated with lower final MEDD ($P = 0.042$). A history of substance abuse was associated with a higher final MEDD but was not statistically significant ($P = 0.064$). Of participants reaching SPC ($n = 297$), 121 had ≥1 opioid switch with the following comparative distribution: 50%, 57.3%, and 51.3% of those aged <60 years, those with a neuropathic pain component, and a history of substance abuse compared to 34%, 31%, and 36.9% in their corresponding categories, ($P = 0.009$, $P < 0.001$, and $P = 0.025$), respectively.

Table 2
Baseline Pain and Psychological Morbidity Assessments

Characteristic	Total $n = 319$ (%)
Pain mechanism category	
Nociceptive, without evidence of an NPC	199 (62.4)
Evidence of NPC (clinical and DN4 screening)	120 (37.6)
Pain classified by topographic level	
Visceral	101 (31.7)
Bone	136 (42.6)
Soft tissue	193 (60.5)
Episodic pain	
Breakthrough pain present	144 (45.1)
Incident pain present	193 (60.5)
Pain duration	
<1 month	56 (17.6)
≥1 month	263 (82.5)
Principal anatomical location of pain	
Multiple sites	14 (4.4)
Upper or lower limb	74 (23.2)
Head and neck	83 (26.0)
Thorax or breast	27 (8.5)
Back	36 (11.3)
Abdomen	45 (14.1)
Pelvis and perineum	40 (12.5)
Brief Pain Inventory (BPI)	
Worst pain	8.1 ± 1.9
Least pain	3.4 ± 1.6
Average pain	5.5 ± 1.5
Pain now	6.1 ± 2.1
Pain relief, percentage	37.9 ± 25.3
BPI Pain interference	
General activity	5.4 ± 2.6
Mood	7.4 ± 2.5
Walking	5.2 ± 2.6
Work	4.5 ± 3.0
Relations with people	3.0 ± 1.9
Sleep	4.9 ± 1.9
Enjoyment of life	7.3 ± 2.4
Cognitive status	
Impaired	43 (13.5)
Addiction history	
Past or current drug or alcohol abuse	82 (25.7)
Psychological distress measures	
HADS anxiety score >7	223 (69.9)
HADS depression score >7	243 (76.2)
ET distress score ≥4	183 (57.4)
Pain management	
Initial MEDD, median [interquartile range]	30 [22.5–60.0]
Negative Pain Management Index (PMI)	77 (24.1)
Use of ≥ 1 adjuvant analgesic	191 (59.9)

NPC = neuropathic pain component; DN4 = Douleur Neuropathique 4; HADS = Hospital Anxiety Depression Scale; ET = Emotion Thermometer; MEDD = morphine equivalent daily dose in mg, oral.

Discussion

Using an SD of SPC, and exceeding the proportional attainment of the same SPC outcome as used in previous studies,[15–17] most (93.1%) participants in this study achieved SPC, with the study's lengthy 70-day follow-up helping to capture this outcome of their CP. The median survival time (time for 50% of the at-risk population to have a "failure" event in survival analysis) of 22 (19–25) days is shorter than estimates from a study of CP,[44] in which 12 of 41 (29%) patients obtained acceptable pain relief (0–4 on a 0–10 scale) by four weeks. However, it is longer than the median survival time ranges of 4–22 and 3–16 days in other study cohorts,[15,16] in which 63% and 50% achieved SPC using the same definition, respectively. The 22-day median survival time seems unacceptably long but should be viewed in the context of a cancer pain clinic referral population whose pain management has warranted pain specialist input. Although the three-day requirements for the SPC definition represented a research standard and were chosen to facilitate comparability, they were also stringent, and perhaps a less conservative SPC definition would have resulted in a shorter median "at-risk" survival time.

Although the study's SPC definition mirrored the ECS-CP-linked definition,[18] use of more patient-centered outcomes has been proposed,[45] particularly the personalized pain goal (PPG).[46,47] A PPG represents the patient's expressed pain intensity level that is acceptable for them.[46,48] In a study of patients with advanced cancer ($n = 231$) and CP, most ($n = 169$, 73%) participants were able to provide a PPG and 67% ($n = 113$) of these reported a PPG of 3 or less.[47] Performance of the PPG in the Portuguese population is unknown, and we can only speculate that there would be comparable findings to a Canadian study, in which most (71.3%) participants who reached their PPG also reached SPC according to the standard ECS-CP definition.[47] As an outcome more closely aligned with patient goals, the PPG merits further evaluation in Portuguese and other CP populations.

The present study identified sex, substance abuse, a neuropathic pain component, soft tissue pain, and adjuvant analgesic use as statistically significant independent predictors of time to SPC in multivariable analysis. There is no compelling evidence to support sex differences in relation to CP intensity,[49] and although female sex status was statistically nonsignificant at univariable level in the present study, it was included as a potential confounder in multivariable analyses. The adjusted TR (1.27) for female versus male sex was statistically significant, reflecting a 27% longer time to reach SPC, and a possible confounding effect. In summary, this finding in a single study warrants replication before more explicit recommendations could be made for the clinical management of pain in females.

The findings for a neuropathic pain component and substance abuse were robust, each associated with 119% and 65% longer times to achieve SPC, respectively. Although adjuvant analgesics were used by 88 (60%) of the patients with a neuropathic pain component ($n = 120$), their use was independently associated with an 18% longer time to SPC and greater opioid use in the present study. A neuropathic pain

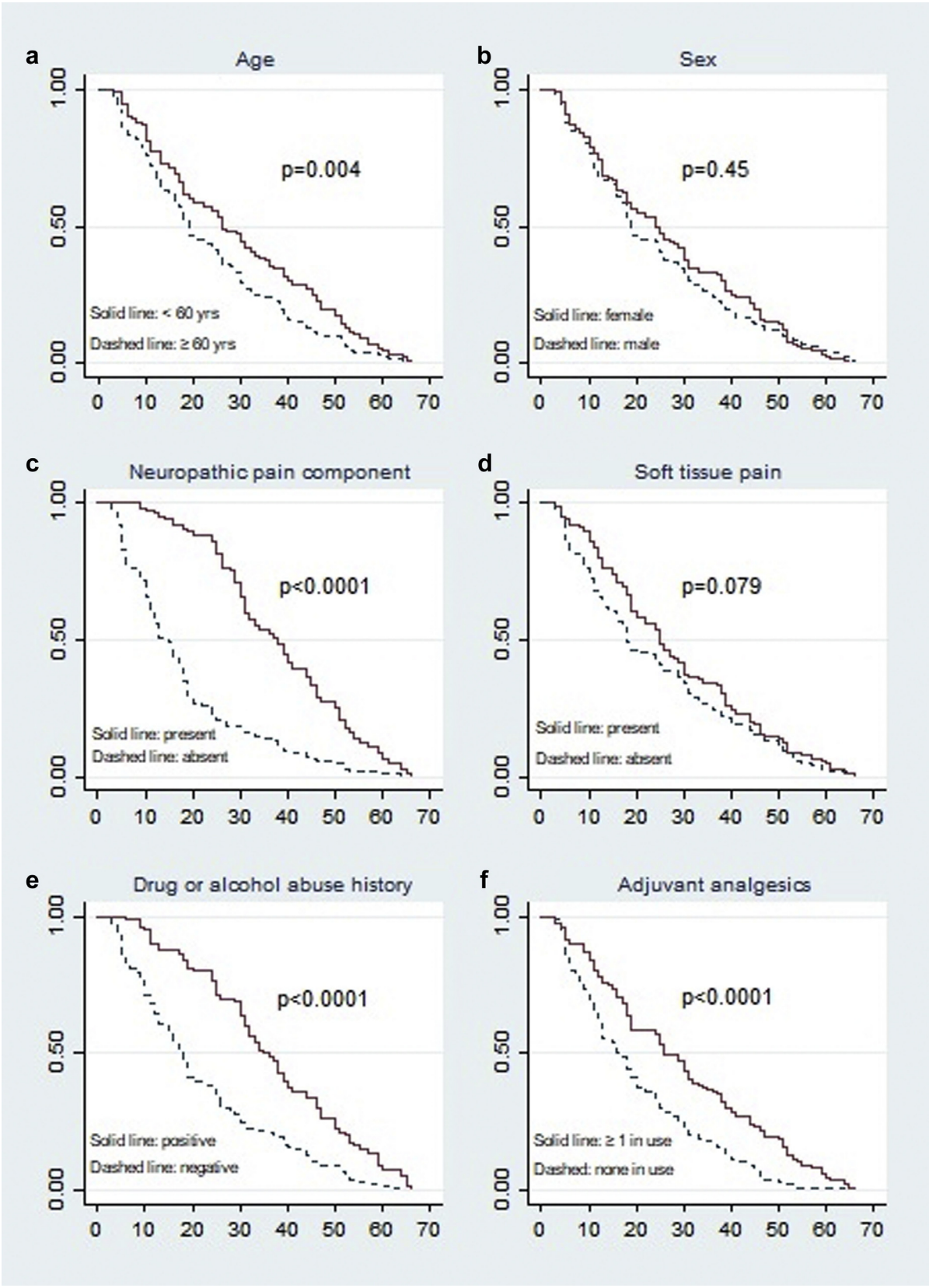

Fig. 2. (a–f) Kaplan-Meier plots of survival times for selected variables with log rank–derived probability estimates; Y axis: proportion of study population at risk; X axis: analysis time (study days).

Table 3
Univariable Survival (Time to Event) Analysis for Baseline Demographic and Clinical Variables

Baseline Variable	$N = 319$ (%)	Median Survival Time[a] (95% CI, Lower–Upper)	Univariable Lognormal AFT		
			Time Ratio	95% CI (Lower–Upper)	*P*-value
Age					
<60 years	122 (38.2)	26 (20–32)	1		
≥60 years	197 (61.8)	19 (17–24)	0.76	0.64–0.92	**0.004**
Sex					
Male	156 (48.9)	19 (18–25)	1		
Female	163 (51.1)	24 (19–30)	1.12	0.93–1.34	0.230
Primary cancer					
Lung or other	52 (16.3)	25 (17–31)	1		
Head & neck	86 (27.0)	24 (18–29)	0.91	0.69–1.21	0.531
Gastrointestinal	74 (23.2)	19 (16–25)	0.84	0.63–1.12	0.241
Breast	35 (11.0)	28 (15–39)	1.11	0.79–1.58	0.544
Genitourinary	72 (22.6)	24 (16–29)	0.93	0.70–1.25	0.640
Palliative care goal					
Not documented	151 (47.3)	19 (16–24)	1		
Documented	168 (52.7)	25 (19–29)	1.05	0.89–1.27	0.527
Functional status					
ECOG 0, 1, or 2	260 (81.5)	22 (19–26)	1		
ECOG 3 or 4	59 (18.5)	19 (15–31)	0.90	0.71–1.14	0.375
Surgery					
No	217 (68.0)	22 (18–25)	1		
Yes	102 (32.0)	20 (17–30)	1.09	0.90–1.32	0.405
Chemotherapy					
No	170 (53.3)	19 (16–23)	1		
Yes	149 (46.7)	26 (20–30)	1.27	1.06–1.52	**0.009**
Radiation therapy					
No	157 (49.2)	19 (16–24)	1		
Yes	162 (50.8)	25 (19–30)	1.21	1.01–1.45	**0.037**

AFT = accelerated failure time program for univariable time to event analysis; ECOG = Eastern Cooperative Oncology Group.
Bold values are statistically significant ($P < 0.05$).
[a]Time to stable pain control in days.

component has been consistently identified in previous studies as a predictor of longer time to SPC,[15–17] and greater opioid and adjuvant analgesic use,[16,17] as also occurred in the present study. Although an addictive history has been associated with greater opioid consumption in CP management,[16,17] less CP relief,[50] and longer time to SPC in univariable analysis,[16] an independent association with time to SPC was not found in three large cancer pain classification studies.[15–17] Few comparable data are available for soft tissue pain as a specific entity, which was associated with shorter time to SPC and lesser opioid use in the present study.

Previous studies have identified younger age,[15–17] higher initial pain intensity,[15,16] incident pain,[16,17] and psychological distress[16] as having associations with longer time to SPC, but with the exception of age, none of these variables had such an association in the present study. Age ≥60 years was associated with 12% shorter time to SPC when compared to age <60 years, which was only statistically significant at a 10% alpha level; final MEDD was also lower in those ≥60 years. In the studies in which initial pain intensity predicted time to SPC,[15,16] the proportion of study participants with mild pain was 44% and 51% compared to a smaller proportion of 10% ($n = 34$) in the present study, which could have been too small to detect differences and thus explain why initial pain intensity was not identified as a predictor in this study. However, it has been reported that higher initial pain intensity merely reflects undertreatment of pain.[21,22] We have already reported undertreatment in the present study population,[10] and although 24.1% of this study cohort were PMI negative, this did not predict time to SPC. Moreover, the comparative changes in opioid use, opioid switching, and other therapeutic interventions between baseline and time of SPC, regardless of PMI status, suggest that resources were optimally applied in pursuit of SPC.

This study's strengths include its prospective longitudinal design, comprehensive assessments, and few missing data. There are many limitations to acknowledge. First, this is a single-site study in a tertiary-level cancer center with its specific sociocultural and referral pattern characteristics, which may collectively limit the generalizability of its findings. Patients with more severe pain may be selectively referred to the CP clinic; further potential for selection bias is evident in the relatively high proportion of patient referrals with head and neck cancer. Second, we acknowledge the potential information bias due to differential misclassification, as in documentation of the palliative treatment goal, and in patient or caregiver reporting by telephone to a single assessor, who was not blinded to the study outcome. Third, we examined baseline

Table 4
Univariable Survival (Time to Event) Analysis for Baseline Pain and Psychological Variables

Baseline Variable	$N = 319$ (%)	Median Survival Time[a] (95% CI, Lower–Upper)	Univariable Lognormal AFT		
			Time Ratio	95% CI (Lower–Upper)	*P*-value
Pain mechanism					
No evidence of NPC	199 (62.4)	15 (12–17)	1		
Evidence of NPC	120 (37.6)	38 (32–41)	2.57	2.2–3.0	**<0.001**
Pain topographic level					
Visceral pain absent	218 (68.3)	24 (19–26)	1		
Visceral pain present	101 (31.7)	19 (16–25)	0.89	0.73–1.08	0.230
Bone pain absent	183 (57.4)	20 (18–25)	1		
Bone pain present	136 (42.6)	24 (19–29)	0.998	0.83–1.20	0.986
Soft tissue pain absent	126 (39.5)	25 (20–30)	1		
Soft tissue pain present	193 (60.5)	18 (16–24)	0.78	0.65–0.93	**0.007**
Breakthrough pain					
Absent	175 (54.9)	24 (18–26)	1		
Present	144 (45.1)	20 (18–26)	0.93	0.77–1.11	0.417
Incident pain					
Absent	126 (39.5)	19 (16–25)	1		
Present	193 (60.5)	25 (19–29)	1.14	0.95–1.37	0.162
Pain duration					
<1 month	56 (17.6)	29 (24–36)	1		
≥1 month	263 (82.5)	19 (18–25)	0.85	0.67–1.08	0.178
Pain location					
Multiple sites	14 (4.4)	18 (5–45)	1		
Upper or lower limb	74 (23.2)	20 (16–26)	1.1	0.69–1.75	0.681
Head and neck	83 (26)	19 (16–25)	0.98	0.62–1.54	0.918
Thorax or breast	27 (8.5)	33 (14–41)	1.39	0.82–2.34	0.221
Back	36 (11.3)	29 (13–38)	1.21	0.73–2.00	0.461
Abdomen	45 (14.1)	22 (16–26)	1.02	0.62–1.66	0.943
Pelvis and perineum	40 (12.5)	19 (13–31)	1.14	0.70–1.87	0.593
BPI pain now					
Mild (0–3)	34 (10.7)	16 (11–26)	1		
Moderate (4–6)	152 (47.7)	19 (16–25)	1.08	0.80–1.45	0.627
Severe (7–10)	133 (41.7)	25 (22–30)	1.29	0.95–1.75	0.097
Cognitive status					
Normal	276 (86.5)	22 (18–26)	1		
Impaired	43 (13.5)	22 (12–39)	0.95	0.73–1.24	0.698
Drug or alcohol abuse					
Negative history	237 (74.3)	18 (16–19)	1		
Positive history	82 (25.7)	36 (31–40)	1.95	1.61–2.36	**<0.001**
HADS anxiety score					
0–7 (normal)	96 (30.1)	26 (18–33)	1		
> 7 (positive screen)	223 (69.9)	19 (18–25)	0.88	0.72–1.07	0.205
HADS depression score					
0–7 (normal)	76 (23.8)	25 (18–29)	1		
>7 (positive screen)	243 (76.2)	20 (18–25)	0.91	0.74–1.12	0.370
ET distress score					
0–3 (normal)	136 (42.6)	20 (17–27)	1		
≥4 (positive screen)	183 (57.4)	22 (19–26)	1.02	0.85–1.22	0.836
Initial MEDD, oral					
0–20 mg	78 (24.5)	19 (16–25)	1		
21–40 mg	118 (37)	20 (18–29)	1.03	0.81–1.30	0.819
>40 mg	123 (38.6)	24 (18–30)	1.09	0.86–1.38	0.473
PMI					
Positive	242 (75.9)	19 (18–25)	1		
Negative	77 (24.1)	25 (19–30)	1.09	0.88–1.35	0.426
Adjuvant analgesic use					
None	128 (40.1)	17 (13–19)	1		
One or more	191 (59.9)	26 (24–31)	1.48	1.24–1.77	**<0.001**

AFT = accelerated failure time program for univariable time to event analysis; NPC = neuropathic pain component; BPI = Brief Pain Inventory; HADS = Hospital Anxiety Depression Scale; ET = Emotion Thermometer; MEDD = morphine equivalent daily dose in mg; PMI = Pain Management Index.
Bold values are statistically significant ($P < 0.05$).
[a]Time to stable pain control in days.

prediction of the time to the SPC outcome that could have been impacted by various competing risks, such as disease progression, compliance with analgesic recommendations, and the emergence of different pain syndromes. Furthermore, baseline covariates were treated as fixed in the analyses, whereas some, such as palliative treatment goal, are potentially time varying. However, the study's objectives were focused on prediction from a baseline perspective to inform clinical practice rather than establish causal inference, for

Table 5
Multivariable AFT[a] Model: Variable Association With Time to Event (Stable Pain Control)

	Multivariable Lognormal Analysis[b]		
Variable	Time Ratio (TR)[c]	95% CI (Lower–Upper)	*P*-value
Age			
Aged 60 years or more	0.88	0.77–1.01	0.077
Sex			
Female	1.27	1.10–1.46	**0.001**
Palliative treatment goal			
Documented	1.11	0.97–1.26	0.148
History of drug or alcohol abuse (DAA)			
Present	1.65	1.40–1.96	**<0.001**
Topographic pain level			
Soft tissue pain	0.71	0.62–0.82	**<0.001**
Pain mechanism			
Neuropathic pain component (NPC)	2.19	1.89–2.54	**<0.001**
Adjuvant analgesics used			
One or more	1.18	1.03–1.36	**0.022**

Bold values are statistically significant ($P < 0.05$).
[a]AFT indicates accelerated failure time using lognormal distribution.
[b]Variables with a *P*-value < 0.2 were retained in the model after backward elimination.
[c]Reference categories for TRs were the same as those presented in Tables 3 and 4.

example, whether pain is due to cancer disease as opposed to cancer treatment. Fourth, this study was completed in 2010. Although pain management guidelines might not have changed dramatically in the interim, the advent of targeted, disease-modifying therapies might alter some of our study findings were it to be conducted today.

For the clinical practitioner, this study highlights that need to recognize the baseline predictors such as a neuropathic pain component and a positive history of substance abuse, which are strongly associated with longer time to achieve SPC; this information on complexity should inform management triage in terms of the most appropriate sites and levels of care, and therapeutic targeting,[24] as demonstrated in use of the ECS-CP tool.[51] For the clinical researcher, this study again highlights the previously identified need for further knowledge synthesis to inform the process of CP classification,[20,52] especially with a view to developing a standardized approach and a common language to facilitate comparison of study populations and meta-analyses. Large multicenter cohort studies will be required to further examine the predictors of time to SPC and other outcomes such as the PPG.[19] It may be possible to use the collective data from past and future studies to develop a predictive index, a composite score that captures the mix of negative and positive predictors of time to SPC, thus guiding specialist referral and triage.

Conclusion

According to the standard definition of SPC for cancer-related pain, most patients will experience this outcome, although it may require some weeks to achieve. A neuropathic pain component, female sex, baseline use of adjuvant analgesics, and a history of substance abuse each predict longer time to SPC, whereas soft tissue pain and possibly older age predict shorter time to achieve this outcome. These and other potential predictors and outcomes require further examination in future studies, whose aim should be to inform the classification of cancer pain and thus expedite SPC through targeted management.

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Supplementary Data

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Appendix

Appendix Table 1

Comparative Use of Therapeutic Interventions for Cancer-Related Pain at Baseline and at the Time of Achieving Stable Pain Control

	Participants Who Achieved Stable Pain Control $n = 297$ (%)[a]		
Therapeutic Intervention	Baseline, (T0) Status	Status at Stable Pain Control	*P*-value[b]
Nonopioid medication			
Nonsteroidal anti-inflammatory drug	—	230 (77.4)	
Corticosteroid	56 (18.9)	113 (38.1)	<0.001
Antidepressant	43 (14.5)	157 (52.9)	<0.001
Antiepileptic	67 (22.6)	205 (69.0)	<0.001
Benzodiazepine	70 (23.6)	115 (38.7)	<0.001
Nonbenzodiazepine muscle relaxant	7 (2.4)	17 (5.7)	<0.001
Bisphosphonate	11 (3.7)	13 (4.4)	<0.001
Flupirtine (centrally acting analgesic)		17 (5.7)	—
Opioid use			
MEDD [Q1−Q3, quartiles]	30 [22.5−60]	60 [30−120]	<0.0001
Neural blockade by injection			
Supraclavicular block	—	22 (7.4)	
Intercostal block	—	7 (2.4)	
Suprascapular block	—	18 (6.1)	

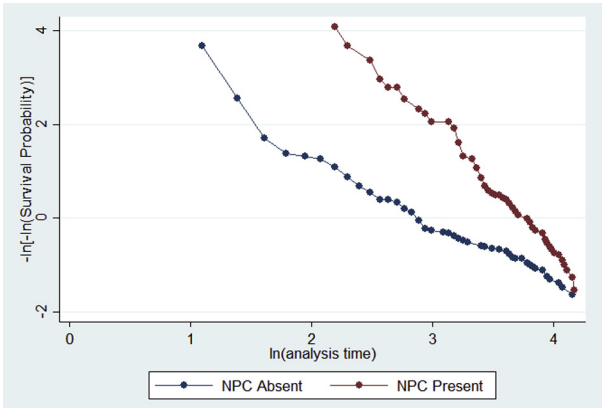
MEDD = morphine equivalent daily dose in mg, oral.
[a]Study participants who died ($n = 22$) without achieving stable pain control are not included in this table.
[b]Chi-square test for proportions and Wilcoxon signed-rank test for matched pairs.

Appendix Table 2

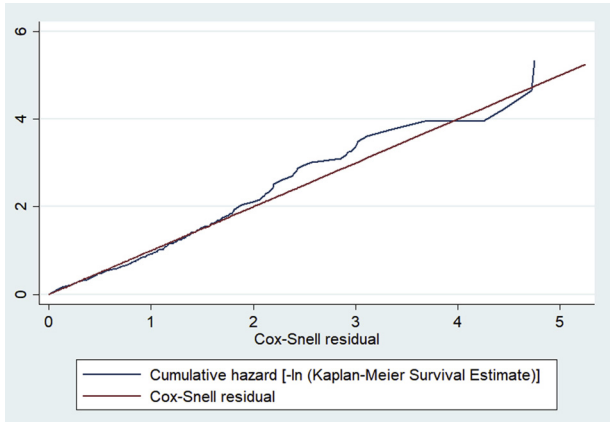
Opioid Use at Stable Pain Control in Relation to Retained Multivariable Model Variables

Variable	Final MEDD[a] (Q1-Q3, Quartiles)	*P*-value[b]
Age		
Ages < 60	90 (40−195)	**0.0001**
Aged 60 years or more	60 (30−90)	
Sex		
Male	60 (35−120)	0.614
Female	60 (30−120)	
Documented palliative treatment goal		
Absent	60 (30−120)	0.697
Present	60 (30−120)	
History of drug or alcohol abuse (DAA)		
Absent	60 (30−120)	**0.064**
Present	60 (38.8−162.5)	
Soft tissue pain		
Absent	80 (40−150)	**0.042**
Present	60 (30−100)	
Neuropathic pain component (NPC)		
Absent	50 (30−90)	**0.0001**
Present	90 (50−180)	
Adjuvant analgesics used at T0		
None	60 (22.5−90)	**0.011**
One or more	60 (37.5−150)	

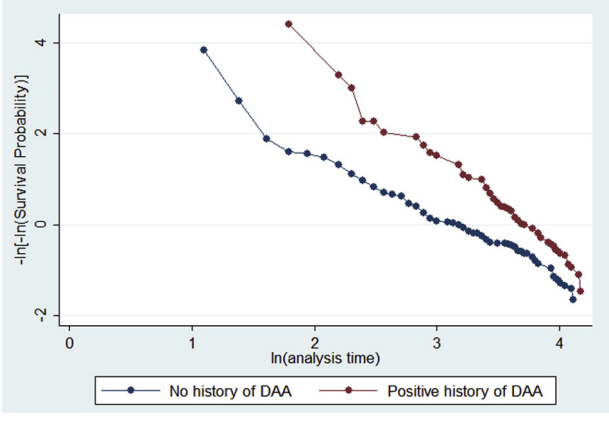
Bold values are statistically significant ($P < 0.05$).
[a]Morphine equivalent daily dose in mg, oral at the time of achieving stable pain control ($n = 296$, one participant was excluded because of a missing value).
[b]Kruskal-Wallis test.



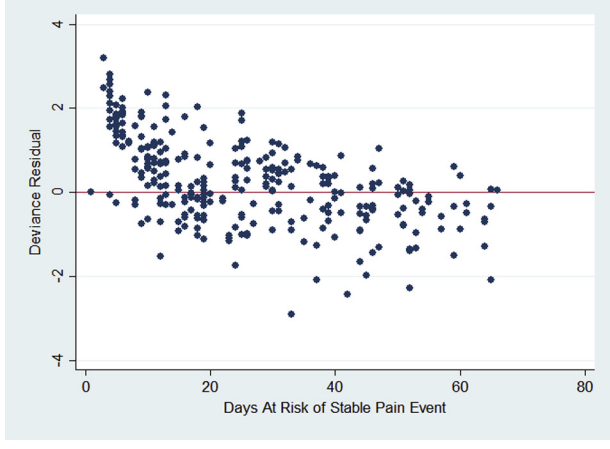
Appendix Fig. 1. Log-log plots for neuropathic pain component (NPC).



Appendix Fig. 3. Cumulative hazard and Cox-Snell residuals (lognormal model).



Appendix Fig. 2. Log-log plots for drug or alcohol abuse (DAA).



Appendix Fig. 4. Deviance residuals for lognormal accelerated failure time model.