

# Epidemiology of Pain Among Patients with Solid Metastatic Cancer During the Last Year of Life

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**Background:** Despite medical advancements, pain is a major source of suffering at the end of life for patients with a solid metastatic cancer. We aimed to assess the trajectory of pain prevalence, severity, interference, and inadequacy of analgesia during the last year of life.

**Methods:** We analysed data from the last year of life of 345 decedents from a prospective cohort study of 600 patients with a solid metastatic cancer in Singapore. Patients were surveyed every 3 months and their pain outcomes (prevalence, severity, and interference) and inadequacy of analgesia were analysed. We used mixed-effects regressions to assess the association of pain outcomes with patients' time from death, demographics, and planned or unplanned hospitalisations.

**Results:** Prevalence of pain was higher in the last 2 months (65%) compared to 11 to 12 months (41%) before death. Pain severity and interference scores (mean  $\pm$  SD) were also higher in the last month (severity:  $2.5 \pm 2.6$ ; interference:  $2.6 \pm 3.0$ ) compared to 12 months before death (severity:  $1.4 \pm 2.0$ ; interference:  $1.4 \pm 2.0$ ). At any time during the last year of life, 38% of the patients were prescribed non-steroidal anti-inflammatory drugs, 11% were prescribed weak-opioids and 29% were prescribed strong opioids. These analgesics were prescribed through either oral, topical or injectable route. Pain outcomes were significantly worse ( $p$ -value  $< 0.05$ ) for younger patients, those with higher education, and more financial difficulties, while interference was higher after an unplanned hospitalisation in the last month. Females reported higher pain severity score during their last year of life compared to males. For patients reporting moderate to severe pain, inadequacy of analgesia was lower in the last 2 months (43%) compared to 11 to 12 months before death (83%).

**Conclusion:** Findings highlight the need for greater attention in monitoring and treatment of pain even earlier in the disease trajectory, and increased attention to patients discharged from an unplanned hospitalisation.

**Keywords:** pain prevalence, severity, interference, inadequate analgesia

## Introduction

Despite medical advancements, more than 60% of patients with a solid metastatic cancer experience pain, with about one-third receiving inadequate analgesia.<sup>1-6</sup> Studies also show that pain prevalence among cancer patients increases with approaching death.<sup>7</sup> However, the trajectory of pain severity, interference, and inadequacy of analgesia during the last year of life among patients with a solid metastatic cancer is not clearly understood.

Previous studies conducted in other patient groups or in diverse settings show that pain prevalence is higher among patients who are younger,<sup>6</sup> have lower socio-economic status,<sup>8,9</sup> and after hospitalisation,<sup>10</sup> and that patients with primary tumours in the breast or genitourinary system report higher pain severity/interference.<sup>1,3</sup> Although the World Health Organisation recommends that moderate to severe pain be treated by opioids,<sup>11</sup> many patients and physicians are reluctant to use these due to fear of adverse effects.<sup>12</sup>

We aimed to assess the trajectory of pain prevalence, severity, and interference, and the inadequacy of pain analgesia during the last year of life. We hypothesized that pain prevalence, severity, and interference will be higher close to death, among patients who are younger, have lower socio-economic status, have a diagnosis of breast or genitourinary cancer,

and after a hospitalisation. We also postulated that patients with moderate and severe pain will be more likely to receive inadequate analgesics.

## Methods

### Study Participants

We used data from a prospective cohort study of patients with a solid metastatic cancer conducted in Singapore titled Cost of Medical Care of Patients with Advanced Serious Illness in Singapore (COMPASS). Study details are published.<sup>9,13</sup>

Participants were recruited from outpatient clinics at the Departments of Medical Oncology of two specialty cancer centres in Singapore between July 2016 and March 2018. Eligible patients included those with stage IV solid malignancy, aged  $\geq 21$  years, Singapore citizens or permanent residents, cognitively able to consent and self-report, and Eastern Cooperative Oncology Group performance status  $\leq 2$  (to allow a period of follow-up before death or end of study period).<sup>14</sup> Written consent was obtained. We surveyed patients every 3 months until patient's death. SingHealth Centralized Institutional Review Board approved the study (2015/2781). This study was performed in compliance with the Declaration of Helsinki.

### Study Measures

#### Outcomes

##### Patient-Reported Pain

We used a modified version of the brief pain inventory (BPI)<sup>15</sup> at each time point. We measured pain severity as an average score of four self-reported items: worst and least pain in the past 24 hours, average pain, and pain at the time of survey. Each item was assessed on a scale of 0 to 10; higher score indicating greater severity. We calculated the prevalence of pain as pain score  $>0$  and prevalence of moderate to severe pain as pain score  $>3$  on any item of the pain severity score. We assessed pain interference as an average of seven self-reported items on general activity, mood, walking ability, normal work, relations with others, sleeping well, and enjoyment of life in the past 24 hours on a scale of 0 to 10; higher score indicating higher pain interference.

##### Inadequacy of Analgesia

We obtained data for analgesics from patients' inpatient, outpatient, and emergency room billing records. Analgesics were scored as 0=no analgesic; 1="non-steroidal anti-inflammatory drugs (NSAIDs)"; 2="weak opioids"; and 3="strong opioids". In cases of more than one type of analgesic prescribed, the stronger analgesic was used to compute the analgesia score. We categorized the worst-pain score from the BPI at each time point as 0=no pain; 1=mild pain (score 1–3); 2=moderate pain (score 4–7); 3=severe pain (score 8–10). We used Cleeland's<sup>15</sup> method to calculate the pain management index (PMI) as the difference between the worst-pain score category and the analgesic score at each time point. PMI scores ranged from  $-3$  to  $+3$ ; scores  $<0$  and  $\geq 0$  indicated inadequate and adequate analgesia, respectively.

##### Palliative Care Use

We asked patients whether they had ever used any palliative care service, and if they had used any in-patient, home care, or day care palliative/hospice care facility in the last 3 months.

### Independent Variables

Patient socio-demographics: included age, education (below high school vs high school and above), financial difficulties, and type of cancer (gastrointestinal, respiratory, genitourinary or gynaecological, breast, and others). Patients' financial difficulty was assessed using three items asking how well the amount of money they had enabled them to cover the cost of treatment, take care of their daily needs, and buy those little extras. Responses for each item (very well, fairly well, poorly) were summed. Total score ranged from 3 to 9; higher score indicated greater level of financial difficulties.

Hospitalisations: Using patients' medical records, we assessed whether they were discharged from a planned or unplanned hospitalization in the previous month.

## Statistical Analysis

We analysed data of patients who died between July 2016 and December 2019, and who answered  $\geq 1$  survey within the last year of life. We rearranged the dataset to investigate the outcomes from patients' death date (see [Supplementary Tables 1](#) and [2](#) for more details).

We described prevalence of pain, prevalence of moderate and severe pain, and the inadequacy of analgesia using PMI for the available sample of patients at each time point during the last year of life. We used a chi-square test to compare the difference in pain outcomes between 11 to 12 months and 2 months before death, and a *t*-test to compare the differences in pain interference and pain severity scores between 12 months and 1 month before death. We also described pain outcomes (pain prevalence, prevalence of moderate to severe pain, pain severity and pain interference) in the last year of life stratified by gender. We used *t*-test to compare the difference in pain outcomes by gender.

We conducted mixed-effects logistic regression to assess variation in prevalence of pain and separate mixed-effects linear regressions for pain severity and pain interference by time from death, patients' age, education, financial difficulties, type of cancer, and discharge from a planned or unplanned hospitalization in the previous month. Since patient gender and type of cancer were correlated, we performed a separate sensitivity analysis including gender as a covariate and excluding type of cancer from the mixed effects regression models to investigate the predictors of pain outcomes. Mixed-effects regression takes into account the variability in the number of observations between individuals and individuals with single observations can also be included to estimate the population level effects.<sup>16–18</sup> We conducted separate mixed-effects logistic regressions to assess the association between the use of hospice or palliative care services and pain measures (prevalence, severity, and interference). We included the patient identification number as a random effect in all regressions. We used Stata version 16.1 for analyses.

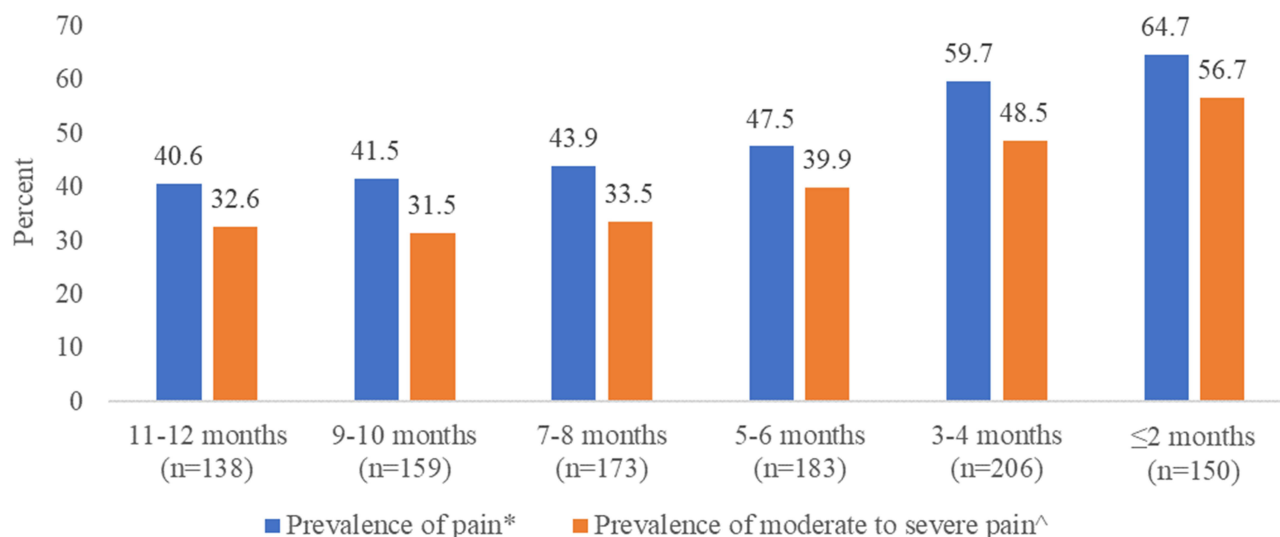
## Results

Of the 600 eligible patients participating in COMPASS, 47 patients (8%) dropped out during the study period. A total of 354 patients (59%) had deceased by 31st December 2019. Among them, 345 (97%) patients answered  $\geq 1$  survey during their last year of life and were included in our analytic sample ([Supplementary Table 2](#)).

Prevalence of pain and of moderate to severe pain was higher in the last 2 months (65% and 57%, respectively) compared to 11 to 12 months before death (41% and 33%, respectively) ( $p$ -value $<0.01$  for both, [Figure 1](#)). Average (mean  $\pm$  SD) pain severity and pain interference scores were also higher in the last month (pain severity score:  $2.5 \pm 2.6$ ; pain interference score:  $2.6 \pm 3.0$ ) compared to 12 months before death (pain severity score:  $1.4 \pm 2.0$ ; pain interference score:  $1.4 \pm 2.0$ ) ( $p$ -value $<0.01$  for both) ([Supplementary Table 3](#)). Female patients reported higher pain prevalence (54%), average pain severity score ( $2.1 \pm 2.4$ ) and pain interference score ( $2.0 \pm 2.7$ ) compared to male patients (pain prevalence: 46%, pain severity score:  $1.7 \pm 2.2$ , pain interference score:  $1.6 \pm 2.4$ ) during the last year of life ( $p$ -value $<0.05$  for all outcomes) ([Supplementary Table 4](#)). More than one-third of patients (36.5%) reported using palliative care and 81% of the patients had received chemotherapy in their last year of life ([Supplementary Table 3](#)).

Out of 345 patients, 38% were prescribed NSAIDs, 11% were prescribed weak-opioids and 29% were prescribed strong opioids at any time during the last year of life. These analgesics were prescribed through either oral, topical or injectable route ([Supplementary Table 5](#)). The inadequacy of analgesia during the last year of life ranged from 22% to 32% in the overall sample reporting any pain. However, in the sub-group of patients reporting moderate to severe pain at each time point, the inadequacy of analgesia was lower in the last 2 months (43%) compared to 11 to 12 months before death (83%) ( $p$ -value $<0.01$ ) ([Figure 2A](#) and [B](#)).

Odds of experiencing pain were lower farther from death and for older respondents. Odds were higher for those with above secondary education and with higher levels of financial difficulty ([Table 1](#)). Similar findings were observed for pain severity and interference. Patients with genitourinary/gynaecological cancers reported significantly higher pain severity and pain interference scores during their last year of life. Patients discharged from an unplanned hospitalisation in the last month reported significantly higher pain interference. Results from sensitivity analysis showed that female (vs male) patients reported a higher pain severity score during their last year of life ([Supplementary Table 6](#)).



**Figure 1** Prevalence of pain during the last year of life (N=345). \*Pain score>0 on any item of the pain severity score; ^Pain score>3 on any item of the pain severity score.

Patients reporting higher pain severity (OR(95% CI): 1.37(1.20, 1.56)), pain interference (1.45(1.28, 1.65)), and pain prevalence (3.28(2.04, 5.29)) reported higher odds of utilising palliative care in the last year of life.

## Discussion and Conclusions

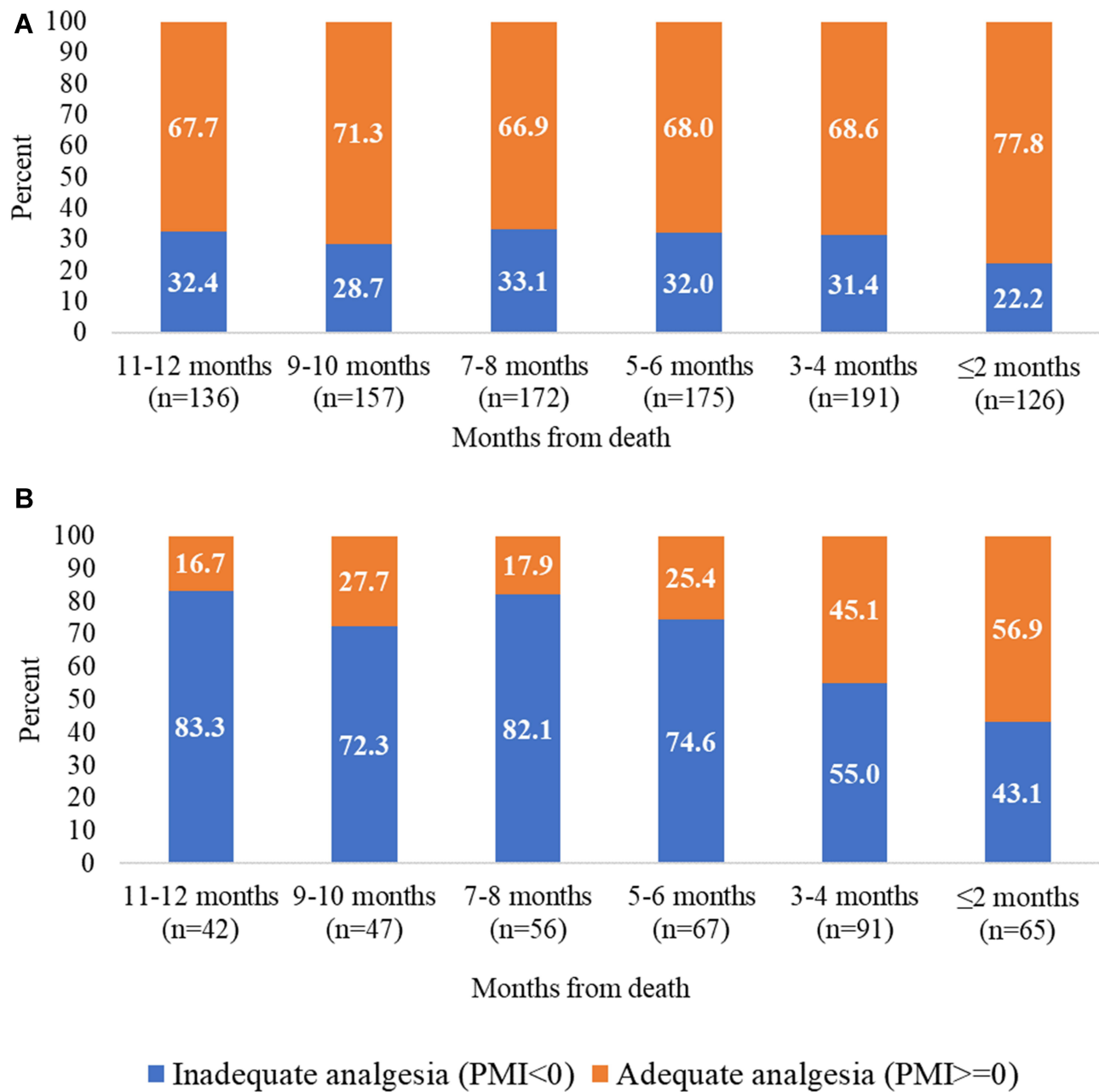
Although Singapore ranks 12th on the worldwide quality of death index,<sup>19</sup> the prevalence of pain, especially that of moderate to severe pain, was surprisingly high in our study sample. Further, among the sub-group of patients reporting moderate to severe pain, close to half (43%) had inadequate analgesia in the last 2 months before death, and this percentage was higher farther from death (83% at 11 to 12 months before death). Findings suggest that pain remains undertreated among patients with advanced cancer and the use of opioids to alleviate pain becomes more frequent only closer to death. This is supported by other studies.<sup>20</sup>

It should be noted that while calculating PMI, we considered pain medications prescribed over a 4-month period. The inadequacy of analgesia remained high despite using this conservative calculation. The literature has also documented multiple patient factors that influence pain management.<sup>21</sup> Patients and physicians may be hesitant to use strong and effective analgesics such as opioids because of their side effects and addiction potential.<sup>22,23</sup> One way of overcoming this is patient education and shared decision-making by involving patients in the pain management plan.<sup>24</sup> Regularly screening for pain during and in-between clinic visits starting early in the disease trajectory and educating both primary care physicians and oncologists regarding pain management guidelines could also help improve prescription of adequate analgesia and thus pain control even earlier in the disease trajectory.<sup>25</sup>

We also found that pain severity and pain interference scores were higher in the last month compared to 12 months before death; this difference was similar to previously discussed thresholds for minimally clinically significant differences in pain scores (1.2 (0.9–1.5)).<sup>26</sup> Younger patients and those with greater financial difficulties were more likely to experience pain during their last year of life. Younger patients may have less effective coping mechanisms<sup>27</sup> and may be less satisfied with pain treatment<sup>28</sup> than their older counterparts, and therefore report higher pain.

We find that female patients reported a higher pain severity score during their last year of life compared to male patients. While some previous studies report gender difference in pain severity and intensity,<sup>29,30</sup> others have found no difference in pain outcomes by gender.<sup>31</sup> Future research should explore whether these differences are due to differences in biology, reporting behaviour or inadequate analgesic prescription, and design gender-specific interventions to address these differences.

Patients experiencing greater financial difficulties may have reduced compliance or lower access to pain medications and interventions, and experience greater psychological distress, thus reporting greater pain.<sup>9,32</sup> Contrary to the literature,<sup>33</sup> we showed that patients with higher education experienced more pain than those with lower education. A possible explanation



**Figure 2** Adequacy of analgesia during the last year of life in (A) patients with any pain\*, (B) patients with moderate to severe pain<sup>^</sup>. \*Pain score>0 on any item of the pain severity score. <sup>^</sup>Pain score>3 on any item of the pain severity score.

could be that highly educated patients are more involved in their treatment decisions<sup>34</sup> and therefore better communicate the extent of their pain than those with lower education. Previous studies have shown that pain is a common reason for hospitalisation;<sup>35</sup> our study further adds that pain-related interference on daily activities and mood continues to remain high one month after an unplanned hospitalisation suggesting that pain should be monitored even after discharge from the hospital.

One of the strengths of our study is that it explores the pattern of pain prevalence longitudinally in patients with metastatic cancer throughout their last year of life. Moreover, the attrition rate in our study was lower compared to other studies on advanced cancer patients.<sup>36,37</sup> A limitation of our study is that we used the original method by Cleeland to calculate the inadequacy of analgesia.<sup>15</sup> This method does not take into account patient compliance, route of administration of analgesics, prescription of adjuvant analgesics<sup>38,39</sup> or patient preferences for pain control<sup>40,41</sup> and therefore may not reflect the actual extent of inadequacy of analgesia in the patient population. Second, although attrition was very

**Table 1** Predictors of Prevalence of Pain, Pain Severity and Pain Interference During Last Year of Life, N=345

	Prevalence of Pain <sup>a</sup>	Pain Severity <sup>b</sup>	Pain Interference <sup>c</sup>
	Odds Ratio (95% CI)	Coeff (95% CI)	Coeff (95% CI)
Months from death <sup>d</sup>	0.85 (0.81, 0.91)**	-0.15 (-0.19, -0.11)**	-0.38 (-0.57, -0.20)**
Months from death square <sup>e</sup>	-	-	0.01 (0.00, 0.03) *
Age	0.97 (0.95, 1.00)*	-0.01 (-0.03, 0.01)	-0.02 (-0.04, -0.00)*
Education (ref: secondary or below)			
Above secondary	1.95 (1.08, 3.53)*	0.65 (0.19, 1.12)**	0.84 (0.35, 1.34)**
Type of cancer (ref: others)			
Genitourinary/Gynecological	2.73 (0.96, 7.72)	1.01 (0.20, 1.82)*	1.42 (0.56, 2.29)**
Gastrointestinal	1.19 (0.45, 3.16)	0.52 (-0.25, 1.28)	0.75 (-0.07, 1.57)
Respiratory	1.34 (0.50, 3.54)	0.49 (-0.28, 1.26)	0.75 (-0.07, 1.57)
Breast	0.80 (0.28, 2.25)	0.08 (-0.75, 0.90)	0.17 (-0.71, 1.05)
Financial difficulty	1.16 (1.02, 1.33)*	0.15 (0.05, 0.25)**	0.11 (0.00, 0.21)*
Discharged from unplanned hospitalisation in the previous month (ref: No)			
Yes	1.31 (0.67, 2.56)	0.31 (-0.19, 0.80)	0.61 (0.08, 1.14)*
Discharged from planned hospitalisation in the previous month (ref: No)			
Yes	0.89 (0.49, 1.64)	0.24 (-0.21, 0.70)	0.27 (-0.21, 0.76)

**Notes:** \*\* and \*Denotes p-value<0.01 and p-value<0.05. <sup>a</sup>Binary variable; 1=yes if pain score>0 on any item of the pain severity score, 0 otherwise. <sup>b</sup>Average score of four self-reported items: worst and least pain in the past 24 hours, average pain, and pain at the time of survey. Each item was assessed on a scale of 0 to 10; higher score indicating greater severity. <sup>c</sup>Average of seven self-reported items on general activity, mood, walking ability, normal work, relations with others, sleeping well, and enjoyment of life in the past 24 hours on a scale of 0 to 10; higher score indicating higher pain interference. <sup>d</sup>Indicates time from patient's death; ranges from 1 to 12. <sup>e</sup>Included the quadratic term on time from death since it was not linear for pain interference.

small, it is possible that patients who did not respond to the survey were in greater pain. In that case, the prevalence and severity of pain may be even higher than what we have estimated. Third, we did not investigate the extent to which changes in pain scores resulted in changes in prescribed analgesics within the same patient; this could be a topic of future research. In conclusion, we demonstrate that prevalence of pain, particularly moderate to severe pain, is high closer to death among patients with metastatic cancer. Patients discharged from an unplanned hospitalisation reported high levels of pain interference. Health care professionals treating metastatic cancer patients should thus regularly monitor patients' pain levels, especially after discharge from an unplanned hospitalisation. Inadequacy of analgesia is likely to be higher for moderate to severe pain even earlier in the disease trajectory and requires greater attention. Future research should further explore reasons underpinning inadequate analgesic prescription.

## Declaration

SingHealth Centralized Institutional Review Board approved the study (2015/2781). This study was performed in compliance with the Declaration of Helsinki.

## Significance

The study reports the epidemiology of pain during the last year of life among patients with a solid metastatic cancer. The findings highlight a need for greater attention in monitoring and treatment of pain earlier in the disease trajectory, and increased attention to patients discharged from an unplanned hospitalisation.

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## Disclosure

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