The impact of pain and opioids use on survival in cancer patients
Results from a population-based cohort study and a meta-analysis

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Abstract

The study aimed to explore whether cancer-related pain and opioids use are associated with the survival of cancer patients, and perform a cohort study and a meta-analysis to quantify the magnitude of any association.

A retrospective cohort study was performed to analyze the impact of pain level, and opioids use on cancer-specific survival (CSS) in advanced cancer patients. Patients and relevant medical records were selected from the registry of the Radiation and chemotherapy division of Ningbo First Hospital between June 2013 and October 2017. Hazard ratios (HRs) and 95% confidential intervals (CIs) for CSS by opioids use were calculated by univariate and multivariate Cox regression analyses. The systematic review included relevant studies published before October 2018. The combined HRs and 95% CIs for overall survival (OS) and progression-free survival (PFS) were calculated using random-effect models.

A total of consecutive 203 cancer patients were included in the cohort study. Kaplan–Meier curves indicate a negative association between CSS and cancer-related pain or opioids requirement, but less evidence of an association with the dose of opioids use. Multivariate models revealed that the pain level and opioids requirement were associated with shorter CSS, after adjusting for significant covariates. The results of the meta-analysis indicated that postoperative opioids use had a poor effect on PFS, and opioids use for cancer-related pain was associated with poor OS in cancer patients, while intraoperative opioids use was not associated with cancer survival.

We concluded that cancer-related pain and opioids requirements are associated with poor survival in advanced cancer patients, and postoperative opioids use and opioids use for cancer-related pain may have an adverse effect on the survival of cancer patients.

Abbreviations: ANOVA = analysis of variance, CIs = confidential intervals, CSS = cancer-specific survival, DFS = disease-free survival, HRs = Hazard ratios, MOR = mu-opioid receptor, NOS = Newcastle-Ottawa Scale, OME = oral morphine equivalents, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, VAS = visual analogue score.

Keywords: cancer, opioids, pain, survival

1. Introduction

With the development of multiple anti-tumor treatment methods such as targeted therapy and immunotherapy, more and more patients with tumors can extend their survival, which lead to an increase in cancer survivors.[1] A major clinical challenge in treating cancer patients is the management of cancer pain. Cancer-related pain is significantly related to tumor stage. A systematic review reported that the prevalence of cancer pain rises with cancer progression and affects nearly 64% of patients with advanced cancer.[2] Cancer-related pain not only adversely

affects the quality of life of patients with advanced cancer, but also induces cancer progression through several mechanisms.[3] Successfully controlling cancer-related pain is an indispensable and important work in clinical practice.

Cancer-related pain management mainly relies on the three-step analgesic principle recommended by World Health Organization (WHO).[4] The use of analgesics is gradually transitioning from non-opioids to weak opioids to strong opioids. Although non-opioid analgesics such as adjuvant analgesia, glucocorticoids, radiation therapy, and acupuncture play a role in pain relief, opioids are still the most effective treatment for severe advanced cancer pain.[5] However, in addition to social issues such as drug addiction, the use of opioids can also cause some adverse effects in pain patients, such as respiratory depression, constipation, nausea, and dizziness, which may contribute to increasing mortality in pain patients.[6] Additionally, evidence indicates that opioids may promote cancer progression by activating the mu-opioid receptor (MOR), by increasing angiogenesis or by inducing immunosuppression.[7] Despite the many adverse effects of opioid use, the priority is to control cancer pain. Until the new non-pharmacological analgesics and non-opioids approaches can replace opioids to treat severe advanced cancer pain, the adverse effects of opioids on tumor patients are still worth studying.

As for the concerns of the potential adverse effects related to opioids use and pain, the current evidence regarding the association among opioids use, pain, and cancer survival remains debatable.[8,9] To address this problem, we conduct the cohort analysis and meta-analysis evaluating the independent contribution of cancer-related pain and opioids use to the overall survival (OS), progression-free survival (PFS) and cancer-specific survival (CSS) of cancer patients.

2. Materials and methods

2.1. Cohort study
2.1.1. Patients.
The study was approved by the ethic community of Ningbo First Hospital (No. R39, 20181220). Informed consent was signed at the time of admission. The consecutive advanced cancer patients who suffered cancer-related pain and were treated with opioids at the Radiation and chemotherapy division of Ningbo First Hospital between June 2013 and October 2017 were included as the opioid group, which was further divided into two subgroups of a low-dose group and a high-dose group. We also selected the consecutive contemporary inpatients who suffered advanced cancer but without opioids treatment as the non-opioid group. The patients in the non-opioid group are mainly patients with mild pain that can be controlled by non-steroidal anti-inflammatory drugs. These patients have no need for opioids. A total of 203 patients were enrolled in the analysis, with 97 in the opioid group (46 in the low-dose group, and 51 in the high-dose group) and 106 in the non-opioid group. Among these patients with advanced cancer included in this study, patients with nasopharyngeal carcinoma are mainly treated with radiation therapy, and other cancer patients are mainly treated with chemotherapy-based palliative treatment. Follow-up was conducted by telephone contact with the patients or their families.

2.2. Variables and Endpoint

Patient clinicopathological characteristics, visual analog score (VAS) for pain, and pharmacy data were obtained from patient records in Radiation and chemotherapy division. All oral and transdermal opioid prescriptions were collected. All opioids were concerted to Oxycontin equivalents per 12 h according to the transformation equation "Fentanyl patch 4.2 mg Q72h = MS Contin 30 mg Q12h = Oxycontin 15 mg Q12h".[10] The dose of opioids less than median dose 20 mg Oxycontin per 12 h was deemed as low dose, otherwise as the high dose. Pain levels were measured by VAS and categorized as three levels: low (0–3), moderate (4–6), and severe (7–10). We used the patients' maximum reported pain level before opioid treatment to analyze the effect of pain on the CSS. The primary endpoint of this study was CSS, defined as the time in months from first admission in Radiation and chemotherapy division to death due to cancer. For the patients alive, CSS was defined as the time between first admission and the data of the last follow-up.

2.3. Statistical analysis

After the normal distribution test of the clinicopathological characteristics data, the Chi-square test is used to compare differences in categorical variables, and analysis of variance (ANOVA) is used to compare differences in continuous variables. The CSS curves were constructed using the Kaplan–Meier methods, and log-rank test was used for pairwise comparison of survival. Univariate and multivariate Cox proportional hazards models were used to assess the effects of clinicopathological variables on CSS. The software SPSS 19.0 (SPSS Inc., Chicago, IL) was used for all analyses. A two-tailed $P < .05$ was considered significant in statistical tests.

2.4. Systematic review and meta-analysis
2.4.1. Search strategy.
This systematic review and meta-analysis were conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11] The electronic databases including PubMed, PubMed Central (PMC), Ovid, EMBASE, and Web of Science were searched from inception to October 20, 2018, for articles investigating the effects of pain and opioids use on cancer survival. Our search strategy included terms for opioids use (opioid, anesthetic, or analgesia), cancer (cancer, tumor neoplasm, or carcinoma), and survival (survival, prognosis, death, or mortality). The references in identified articles were also reviewed manually for possible inclusions.

2.4.2. Selection and exclusion criteria.
Eligible studies were enrolled in this meta-analysis in line with the following criteria:

1. they included a cohort of cancer patients in which exposure to opioids treatment for cancer-related pain was measured and recorded;
2. the outcomes of follow-up were in terms of PFS, recurrence-free survival (RFS), disease-free survival (DFS), OS or CSS;
3. they included sufficient data to estimate the hazard ratio (HR) and its 95% CI according to the opioids use.

When multiple articles based on the same population, the most recent or complete one was enrolled. The exclusion criteria were the following:

1. articles without adequate survival data for extracting HR and its 95% CI;
2. case reports, reviews, letters to the editor, and summary of the meeting.

Titles and abstracts were screened to identify eligible studies, and then the full-text manuscripts were evaluated carefully. Any disagreement was resolved by mutual discussion.

2.4.3. Data extraction and quality assessment.
Relevant data was extracted from all the eligible studies by two reviewers independently using a purpose-designed form. Any discrepancy was resolved via consensus. The following items were recorded: first author's name, publication year, country, study years, patient's age, gender, tumor type, tumor stage, sample size, basis for grouping, cutoff value, the time of opioids treatment, the formulation of opioids, period of follow-up, and assessments for outcomes. HRs and 95% CIs were also collected as applicable. If the survival outcomes in the eligible studies were presented by both univariate and multivariate Cox regression analyses, the results of multivariate Cox regression analyses were primarily selected. For studies in which HRs was not provided explicitly, we extracted the survival estimates from the original data or Kaplan–Meier curves using Tierney's methods.[12,13] Quality assessment for studies was performed by the Newcastle-Ottawa Scale (NOS).[14] A study achieving a score of six or more was regarded as a high-quality one.

2.5. Statistical analysis

The statistical analysis was conducted using software STATA 12.0 (Stata Inc., TX). Pooled HRs and 95% CIs were used to assess the effect of opioids use on cancer survival. Heterogeneity was evaluated using I-squared statistics.[15] A random-effect model was applied if $I^2 > 50\%$; otherwise, a fixed-effect model was used. To explore the possible sources of heterogeneity and further investigate the effect in different applications, subgroup analyses were adopted. Potential publication bias was evaluated by the Begg's and Egger's test. Finally, we also performed sensitivity analyses by removing each single study to assess the stability of the results.

3. Results

3.1. Cohort study
3.1.1. Association of opioids use and dose with clinico-pathological characteristics.
A total of 203 patients were included in the cohort study. Among them, 106 patients never required opioids. The opioids were required in 97 patients, which were further divided into the low-dose group (n = 46) and high-dose group (n = 51). Two patients in the non-opioids group were missing during the follow-up. The patients' clinicopathological factors and their association with opioids requirement and dose were presented in Table 1. When age was analyzed as continuous variable, the opioids required group was younger than the non-opioid group, and high-dose group was younger than the low-dose group ($P < .01$). When age was converted as a categorical

Table 1
Association of opioids use with the clinicopathologic characteristics of 203 patients with advanced cancer.

Characteristic	Total, n=203	Non-opioid, n=106	Opioid, low-dose, n=46	Opioid, high-dose, n=51	P
Gender, n (%)					
Male	117 (57.6)	55 (51.9)	26 (56.5)	36 (70.6)	.084
Female	86 (29.8)	51 (48.1)	20 (43.5)	15 (29.4)	
Age, years					
Mean (SD)	56.61 (10.205)	57.49 (8.887)	56.41 (11.811)	54.96 (11.175)	<.01
≤60	130 (64.0)	65 (61.3)	31 (67.4)	34 (66.7)	.699
>60	73 (36.0)	41 (38.7)	15 (32.6)	17 (33.3)	
Primary cancer, n (%)					
Bladder cancer	2 (1.0)	1 (0.9)	0 (0)	1 (2)	.903
Brain cancer	5 (2.5)	3 (2.8)	1 (2.2)	1 (2.0)	
Breast cancer	19 (9.4)	11 (10.4)	3 (6.5)	5 (9.8)	
Cervical cancer	26 (12.8)	13 (12.3)	8 (17.4)	5 (9.8)	
Colorectal cancer	18 (8.9)	10 (9.4)	6 (13.0)	2 (3.9)	
Esophageal cancer	7 (3.4)	4 (3.8)	0 (0)	3 (5.9)	
Gastric cancer	9 (4.4)	6 (5.7)	2 (4.3)	1 (2.0)	
Kidney cancer	1 (0.5)	1 (0.9)	0 (0)	0 (0)	
Liver cancer	6 (3.0)	3 (2.8)	0 (0)	3 (5.9)	
Lung cancer	50 (24.6)	25 (23.6)	12 (26.1)	13 (25.5)	
Malignant thymoma	2 (1.0)	1 (0.9)	0 (0)	1 (2.0)	
Nasopharyngeal cancer	42 (20.7)	20 (18.9)	12 (26.1)	10 (19.6)	
Oral cavity cancer	3 (1.5)	1 (0.9)	1 (2.2)	1 (2.0)	
Ovarian cancer	3 (1.5)	3 (2.8)	0 (0)	0 (0)	
Pancreatic cancer	2 (1.0)	1 (0.9)	0 (0)	1 (2.0)	
Pharyngeal cancer	4 (2.0)	1 (0.9)	1 (2.2)	2 (3.9)	
Prostate cancer	3 (1.5)	2 (1.9)	0 (0)	1 (2.0)	
Pain level					
Low	143 (70.4)	106 (100)	19 (41.3)	18 (35.3)	<.001
Moderate	52 (25.6)	0 (0)	23 (50.0)	29 (56.9)	
Severe	8 (3.9)	0 (0)	4 (8.7)	4 (7.8)	
Opioid type					
Fentanyl	5 (5.2)	NA	4 (8.7)	1 (2.0)	.296*
MS Contin	3 (3.1)	NA	1 (2.2)	2 (3.9)	
OxyContin	89 (91.8)	NA	41 (89.1)	48 (94.1)	

n = number, NA = not applicable, SD = standard deviation.
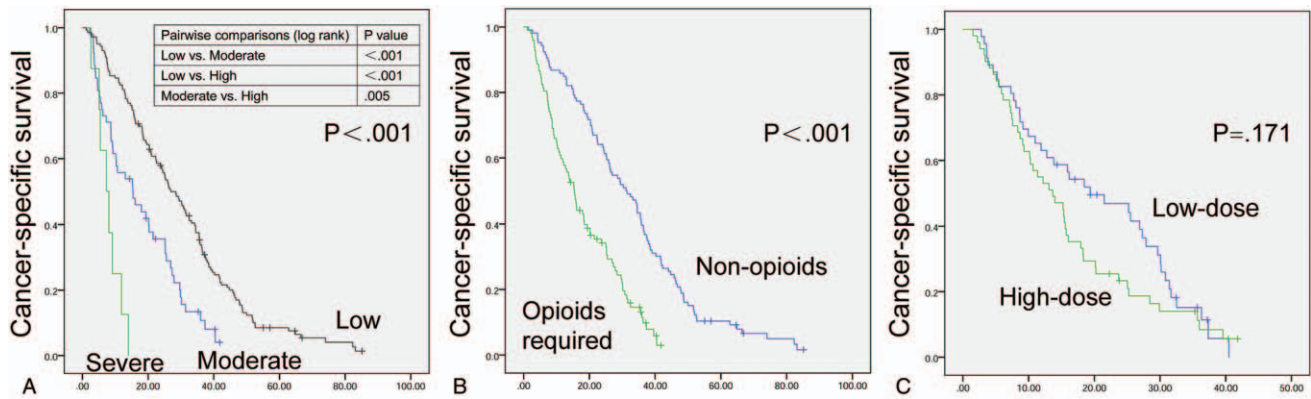* The low-dose group vs the high-dose group.

Figure 1. Kaplan–Meier survival curves depicting cancer-specific survival according to pain level (A), opioids requirement (B) and opioids dose (C). (A) Kaplan–Meier curves of high-dose and low-dose groups.

variable, there was no difference among the three groups. The pain level in the opioid required group was more severe than that in the non-opioid group, but there was no significant difference between the low-dose group and the high-dose group. Oxy-Contin was the most common drug used in both the low-opioid group and the high-opioid group, and there was no significant difference in the opioid type between the two groups (*P*=.296). The gender and the cancer types did not differ among the three groups.

3.1.2. Influence of pain and opioids requirement on the survival of cancer patients.
Kaplan–Meier survival curves for CSS based on the pain level and opioids requirement are shown in Figure 1A and B. It shows that the patients with low pain level had better CSS than those with moderate and severe pain (*P*<.001), and patients with moderate pain had better CSS compared with those suffering from severe pain (*P*<.01). Opioids requirement is significantly associated with shorter CSS (*P*<.001). Results of univariate and multivariate Cox regression of prognostic factors for CSS are presented in Table 2. In univariate Cox regression analysis, age and gender are not associated with survival, but more severe pain (*P*<.001) and

opioids requirement (*P*<.001) predict short CSS. In multivariate Cox regression analysis that adjusted for the pain level and opioids requirement, the severe pain (*P*<.001) and opioids requirement (*P*<.01) are still related to worse CSS. Still, moderate pain is no longer associated with CSS (*P*=.381).

3.1.3. Influence of opioids dose on the survival of cancer patients.
The opioids high and low dose groups were analyzed for exploring the effect of opioid dose on CSS. Kaplan–Meier survival curves for CSS based on the opioids dose are presented in Figure 1C. There was no significant separation between the low-dose group and the high-dose group (*P*=.171). The Cox regression analyses are shown in Table 3. Based on the univariate and multivariate Cox regression analyses, gender, age, moderate pain, and opioids dose are not related to the CSS. Still the patients with severe pain levels exhibited the poor prognosis (*P*<.01).

3.2. Systematic review and meta-analysis
3.2.1. Search results and study characteristics. We searched 32,715 articles through the electronic databases and three articles from the references. After scanning the titles and abstracts, only 28 records were deemed eligible (Fig. 2). They were all cohort

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Table 2

Univariable and multivariate Cox regression analyses predicting CSS in 203 advanced cancer patients.

Characteristic	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Female	1			
Male	1.20 (0.90, 1.61)	.217		
Age, years				
≤60	1			
>60	1.13 (0.84, 1.51)	.438		
Pain level				
Low	1		1	
Moderate	2.14 (1.50, 3.04)	<.001	1.23 (0.78, 1.94)	.381
Severe	7.38 (3.44, 15.80)	<.001	4.38 (1.96, 9.82)	<.001
Opioids requirement				
No	1		1	
Yes	2.50 (1.81, 3.46)	<.001	2.10 (1.37, 3.23)	<.01

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio.

Table 3

Univariable and multivariate Cox regression analyses predicting CSS in 97 opioids required patients.

Characteristic	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Female	1			
Male	1.31 (0.83, 2.08)	.242		
Age, years				
≤60	1			
>60	1.54 (0.98, 2.42)	.063		
Pain level				
Low	1		1	
Moderate	1.23 (0.78, 1.95)	.375	1.20 (0.75, 1.90)	.449
Severe	4.27 (1.88, 9.70)	<.01	4.22 (1.86, 9.57)	<.01
Opioids dose				
Low	1		1	
High	1.35 (0.88, 2.08)	.172	1.34 (0.87, 2.06)	.190

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio.
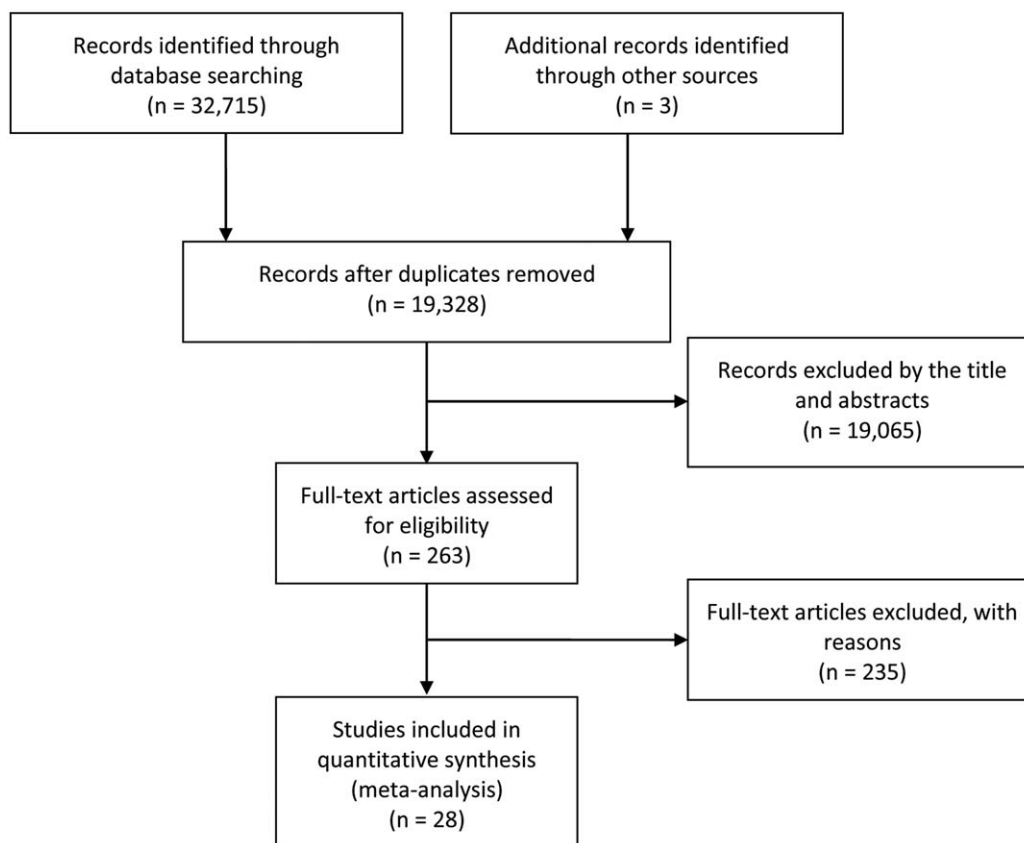
Figure 2. Flow diagram of the study selection process.

studies, which included one prospective cohort study[8] and 27 retrospective cohort studies. Seven studies reported outcomes for intraoperative opioids use; four studies reported postoperative opioids use, and 17 reported opioids use in the treatment of cancer-related pain. According to the NOS, the quality of these 28 articles ranged from 5 to 9, with a mean of 7.4. The main characteristics of the included studies were listed in Table 4.

3.2.2. Meta-analysis results. In our analysis, we merged PFS, DFS, and RFS together considering the similarities among them. Since only one study[16] reported CSS and most studies used OS, it was difficult to conduct a meta-analysis by listing the single study separately. The purpose of this study was to explore the impact of experimental factors on the long-term survival of cancer patients, and CSS could more accurately describe the effects of experimental factors on the patient's long-term survival than OS, so we boldly merged CSS and OS together.[17] A total of 26 articles with 28 studies evaluated OS, and 11 articles with 12 studies evaluated PFS. The random-effects models were used to pool the HRs and 95 CIs because of obvious statistical heterogeneity. Compared with the patients with no opioids use or low-dose opioid use, the opioids use, or high-dose opioids use groups were associated with an inferior PFS (HR = 1.086, 95%CI 1.011–1.166, P = .024) and OS (HR = 1.006, 95%CI 1.001–1.012, P = .015) (Fig. 3A and B).

The included studies reported opioids used for different therapeutic purposes and in various types of cancer. To explore the possible correlation between opioids use and cancer survival

based on three main features, including therapeutic purpose, therapeutic dose, and cancer type, we performed a series of subgroup analyses. The first subgroup analysis was performed based on therapeutic purposes. The results indicated that intraoperative opioids use (HR = 1.009, 95%CI 0.913–1.116, P = .857) and opioids used for cancer pain management (HR = 1.051, 95%CI 0.979–1.130, P = .171) had no effect on PFS, while postoperative opioids use (HR = 1.760, 95%CI 1.264–2.450, P = .001) was associated with poor PFS (Fig. 4A). As for the OS, the intraoperative opioids use (HR = 1.006, 95%CI 0.923–1.097, P = .888) and postoperative opioids use (HR = 1.300, 95%CI 0.948–1.781, P = .103) had no effect on the OS. Still, opioids use for cancer pain treatment (HR = 1.100, 95%CI 1.061–1.141, P < .001) had poor effect on the OS (Fig.4 B).

In the opioids used for cancer pain treatment subgroup, we analyzed the effect of opioids on PFS and OS stratified by therapeutic dose or cancer type. High-dose opioids use (HR = 1.080, 95%CI 1.045–1.116, P < .001) was associated with poor PFS, whereas the requirement of opioids had no effect on PFS (Fig. 5A). Opioids use in prostate cancer (HR = 1.080, 95%CI 1.045–1.116, P < .001) had a bad effect on PFS, whereas that in breast cancer did not (Fig. 5B). With respect to OS, opioids required (HR = 1.532, 95%CI 1.253–1.873, P < .001) and high-dose opioids use (HR = 1.053, 95%CI 1.019–1.088, P = .002) were all related to poor OS (Fig. 5C). Opioids use was associated with poor OS in breast cancer (HR = 1.590, 95%CI 1.302–1.942, P < .001), malignant hematological diseases (HR = 1.509, 95% CI 1.092–2.085, P = .013), colorectal cancer (HR = 1.564, 95%

Table 4

Main characteristics of studies included in the meta-analysis.

Author	Year	Country/region	Study recruitment years	Age (years)	Gender	Tumor type	Stage	Sample size (n)	Grouping (n)	Cut off	Using time	Opioid formulations	Follow-up (months)	Outcomes	NOS
Hasegawa T [8]	2018	Japan	2013–2015	Median 75.2, range (43–95)	M 98; F 52	NSCLC	Advanced/recurrent	150	No opioid (86) vs opioid (64); High (19) vs Low (45) doses	0mg; <60mg OME	Pain management	NA	Median 20.1, interquartile range (9.37–27.3)	OS	7
Du KN [26]	2018	USA	2000–2015	Mean 62.43	M 664; F 109	Esophageal cancer	I 132; II 266; III 375	725	High (607) vs low (166) doses	<710 µg fetanyl equivalents	Intraoperative	Fentanyl, sufentanil, remifentanil, hydromorphone	Median 79.44, range (3.88–186.56)	RFS; OS	9
Oh TK [27]	2018	Korea	2005–2011	Mean 63.5 (SD 8.9)	M 116; F 5	Esophageal cancer	I 40; II 58; III 23	121	NA	0 mg; <630mg OME	Intraoperative; postoperative	Remifentanil; morphine, hydromorphone, fentanyl, oxycodone, codeine and tramadol	NA	OS; RFS	5
Zyla D [9]	2018	USA	2005–2013	Mean 69, range (23–98)	M 778; F 608	Non-hematologic malignancies; lung cancer	IV	1386	High (624) vs low (782) doses	<5mg OME	Pain management	NA	NA	OS	8
Kimura M [28]	2018	Japan	2014–2016	Median 67, range (37–83)	M 29; F 18	Colorectal cancer	Advanced/recurrent	47	No opioid (42) vs opioid (5)	0 mg	Postoperative	NA	NA	OS	7
Oh TK [29]	2017	Korea	2006–2010	Mean 65.12, SD 7.87	M 147; F 11	Esophageal squamous cell carcinoma	I 83; II 93; III 82	258	High-dose (135); low-dose (123)	1783.5mg cumulative opioid use	Postoperative	Morphine, fentanyl	At least 60	RFS; OS	9
Patino MA [30]	2017	USA	2003–2016	Median 60.5,IQR (53–71)	M 189; F 79	Oral cancer	pT1 58; pT2 91; pT3 19; pT4 100	268	High-dose (134); low-dose (134)	1081.63 µg fentanyl equivalents	Intraoperative	Fentanyl, sufentanil, remifentanil, hydromorphone and morphine sulfate	NA	RFS; OS	8
Tai YH [31]	2017	China	2011–2014	68±14	M 1017; F 662	Colorectal cancer	I 443; II 653; III 583	1679	High-dose (802); low-dose (877)	3.0 µg/kg fentanyl dose	Intraoperative	Fentanyl	Median 31.54, IQR(20.76–46.62)	RFS; OS	8
Tan X [32]	2017	USA	2006–2012	Mean 72.3, range (29, 103)	F 10773	Breast cancer	I 6470; II 3510; III 793	10773	Yes (1280); no (9493)	Use of opioids for at least 90 days	Pain management	Codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, methadone, oxycodone, oxymorphone, tapentadol, tramadol, pentazocine	At least 2 years	OS	8
Sathornviyapong A [33]	2016	Thailand	2013–2015	Median 63, range (19–95)	M 162; F 155	Gastrointestinal cancer 127, primary lung cancer 57, head and neck cancer 43, genitourinary cancer 34, breast cancer 22, and others 34	Advanced/recurrent	317	High-dose (73); low-dose (244)	≤ 30 mg/day OME	Pain management	Tramadol hydrochloride, morphine sulfate, pethidine hydrochloride, fentanyl, codeine phosphate and methadone hydrochloride	NA	OS	7
Chang WP [34]	2015	China	2004–2007	Median 67, IQR (53–76)	M 1544; F 758	Digestive tract cancer 1075, respiratory tract cancer 281, breast cancer 95, genitourinary tract cancer 446; head and neck cancer 213, and other cancers 192	NA	2302	Yes (1088); No (1214)	0mg	Pain management	Codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, and oxymorphone	36 months	OS	6
Cata JP [35]	2015	USA	2004–2012	Median 64.99, IQR (57.95–71.13)	M 160; F 35	Laryngeal squamous cell cancer	I/II 14; III/IV recurrent 181	195	NA	NA	Intraoperative	Fentanyl, sufentanil, remifentanil, hydromorphone	60 months	RFS; OS	6
Wang K [23]	2015	China	2006–2011	Median 60, range (20–79)	M 698; F 286	NSCLC	Early stage	984	Use (302) vs. No use (682)	0 mg	Postoperative	Pethidine 4%; Fentanyl 0.2%; dihydrocodeine 3.3%; morphine 13.8%; tramadol 2.9%; codeine 5%; bucinnazine 1.4%	Median 49, range (1–92)	OS; DFS	9

(continued)

Table 4
(continued).

Author	Year	Country/ region	Study recruitment years	Age (years)	Gender	Tumor type	Stage	Sample size (n)	Grouping (n)	Cut off	Using time	Opioid formulations	Follow-up (months)	Outcomes	NOS
Cronin-Fenton DP [36]	2015	Denmark	1996–2008	≤29 120; 30–39 1591; 40–49 5962; 50–59 10395; 60–69 10450; 70–79 4742; ≥80 928	F 34188	Breast cancer	I 12962; II 15254; III 5972	34188	Use (15957) vs No use (18231)	0mg	Pain management	Tramadol 36%; Codeine 23%; Oxycodone 11%; Ketobemidone 10%; Morphine 9%	Median 85.2	RFS	8
Minami S [37]	2015	Japan	2008–2013	Mean 70.6, SD 8.8	M 271; F 98	Lung cancer	Advanced/ Recurrent	369	High-dose (101); low-dose (268)	<60mg OME	Pain management	Oxycodone, fentanyl, morphine, tramadol	NA	OS	6
Call TR [38]	2015	USA	2001–2012	Median 66, range (56–73)	M 76; F 68	Pancreatic adenocarcinoma	I 15; II 108; III 18; IV 3	144	NA	NA	Intraoperative	Fentanyl, sufentanil; Morphine, hydromorphone	Median 14.6, IQR (8.1–27.7)	OS	6
Zylla D [39]	2014	USA	2003–2010	Median 63, range (45–83)	M 205; F 4	NSCLC	IIIB 61; IV 148	209	High-dose (121); Low-dose (88)	<5mg OME	Pain management	NA	NA	OS	7
Cata JP [40]	2014	USA	2004–2009	Median 66	M 476; F 425	NSCLC	I 486; II 187; III 226	901	High-dose (450); Low-dose (449)	10.15 μg/kg fentanyl equivalents	Intraoperative	Sufentanil, remifentanil, and fentanyl	60 months	RFS; OS	8
Halabi S [41]	2014	USA	2005–2013	Median 69, IQR (63–75)	M 345	Prostate cancer	IV	345	Users (108) vs Non-users (174)	0 mg	Pain management	Opioid analgesic	NA	OS	8
Kripp M [42]	2014	Germany	1998–2008	Median 70.5, range (15–98)	NA	Malignant hematological diseases	NA	290	Users (165) vs non-users (125)	0 mg	Pain management	Morphine derivatives	NA	OS	7
Zylla D [43]	2013	USA	1995–2010	NA	M 593	Prostate cancer	IV	113 in test cohort, 480 in validation cohort	NA	<5mg OME	Pain management	Oxycodone, hydrocodone, codeine, morphine, hydromorphone, fentanyl, and methadone	NA	PFS; OS	7
Alsiraty SA [44]	2013	Egypt	2008–2011	Median 53, range (18–81)	M 53; F 70	Breast 22, colorectal 15, liver 12, pancreas 9, lung 8, urinary bladder 8, pleural mesothelioma 6	Advanced/ recurrent	123	High-dose (66); low-dose (57)	<120 mg OME	Pain management	Fentanyl, morphine, and tramadol	NA	OS	7
Inoue Y [16]	2013	Japan	2000–2011	Mean 64, range (29–85)	M 146; F 99	Colorectal cancer	Advanced/ recurrent/ metastatic	245	Users (117) vs non-users (128)	0 mg	Pain management	Morphine, oxycodone, fentanyl	NA	CSS	7
Azoulay D [45]	2011	Israel	2006–2007	Mean 71.7±13.9	M 48; F 66	90% solid tumor, 10% hematologic	Advanced/ recurrent/ metastatic	114	High-dose (39); Low-dose (75)	<120 mg OME	Pain management	Morphine, fentanyl, oxycodone, and methadone	NA	OS	6
Skipworth RJ [46]	2011	UK	NA	Median 67, range (43–94)	M 90	Pancreatic cancer	Advanced	90	Users (25) vs non-users (65)	0 mg	Pain management	Opioids	NA	OS	6
van Hooft JE [47]	2010	Netherlands	2005–2008	Median 69, range (39–88)	M 54; F 47	Malignant GOO (pancreatic cancer 64, cholangiocarcinoma 12, gastric cancer 9, metastatic disease 8, duodenal cancer 4, gallbladder cancer 2, cancer of the ampulla of vater 2	Advanced/ recurrent/ metastatic	101	Users (19) vs. Non-users (82)	0 mg	Pain management	Morphinomimetics stronger than tramadol	NA	OS	7
Forget P [48]	2010	Belgium	2003–2008	Mean 59, SD 14	F 319	Breast cancer	Early stage	319	Users (227) vs non-users (92)	0 mg	Intraoperative	Sufentanil	Median 27.3, range (13–44)	RFS	8
Bengoechea I [49]	2010	Spain	2003-2007	Mean 68, SD 12	M 137; F 86	Respiratory 46, digestive 101, gynecologic 20, urologic 22, nervous system 10, other 24	Advanced/ recurrent	223	High-dose (99); low-dose (124)	<120 mg OME	Pain management	Morphine	NA	OS	6

CSS = cancer-specific survival, DFS = disease free survival, F = female, M = male, NA = not acquired, NSCLC = non-small cell lung cancer, OME = oral morphine equivalents, OS = overall survival, PFS = progression free survival, RFS = relapse free survival.
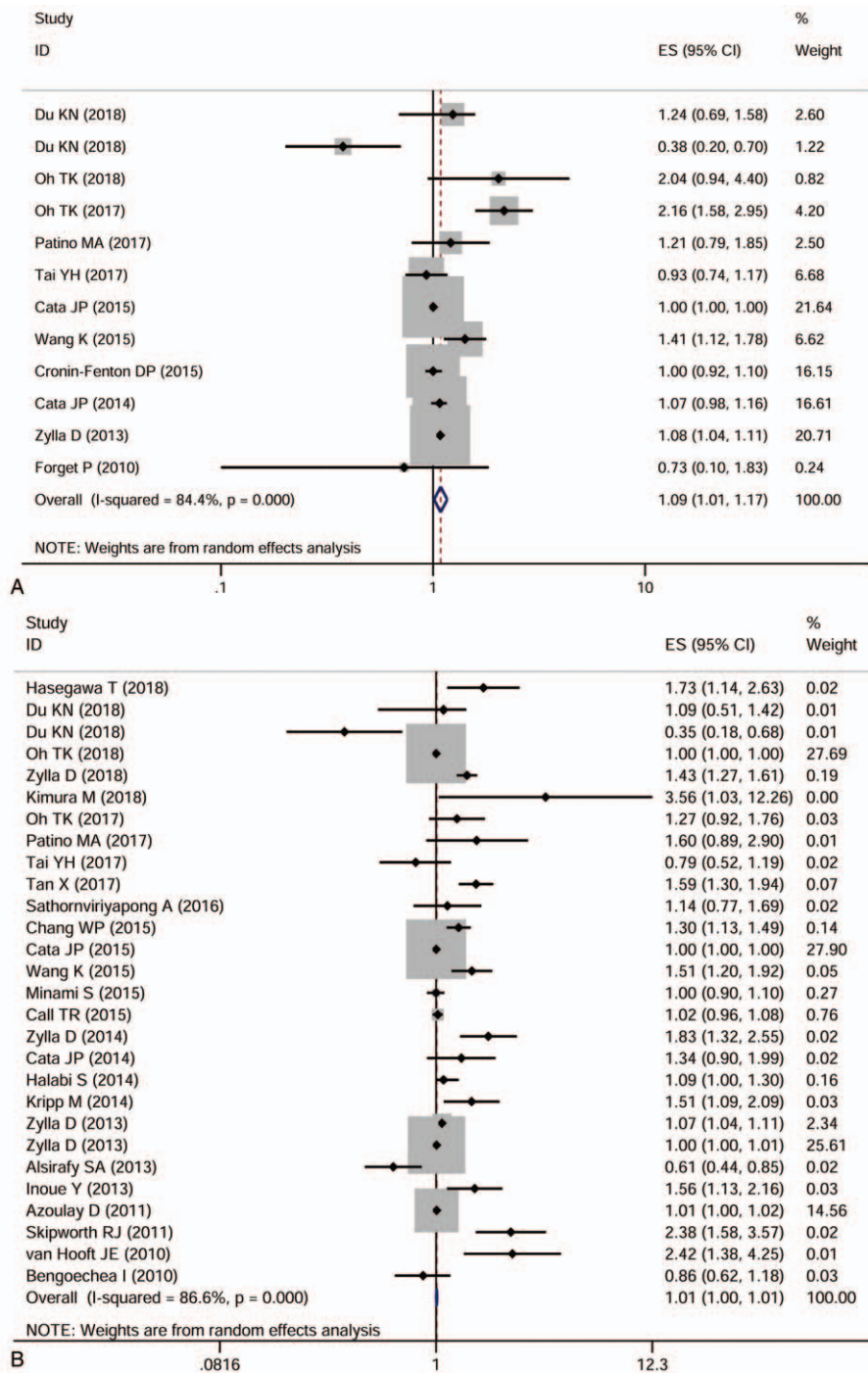
Figure 3. Forest plots of studies evaluating the effect of opioids use on cancer progression-free survival (A) and overall survival (B).

CI 1.134–2.158, $P = .006$) and pancreatic cancer (HR = 2.378, 95%CI 1.583–3.572, $P < .001$), but not in lung cancer, prostate cancer, and mixed cancer types (Fig. 5D).

3.2.3. Publication bias and Sensitivity analysis. Publication bias for PFS and OS were not significant based on the Begg's and Egger's test. Sensitivity analysis performed by removing omitting each single study sequentially indicated that the synthetic estimates of the effect of opioids use on PFS and OS did not vary significantly, which meant that the results of this meta-analysis were robust.

4. Discussion

In this study, we found that moderate to severe pain and the requirement of opioids were associated with reduced CSS in a variety of cancer patients. Cancer-related pain is one of the most morbidities experienced by patients with advanced cancer.
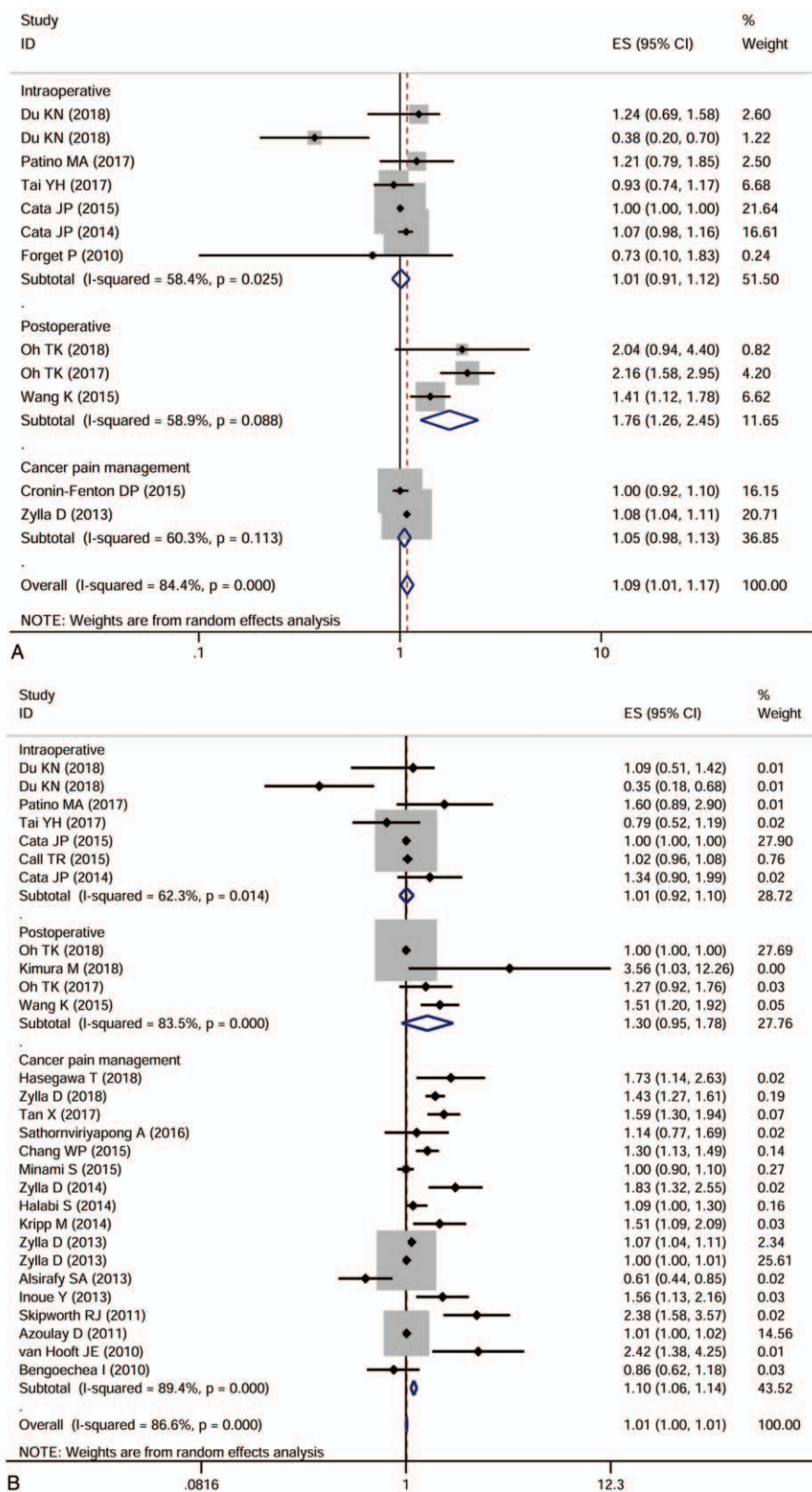
Figure 4. Forest plots of subgroup analyses evaluating the effect of opioids use on cancer progression-free survival (A) and overall survival (B) according to different therapeutic purposes.
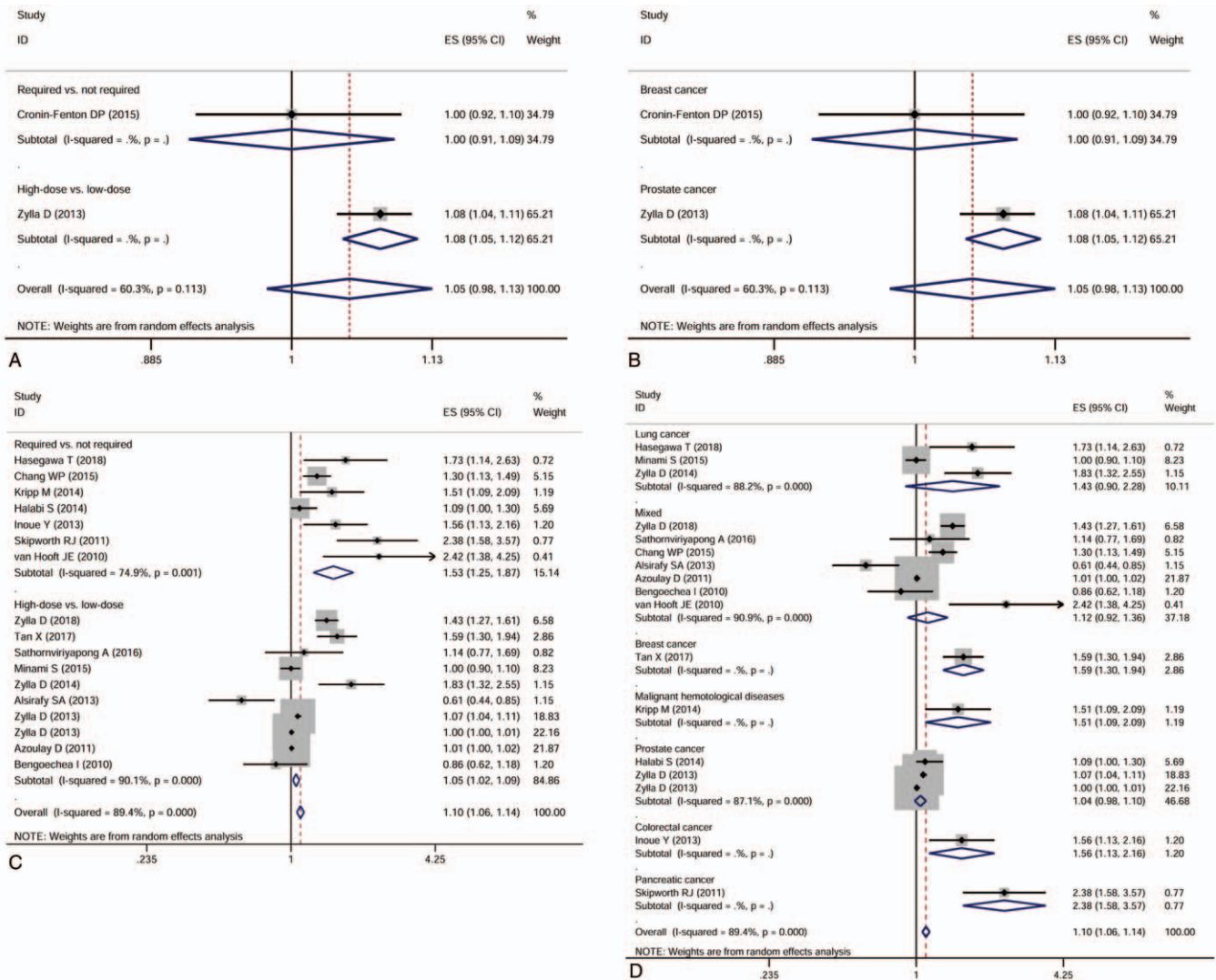
Figure 5. Forest plots of subgroup analyses evaluating the effect of opioids use on cancer progression-free survival based on therapeutic dose (A) and cancer types (B), and the effect of opioids use on overall survival based on therapeutic dose (C) and cancer types (D).

Recent studies reported that pain was an important predictor of clinical outcome in patients with cancer.[15,18,19] Armstrong et al[19] considered that pain could be a statistically significant prognostic factor for OS based on the TAX 327 trial. Roviello et al[15] identified pain as a predictive factor for OS in men with prostate cancer. The results in the present study are consistent with previous researches on other cancers. Increased pain and opioid demand were mostly due to disease progression (e.g., bone metastases, extensive pleural invasion, and vital organs compression), which were associated with significant morbidity and mortality.[18,20] Pain itself also affects the survival of patients, because pain can make it hard for patients to eat, sleep, or even continue cancer treatments.[20] Accurate assessment of pain and coverage of all patients in studies using pain as a variable is important. Pain assessment in most previous studies and in this study has used patient self-reporting methods. For non-verbal patients who suffer pain, the Critical Care Pain Observation Tool (CPOT) and Behavioral Pain Scale (BPS) behavioral pain scales can play a major role in pain assessment.[21]

In addition to pain, opioids may also affect cancer patients' survival through respiratory depression, delirium, addiction, or directly acting on tumor cells.[7,8,22] The patients who suffered severe pain were more likely to require opioids treatment. Based on the comparison between the non-opioid group and opioid group, we couldn't distinguish this poor effect owing to opioids use or pain because there were more patients with moderate to severe pain in the opioid demand group. To explore the effect of opioids use on cancer survival, we compared the high-dose group with the low-dose group. The high-dose group survived worse than the low-dose group, but the statistical difference was not obvious. These results were not consistent with the previous results, which reported that opioids use, especially at high-dose, was associated with short survival in cancer patients.[9,23] The inconsistency may be due to our small sample size, as the sample size of each subgroup after subgrouping is reduced.

In terms of the purpose of opioid use, we found that intraoperative opioids use was not associated with cancer survival. In contrast, postoperative opioids use and opioids use

for cancer pain treatment had a bad effect on cancer survival. Bimonte summarized in his review that different outcomes might be due to different concentrations and/or duration of use of opioids.[22] Intraoperative analgesia tends to use a large dose of intravenous short-acting analgesics; Postoperative analgesia with optimal analgesia and minimum dose as a principle is more likely to continue to use short-acting analgesic drugs for a certain period time; while the analgesic effect of cancer pain is often based on oral long-acting analgesics. At present, oxycodone has an increasing trend in the application of cancer pain. In addition to the total dose of opioids, drug type, frequency, single-dose, and duration of medication may be the factor that affects the outcomes.[22]

The strength of the study lies in conducting a meta-analysis with a large population to assist the cohort study for exploring the effect of pain and opioids use on cancer survival. There are also some limitations to this study. First, our cohort study and the studies included in the meta-analysis are observational studies, so there is the potential residual confounding that we could not control. Second, the follow-up period in some included studies was relatively short (median 20 months), which may not be sufficient to assess the effect of opioids use fully. Considering the short life span of advanced cancer patients, the 2-year follow-up may be enough to draw statistical conclusions. Third, the patients included in this study were mainly palliative care patients with relatively poor physical conditions, and patient self-reporting assessment of pain levels for such patients may have some deviations. Using patient self-reporting assessment methods in combination with CPOT and BPS tools to evaluate pain values in future studies may lead to more accurate results.[24,25] Fourth, the dose and formulation of opioids in different studies varied, so it is hard for us to determine the dose and opioids form at work accurately. In our cohort study, the main form of opioids is Oxycontin. As for the studies included in the meta-analysis, the dose of different opioids form was converted to OME, which may play a clinical reference role in opioids dose and formulations. Based on the above limitations, the results should be interpreted with caution.

In conclusion, combining the results of this cohort study and the meta-analysis suggest that cancer-related pain and opioids requirements are associated with poor survival in advanced cancer patients, and postoperative opioids use and opioids use for cancer-related pain may have a negative effect on survival of cancer patients. Although opioids may promote cancer progression in some cases, controlling severe pain symptoms remains a priority. The development of other analgesic modes such as non-pharmacological and non-opioids modes, and improvements in opioids should address this clinical problem. Further prospective studies are needed to clarify the effect of pain and opioids use on cancer survival.

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