The negative impact of opioids on cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis

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Abstract

Background

As one of the most effective analgesics, opioids are essential for patients with cancer-related pain, even in the context of the opioid abuse crisis. The current meta-analysis aimed to identify whether concomitant exposure to opioids can affect the efficacy of ICIs and lead to a worse prognosis.

Methods

PubMed, Embase, and the Cochrane Library were searched Based on the PRISMA checklist, through April 2022, for the following terms: ("opioids" OR "concomitant medication") AND ("Neoplasm" OR "Carcinoma" OR "Cancer" OR "Tumor") AND ("Immunotherapy" OR "Immune Checkpoint Inhibitor" OR "PD-L1 Inhibitor" OR "PD-1 Inhibitor" OR "CTLA-4 Inhibitor"). The outcomes considered were overall survival (OS) and progression-free survival (PFS) calculated using the random-effects or fixed-effects model.

RESULTS

After screening 531 studies, a total of 7 articles involving 2690 patients were eligible for quantitative analysis. The use of opioids was negatively correlated with OS (HR = 1.75, 95%CI = 1.32–2.31, $P < .001$; $I^2 = 81\%$, $P < .001$) and significantly reduced the PFS (HR = 1.61, 95%CI = 1.41–1.83, $P < .001$; $I^2 = 0\%$, $P = .63$) of patients treated with ICIs. Similar results were obtained in each subgroup analysis. While NSAIDs could lead to poor OS (HR = 1.25, 95% CI = 1.03–1.51, $P = 0.02$) but not PFS (HR = 1.11, 95% CI = 0.89–1.39, $P = 0.36$) for ICIs patients. And sensitivity analyses confirmed the reliability of the results.

CONCLUSIONS

Opioids significantly reduced OS and PFS in patients receiving ICI therapy. Thus, the use of different types of opioids should be considered with caution, and it is necessary to actively develop alternative treatments.

Introduction

Since being approved in 2014, immune checkpoint inhibitors (ICIs), represented by PD-1, PD-L1, and CTLA-4, have significantly improved the prognosis of patients and changed the treatment paradigm for several solid tumors[1-4]. However, ICIs also show some shortcomings in clinical application, including inconsistent efficacy and susceptibility to influence by other factors. Some concomitant medications, such as antibiotics or proton pump inhibitors (PPIs), have been indicated to reduce the survival benefit of ICIs[5-7]. Thus, the combined utilization of ICIs and other drugs deserves more attention.

Pain is a common symptom in advanced and metastatic cancer. Nearly 80% of patients who died of cancer suffered moderate-severe pain for an average of 90 days in less-developed countries[8, 9]. The World Health Organization (WHO) guidelines suggest the use of opioids in adults or adolescents with cancer-related pain based on clinical assessment and pain severity[10]. Thus, even in the crisis of opioid abuse, pain management using opioids is still necessary for cancer patients and remains the best clinical analgesic for cancer-related pain.

With the application of ICIs in the first-line therapeutic regimen, the use of opioids combined with ICIs became common, and there have been inconsistent findings in some studies[11-13].

Therefore, it is urgently necessary to evaluate the actual effect of opioids on ICI efficacy. We wish to provide a reference for the pain management of cancer patients, especially for those who are treated with ICIs.

Methods

Literature search

A systematic search was conducted using the PubMed, Embase, and Cochrane Library databases as well as related references retrieved up to April 2022 using the following search terms: *("opioids" OR "concomitant medication") AND ("Neoplasm" OR "Carcinoma" OR "Cancer" OR "Tumor") AND ("Immunotherapy" OR "Immune Checkpoint Inhibitor" OR "PD-L1 Inhibitor" OR "PD-1 Inhibitor" OR "CTLA-4 Inhibitor").* The search strategy was shown in supplementary table 1 in the Supplement.

Eligibility criteria

Following the PRISMA guidelines[14], the authors searched the database according to the retrieval strategy and independently evaluated all articles. The title and abstract of the search results were browsed, and the full text was read to determine whether it met the inclusion criteria. Discrepancies were resolved by consensus.

The inclusion criteria used for article selection were as follows: (1) adult patients with cancer receiving ICI treatment, (2) patients were treated with opioids before, during, or after ICI administration, and the control group was not treated with opioids within the corresponding period, and (3) the outcomes were the efficacy of ICIs, including overall survival (OS) or progression-free survival (PFS). The exclusion criteria were as follows: (1) conference abstracts, review

papers, papers without original data, and studies with duplicate data; (2) studies published in languages other than English; and (3) full-text article was not available.

Data extraction

We extracted the following data from eligible studies: first author, publication year, country, study type, cancer type, sample size, patient characteristics, ICI type, opioid type, and outcomes. We extracted the hazard ratio (HR) and 95% confidence interval (CI) of the multivariate analysis in the included articles. For the studies that only provided a survival curve we referred to the Engauge Digitizer method reported by Tierney to extract HR and 95% CI indirectly[15].

Quality assessment

The quality of each study was evaluated using the Newcastle–Ottawa scale (NOS)[16]. In the NOS system, studies with scores ≥ 6 are defined as high quality.

Statistical analysis and visualization tools

The effect of opioids on the survival of patients treated with ICIs was explored, and the results were reported as HRs and 95% CIs. OS was the primary outcome, and PFS was the secondary outcome. Heterogeneity was identified using the Q test, and we estimated and quantified it by I^2 values[17]. When I^2 was >50% and/or P<0.10, heterogeneity was considered statistically significant. A random-effects model or fixed-effects model was selected according to the heterogeneity results. Subgroup and sensitivity analyses were performed to determine the potential factors underlying the heterogeneity. Publication bias was evaluated by funnel plot, along with Begg's and Egger's tests. If publication bias existed, trim-and-fill analysis was used to assess it. All p values were two-sided, and the significance level was set at P<0.05. Review STATA 15.1 and Revman 5.4 were used for statistical analysis and visualization.

Results

Study selection

A total of 531 studies were retrieved from the initial broad search through April 2022. Based on the inclusion and exclusion criteria, 7 articles[11-13, 18-21] were eligible for quantitative analysis, with a total of 2690 patients (Figure 1). There were 620 opioid-treated patients and 2070 opioid-free patients. The most common cancer types were non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC). Finally, five studies[11-13, 18, 20] provided both OS and PFS, and the other two[19, 21] only reported OS. The baseline characteristics of the included studies are shown in Table 1.

Table 1. The Baseline Characteristics of Included Studies

Source	Country	Study type	Cancer type	ICI type	Opioid type	Patients, No. (Y/N)	Male, No. (%)	Age, Median, y	Quality evaluation
Botticelli (2021)[13]	Italy	Retrospective	NSCLC, melanoma, renal cancer, Merkel tumor, and colon cancer	Nivolumab, pembrolizumab, atezolizumab, and avelumab	NR	193(42/151)	120(62.0)	70.0	6
Cortellini (2020)[18]	Italy	Retrospective	NSCLC, melanoma, RCC, and other cancers	Pembrolizumab, nivolumab, atezolizumab, and others	NR	1012(68/944)	647 (63.9)	68.5	8
Gaucher (2021)[19]	France	Retrospective	Lung cancer, melanoma, renal and urothelial cancer, head and neck cancer, and other cancers	Ipilimumab, nivolumab and pembrolizumab	NR	372(173/199)	244(65.6)	64.0	6
Kostine (2021)[20]	France	Retrospective	Melanoma, NSCLC, renal cancer, and other cancers	Anti-PD-1/PD-L1, anti-CTLA-4, sequential CPI	Morphine	635(130/505)	443 (70.0)	64.5	7
Miura (2021)	Japan	Retrospective	NSCLC	Nivolumab, pembrolizumab	NR	300(114/186)	226 (75.3)	65.0	7
Santamaría (2019)[11]	Spain	Retrospective	NSCLC, renal cancer, bladder cancer, melanoma, head and neck cancer, and other cancers	Nivolumab, pembrolizumab, atezolizumab, and ipilimumab	NR	102(55/47)	84 (82.4)	66.0	9
Taniguchi (2020)[12]	Japan	Retrospective	NSCLC	Nivolumab	Oxycodone, fentanyl, morphine, hydromorphone, tapentadol	76(38/38)	53 (67.9)	NR	7

*Obtained via correspondence with primary author

Abbreviations: CTLA-4: Cytotoxic T lymphocyte-associated antigen-4; ICIs: Immune Checkpoint Inhibitors; NR, not reported; NSCLC: non-small cell lung cancer; OS, overall survival; PD-1/PD-L1: Programmed cell death protein-1/Programmed cell death-ligand1; PFS, progression-free survival; RCC, renal cell carcinoma; Y/N, opioids use/no opioids use

Quality assessment

According to the NOS criteria, two reviewers independently evaluated the methodological quality of the included studies. Overall, all studies were considered medium or high quality, which was indicated by scores of at least six (Table 1).

Impact of opioids on ICIs (OS)

Opioids were negatively correlated with OS (HR=1.75, 95% CI = 1.32-2.31, P<0.001) with high heterogeneity (I^2=80.4%, P<0.001), as shown in Figure 2A. In the subgroup analysis of NSCLC (HR=1.83, 95% CI=1.46-2.28, P<0.001; I^2=46.1%, P=0.157), opioids had negative effects on ICIs. Moreover, the results were consistent based on the ICI type, sample size, and country, indicating that opioids were significantly related to reduced OS (Table 2). Sensitivity analysis suggested that the studies by Botticelli[13] and Kostine[20] were strongly associated with heterogeneity (supplementary figure 1A). After excluding the two studies, the results of OS were HR=1.87, 95% CI = 1.38-2.52, P<0.001; I^2=77.6%, P<0.001 and HR=1.54, 95% CI = 1.25-1.90, P<0.001; I^2=51.6%, P=0.066, respectively.

Impact of opioids on ICIs (PFS)

Opioids significantly reduced the PFS of patients treated with ICIs (HR=1.61, 95% CI=1.41-1.83, P<0.001) without heterogeneity (I^2=0.0%, P=0.629), as shown in Figure 2B. Subgroup analysis also showed that opioids significantly reduced PFS based on ICI type, sample size, and country obtained similar results (Table 2). Sensitivity analyses reported that the results were not dominated by any single study (supplementary figure 1B).

Impact of NSAIDs or aspirin on ICIs (OS and PFS)

To evaluate the efficacy of non-opioids on ICIs, we analyzed the impact of nonsteroidal anti-inflammatory drugs (NSAIDs) on OS and PFS and further focused on aspirin, which is representative but has been shown to be independent from NSAIDs in some studies. NSAIDs could lead to poor OS (HR= 1.25, 95% CI=1.03-1.51, P=0.02; I^2 =0%, P=0.60) but not PFS (HR=1.11, 95% CI=0.89-1.39, P=0.36; I^2=0.0%, P=0.75) for ICI patients (Figure 3A and B). While aspirin didn't reduce the survival of patients treated with ICI therapy, no matter OS (HR= 0.93, 95% CI = 0.78-1.10, P=0.27; I^2=17%, P=.39) or PFS (HR=0.89, 95% CI=0.69-1.16, P=0.12; I^2=59%, P=0.40) (Figure 3C and D).

Risk of publication bias

The funnel chart (supplementary figure 2) and the results of Begg's test and Egger's test analysis (Table 2) suggested that there was no significant publication bias except for in the overall analysis of PFS ($P_{Begg's}$ =0.027, $P_{Egger's}$ =0.012). Trim-and-fill analysis showed that publication bias did not affect the PFS results (HR=1.55, 95% CI=1.38-1.74, P<0.001).

Discussion

Cancer is the local manifestation of a systemic disease, and cancer patients usually have underlying diseases, such as hypertension, hyperglycemia, infection, and moderate-severe pain, especially in elderly individuals. Based on our search strategy, a total of eight studies[11, 18-24] discussed concomitant medication with ICIs in patients with advanced cancers. The usage rates of analgesics, PPIs, antibiotics, cardiovascular and hypoglycemic drugs were 15.6%, 20.3%, 8.2%, 20.8%, and 5.4%, respectively (supplementary figure 3). Several studies have corroborated that some medications can directly or indirectly influence immunity or immunotherapy[19-24], which has attracted considerable attention. In this meta-analysis, we focused on the impact of opioids on the survival outcomes of ICIs in advanced cancer patients.

In recent decades, the opioid abuse crisis has led to severe financial and social burdens and has been one of the biggest challenges facing public health in the 21st century[25]. Although prescription drug-monitoring programs (PDMPs) have reduced the prescription rate of opioids from 255 million to 153 million in America, they have also limited the adequate usage of opioids for patients with cancer-related pain. The current consensus is that pain management is essential for tumor patients, and opioids are preferred for moderate-severe cancer-related pain and can contribute to a high quality of life and adherence to therapy[26]. Thus, it seems unethical to restrict or forbid the use of opioids for severe cancer-related pain, and some investigators suggest providing exemptions for opioids for patients with cancer. However, based on this article, we believe that prescription opioids should be used with caution for tumor patients treated with ICIs, which is a novel but crucial viewpoint that might improve the long-term survival of tumor patients.

This study was the first meta-analysis to systematically evaluate the clinical efficacy of opioids on ICIs and included seven articles published in the past three years. Our meta-analysis identified the adverse effects of opioids on the efficacy of ICIs, and the results showed that the use of opioids was negatively correlated with OS and PFS in cancer patients treated with ICIs. Considering the heterogeneity in cancer type, ICI type, sample size, and publication country, we divided the study into several subgroups for further analysis. All subgroups consistently showed the negative effect of opioids on the prognosis of patients. We likewise found similar studies in two conference abstracts[27, 28], of whose results were consistent but were not included because of insufficient evidence regrettably.

Sensitivity analysis showed that two studies[13, 20] strongly influenced heterogeneity. In the study of Botticelli[13], ECOG-PS was an independent prognostic factor rather than opioid use, which reflects patients' health status and the ability to tolerate therapy.[28] Considering that patients treated with opioids may be weaker and have more complications than others, there was significant collinearity between opioid use and ECOG-PS, which might be one of the main causes for the heterogeneity in our meta-analysis. In addition, opioids had various immunoregulatory levels according to different targets, and morphine and fentanyl were stronger than others[29-32]. Two included articles[12, 20] disclosed relevant details of the opioid types. Of these, the main opioid in the article by Taniguchi was oxycodone, with a utilization rate of 52.6%, but fentanyl and morphine had utilization rates of 18.4% and 15.8%, respectively[12]. Kostine's study[20] referred only to morphine, which seemed to have more negative effects on ICIs than in other studies and acted as another source of heterogeneity in our meta-analysis.

Multimodal analgesia is a promising therapeutic strategy and is drawing increasing attention to the management of cancer-related pain[33]. Based on previous studies, the opioids with weak or no immune modulation (buprenorphine, oxycodone, hydromorphone, and tramadol) should be considered for the combined utilization with morphine or fentanyl, which can reduce the immunosuppressive effect of opioids for ICIs patients[29-32]. In addition, alternative drugs for chronic pain, including NSAIDs, antidepressants, and anticonvulsants, might be another choice[34]. A network meta-analysis reported that certain nonopioid analgesics and NSAIDs can serve as effectively as opioids for chronic cancer-related pain[35]. In this study, we revealed that NSAIDs could lead to poor OS but not PFS for ICI patients. Even so, NSAIDs seem to have a better effect than opioids on OS. As one of the representative NSAIDs, aspirin was researched independently in some studies because of its anti-thrombogenesis. Thus, we also focus specifically on aspirin for its pain relief efficacy, and aspirin had no additional effect on ICIs in terms of either OS or PFS. Interestingly, a meta-analysis reported that acupuncture and/or acupressure was significantly associated with reduced cancer pain and could decrease use of analgesics, which deserves more attention[36].

Limitations

There are several limitations to this study. First, our meta-analysis was based on retrospective studies. Considering the lower-level evidence and the number of included studies in some subgroups, the results should be interpreted with caution. Second, due to a lack of basic data, we could not perform an in-depth analysis in terms of opioid type, dosage, or drug exposure time, which might be the factors driving nonstatistical heterogeneity. In addition, tumor staging is an independent factor for prognosis, but only two articles provided information on staging, which might affect the accuracy of the results[11, 18]. Third, since one of the included studies did not perform a multivariate analysis, we used the method of Tierney et al. to extract the HR and 95% CI according to the survival curve, which might lead to a certain bias.

Conclusions

As one of the most effective analgesics, adequate application of opioids is essential for patients with cancer-related pain, even in the context of the opioid abuse crisis. However, our study showed that opioids were associated with poor prognosis in patients treated with ICIs. Thus, caution should be taken when prescribing a drug combination. It is necessary to clarify appropriate opioids based on immunoregulatory levels of ICI therapy and actively develop alternative drugs in the future.

Abbreviations

CI
confidence interval
CTLA-4
Cytotoxic T lymphocyte-associated antigen-4
HR
hazard ratio
ICIs
Immune Checkpoint Inhibitors
NR, not reported
NSAIDs
nonsteroidal anti-inflammatory drugs
NSCLC
non-small cell lung cancer
OS, overall survival
PD-1/PD-L1
Programmed cell death protein-1/Programmed cell death-ligand1
PDMPs
prescription drug-monitoring programs
PFS, progression-free survival
PPIs
proton pump inhibitors
RCC, renal cell carcinoma

Declarations

CONFLICT OF INTEREST DISCLOSURES:

The authors have no relevant financial or non-financial interests to disclose

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Contributions:

Formal analysis, Methodology, funding acquisition, visualization, and writing–original draft. Mingguang Ju: Formal analysis, methodology, visualization and writing–original draft. Xiaofang Liu: Formal analysis, data curation, Visualization. Heng Zhou: Investigation, Visualization. Ruiying Wang: Investigation and software. Chen Zheng: Investigation. Daosong Dong: Investigation and methodology. Zhi Zhu: Conceptualization, funding acquisition, supervision, and writing–review and editing. Kai Li: Conceptualization, funding acquisition, project administration, supervision, resources and writing–review and editing. *All authors read and approved the final manuscript.*

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Tables

Table 2 is not available with this version.

Figures

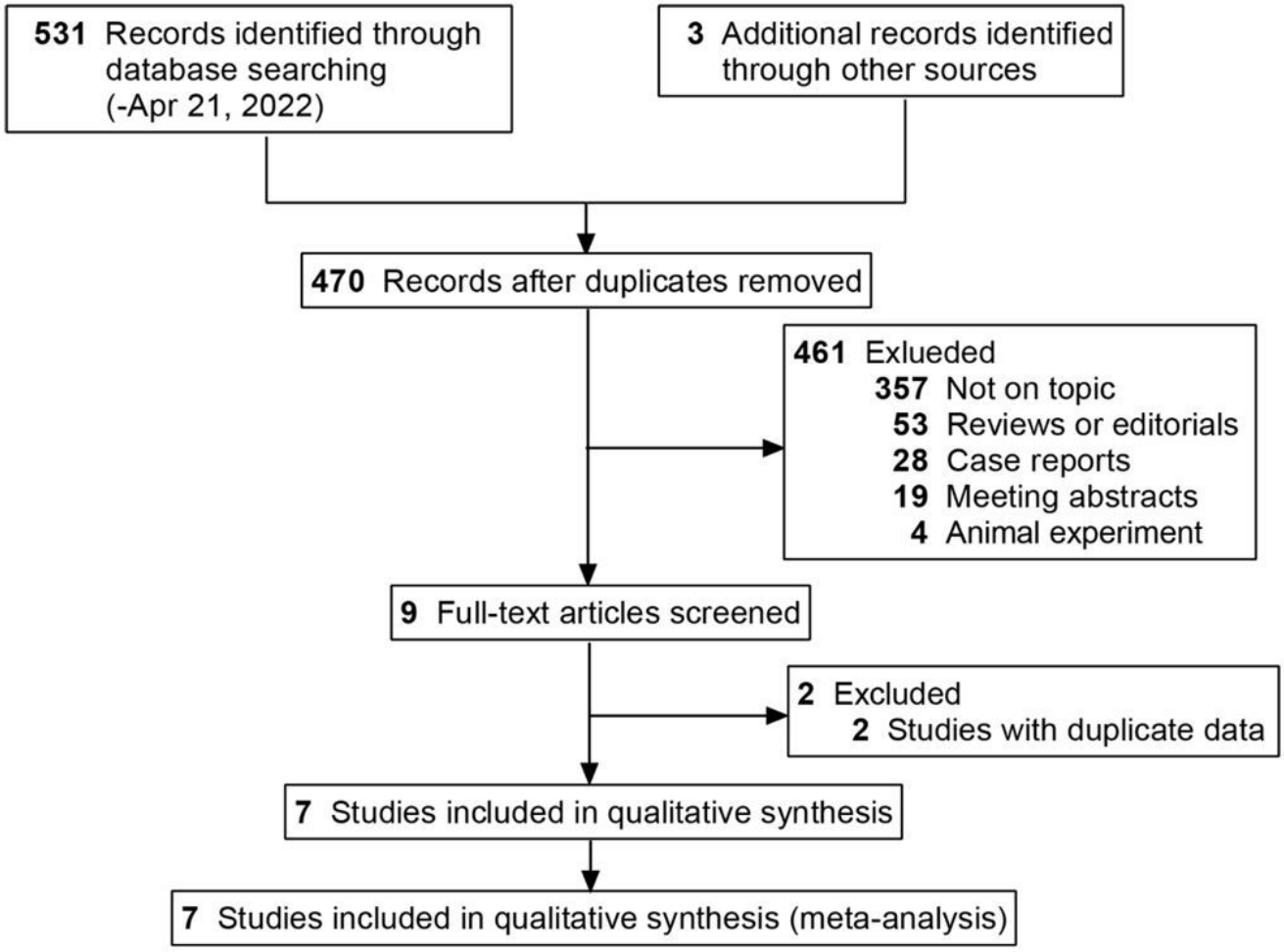

Figure 1

Flowchart of Study Selection.

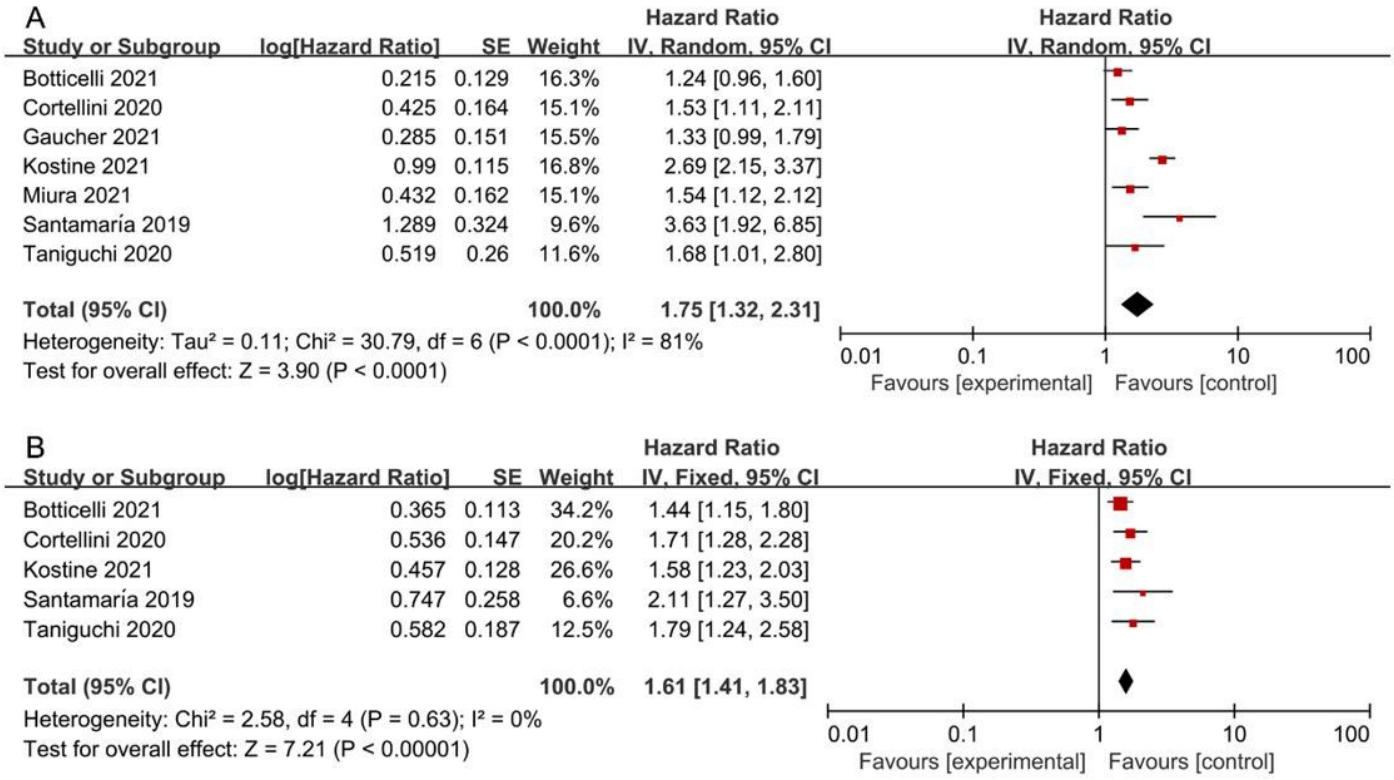

Figure 2

Forest Plots of Opioid Use Associated with OS (A) and PFS (B) in Cancer Patients Treated with ICIs.

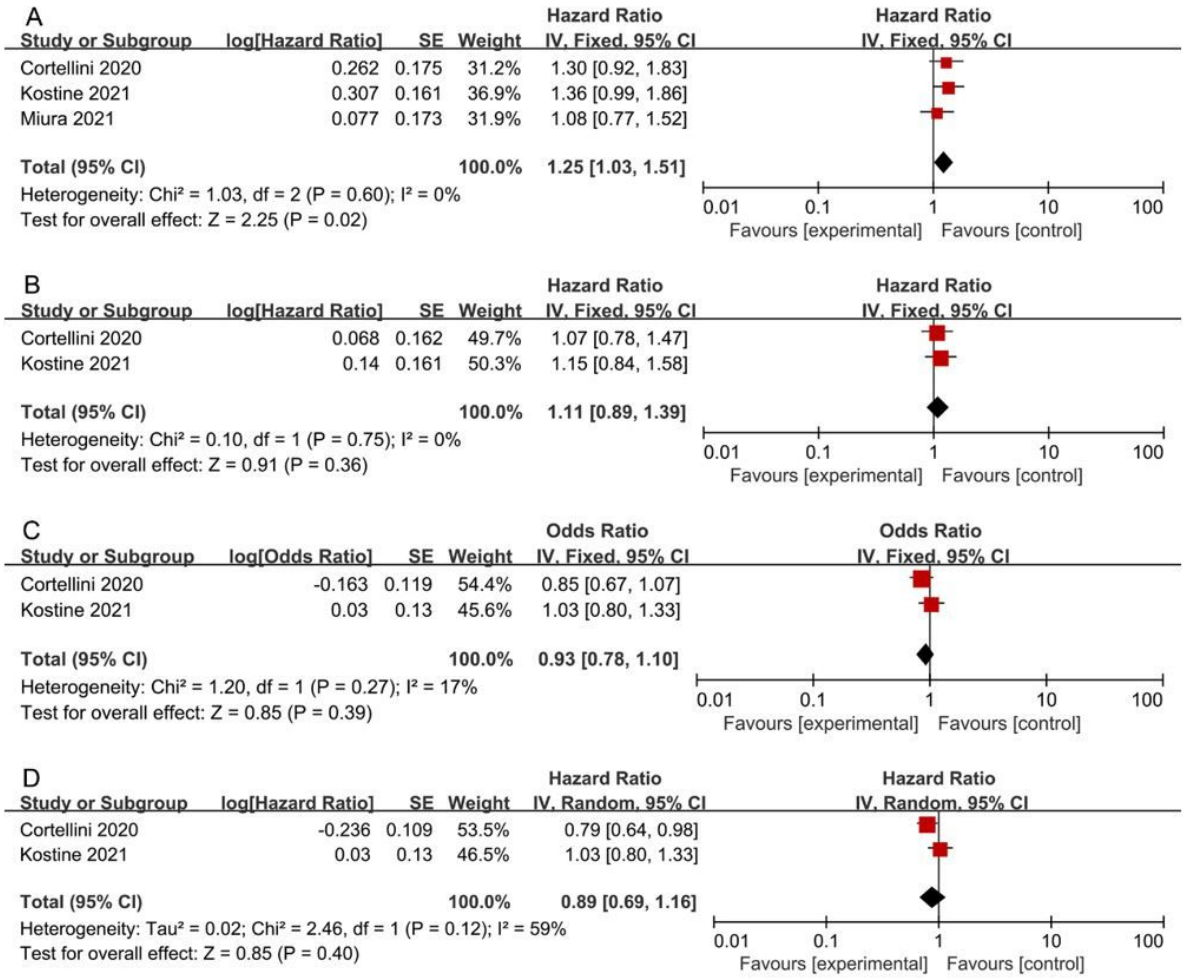

Figure 3

Forest plots of NSAIDs and aspirin use associated with OS (A and C) and PFS (B and D) in cancer patients treated with ICIs.

Supplementary Files

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