Long-term opioid use and mortality in patients with chronic non-cancer pain: Ten-year follow-up study in South Korea from 2010 through 2019

*In-Ae Song,[a,b,1] Hey-ran Choi,[c,1] and Tak Kyu Oh [a,b]**

[a]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[b]Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea
[c]Department of Anesthesiology and Pain Medicine, Inje University Seoul Paik Hospital, Seoul, Republic of Korea

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Summary

Background We aimed to investigate the prevalence and factors associated with long-term opioid use among patients with chronic non-cancer pain (CNCP).

Methods We extracted data from the National Health Insurance Service (NHIS) database in South Korea. As a nationwide database, the NHIS database contains information regarding all disease diagnoses and prescriptions for any drug and/or procedures. A total of 2.5% of adult patients (≥20 years of age) who were diagnosed with musculoskeletal diseases and CNCP from 2010 to 2019 were selected using a stratified random sampling technique and included in the analysis. Patients who were prescribed opioids continuously for ≥90 days were classified as long-term opioid users.

Findings A total of 19,645,161 patients with CNCP were included in the final analysis. The prevalence of long-term opioid use was 0.47% (95% confidence interval [CI]: 0.46%, 0.48%; 8421/1,808,043) in 2010, which gradually increased to 2.63% (95% CI: 2.61%, 2.66%; 49,846/1,892,913) in 2019. Among the 2010 cohort (n = 1,804,019), in multivariable logistic regression: old age, underlying disability, increased Charlson comorbidity index, use of benzodiazepine or Z-drug, rheumatoid arthritis, osteoarthritis, and low back pain were associated with an increased prevalence of long-term opioid use among patients with CNCP. In a multivariable Cox regression, the 10-year all-cause mortality in long-term opioid users was found to be 1·21-fold (hazard ratio: 1.21, 95% CI: 1.13, 1.31; P<0·001) higher than that in opioid-naive patients with CNCP.

Interpretation Long-term opioid use increased in patients with CNCP in South Korea from 2010 to 2019. Certain factors were potential risk factors for long-term opioid use. Moreover, long-term opioid use was associated with increased 10-year all-cause mortality among patients with CNCP.

Funding None.

Keywords: Analgesics; Opioid; Mortality; Pain; Population; Cohort studies

Introduction

Opioids are currently the most commonly prescribed analgesic,[1] and their prescription rates have continuously increased in many countries, such as the United States,[2] United Kingdom,[3] Taiwan,[4] France,[5] China,[6] and South Korea.[7] Over one-third of the 91.8 million non-institutionalized adults in the United States used opioids in 2015.[8] A total of 15.5 million were found to be opioid–dependent globally in 2010.[9] The opioid dependence epidemic arising from opioid use has grown into a major public health issue in many countries.[9–11]

Chronic non-cancer pain (CNCP) is one of the most common indications for long-term opioid therapy.[12–14] Long-term opioid users with CNCP represent a high-risk group for opioid abuse and dependence.[15] Although there have been some reports stating that the prevalence of long-term opioid therapy has increased among

*Corresponding author at: Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gumi-ro, 173, Beon-gil, Bundang-gu, Seongnam, 13620, South Korea; Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University, 103 Daehak-ro, Jongno-gu, Seoul, Republic of Korea.
E-mail address: airohtak@hotmail.com (T.K. Oh).

[1] Equal contributions as co-first authors.

Research in context

Evidence before this study

We searched PubMed from database until March 1, 2022, for observational studies, randomized controlled trials, and meta-analyses published in English, using the search terms "pain", "opioid", "non-cancer pain", "chronic pain", and "analgesics". We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. Although previous literatures reported that chronic non-cancer pain (CNCP) was one of the most common indications of long-term opioid therapy, long-term mortality based on long-term opioid therapy in patients with CNCP have not been identified well.

Added value of this study

This population-based cohort study showed that the prevalence of long-term opioid users had increased from 2010 to 2019 in South Korea among patients with CNCP. Some factors (old age, underlying disability, comorbid status, use of benzodiazepine or Z-drug, rheumatoid arthritis, osteoarthritis, and low back pain) were associated with increased prevalence of long-term opioid use among patients with CNCP. In survival analysis of 10-year follow up, long-term opioid use was a potential risk factor for increased 10-year all-cause mortality among patients with CNCP.

Implications of all the available evidence

Overall, long-term opioid use increased in patients with CNCP in South Korea from 2010 to 2019. Some factors are potential risk factors for long-term opioid use. Moreover, long-term opioid use was associated with increased 10-year all-cause mortality among patients with CNCP.

patients with CNCP,[12,14] its impact on long-term mortality has not been thoroughly assessed. Ray et al. reported that the prescription of long-acting opioids was associated with increased mortality in a retrospective cohort study carried out between 1999 and 2012 among Tennessee Medicaid patients with CNCP.[16] However, the follow-up time for evaluating mortality rates in the study by Ray et al. was only one year,[16] and long-term mortality according to long-term opioid therapy in patients with CNCP warrants close assessment.

Therefore, this study sought to investigate the prevalence of long-term opioid use and its association with all-cause and disease-specific mortality over the course of a period lasting up to 10 years in South Korean patients with CNCP.

Methods

Study design and ethical statement

As a population-based cohort study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17] The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University's Bundang Hospital (IRB approval number: X-2105-685-901). The requirement for informed consent was waived by the IRB because the data were analyzed retrospectively in an anonymous fashion, after masking the individual and sensitive information of the study population.

Data extraction

As the sole public health insurance system, the National Health Insurance Service (NHIS) database contains information regarding all disease diagnoses and prescriptions for any drug and/or procedures. The NHIS manages the diagnosis and prescription information of diseases according to the International Classification of Diseases and Related Health Issues (ICD-10) under the guidance of the central government. The medical records technician from the core data center in the NHIS extracted and provided the data for this research following approval of the study protocol by the NHIS Ethics Committee (NHIS approval number: NHIS-2021-1-615).

Study population (patients with CNCP)

We used the ICD-10 codes in e-Appendix 1 to assess all patients with CNCP. Musculoskeletal disease (MSD)s associated with CNCP include rheumatoid arthritis, osteoarthritis, low back pain, neck pain, gout, and other musculoskeletal disorders. First, the medical record technician selected all patients using the ICD-10 codes of musculoskeletal diseases from 2010 to 2019, and data of approximately 800,000,000 patients from a 10-year period were initially extracted from the NHIS for calculating prevalence of long-term opioid users. Owing to the large sample size, data of 2.5% of adult patients (≥20 years of age) were newly extracted using a stratified random sampling technique. Age and sex were used as an exclusive stratum for sampling. Through the sampling process, the sampled study population was drawn from each of the strata, with sizes proportional to the strata in the overall patients (approximately 800,000,000 patients). Finally, a total of 19,645,161 patients were sampled using a stratified random sampling method using SAS version 9.4 (SAS Institute, Cary, NC).[18] Among these, 874,171 patients diagnosed with cancer as a comorbidity were excluded to focus on those diagnosed with CNCP. Next, 756 patients who had undergone surgery during the year were excluded because postoperative pain might affect opioid prescription, regardless of the presence of CNCP. Therefore, 18,770,234 adult patients were included in the final analysis for NHIS for calculating the prevalence of long-term opioid users as shown in Figure 1.

Second, cohort in 2010 were selected among total patients for the survival analysis to analyze 10-year mortality from 2011 through 2019. The 4024 patients who

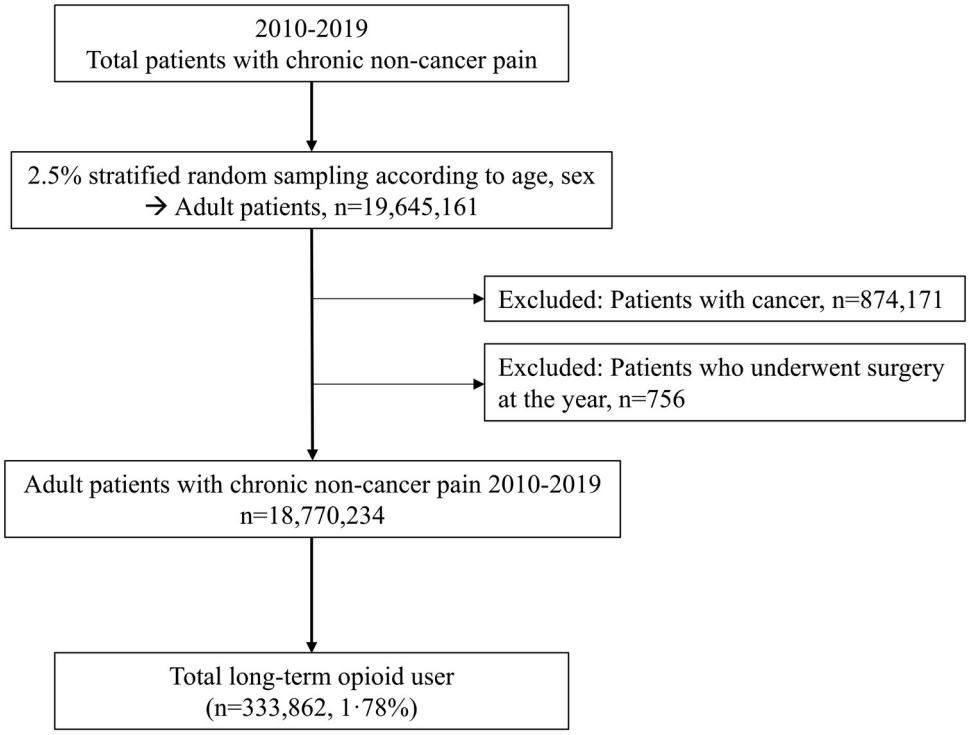

Figure 1. Flow chart representing the patients with chronic non-cancer pain selection process.

had died in 2010 were excluded to focus on long-term survival from 1 January 2011. Therefore, 1,804,019 patients who visited the outpatient clinic or were admitted to the hospital with a diagnosis of MSDs were included in the survival analysis.

Long-term opioid use (exposure)

Although the threshold of long-term opioid therapy has ranged from one week to one year, most of the previous studies had used ≥90 days of continuous opioid therapy to define long-term opioid use.[19,20] Therefore, patients who were prescribed opioids regularly and continuously for ≥90 days were defined as long-term opioid users in this study, while the other patients were considered as opioid-naive.

Study outcomes

First, we assessed the prevalence of long-term opioid use among patients with CNCP from 2010 to 2019 in South Korea. Second, 10-year survival analyses according to long-term opioid use were performed to assess the association between long-term opioid use and mortality. The survival time was assessed from January 1, 2011, to either the date of death or April 30, 2021, in the cohort in 2010. In addition to 10-year all-cause mortality, 10-year mortality according to specific causes was also evaluated. All physicians are to register the main causes of death for all individuals using ICD-10 codes in the Statistics Korea database as mandated by the central government. Statistics Korea approved of the data sharing of information regarding the main causes of death for this study, and the ICD-10 codes of the main causes of death are presented in e-Appendix 2. Moreover, we examined association of long-term opioid use with 3-, 5-, and 7-year all-cause mortality in the cohort in 2010 to evaluate whether long-term opioid use was associated with relative short-term mortality.

Collected variables

For the survival analyses, information was collected as a covariate. Age and sex were collected as demographic variables. Data on employment status, national household income level, and residence were collected to reflect the socioeconomic status of all patients. South Koreans pay a fixed rate for health insurance premiums based on their income, with approximately 67% of their medical expenses subsidized by the government.[21] However, individuals who cannot afford insurance premiums or have difficulty financially supporting themselves are included in the Medical Aid Program. In this program, the government covers nearly all medical expenses to minimize the financial burden of the medical costs. All patients were divided into five groups using the quartile ratio in addition to the Medical Aid Program group. All patients were classified according to their residence, i.e., urban areas (Seoul and other

metropolitan cities) and rural areas (all other areas). To reflect the comorbid status of the patients, information regarding the Charlson comorbidity index (CCI) and underlying disability was collected. In South Korea, all individuals with any form of disability are registered in the NHIS database to receive benefits from the social welfare system. Disabilities were divided into six grades based on severity (grade 1, most severe; grade 6, mildest). Patients with grades 1, 2, or 3 constituted the severe disability group, while those with grades 4, 5, or 6 constituted the mild-to-moderate disability group. CCI scores were calculated using the ICD-10 codes for individual diseases (e-Appendix 3). In addition, long-term (≥90 days) data on gabapentin or pregabalin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and Z-drugs were collected.

Statistical analysis

The continuous variables of clinicopathological characteristics are presented as median value with interquartile range [IQR], because the distribution of continuous variables (age and CCI) were not normal distribution in Kolmogorov–Smirnov test. The categorical variables of clinicopathological characteristics are presented as numbers with percentages. Among the 2010 cohort with CNCP, clinicopathological characteristics between the long-term opioid users and the control group were compared using a Kruskal-Wallis test for continuous variables and a Chi-squared test for categorical variables. Next, we constructed a multivariable logistic regression model to assess which factors were associated with long-term opioid use in patients with CNCP. All covariates were included in the model for adjustment, and Hosmer–Lemeshow statistics were used to confirm that the goodness of fit in the model was appropriate. The results of the logistic regression are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Next, we carried out survival analyses using multivariable Cox regression modelling for all-cause mortality factors spanning a 10-year period. For the time-to-event analysis, any death from January 1, 2011, to April 30, 2021, was considered an event, while survival time from January 1, 2011, onwards was considered the total duration. All covariates were included in the adjusted model. Subsequently, we performed multivariable Cox regression analyses considering the combination of opioids with other drugs acting at the level of the central nervous system (gabapentin or pregabalin, benzodiazepines, and Z-drugs) and its influence on 10-year all-cause mortality. We also performed multivariable Cox regression analyses for 3-, 5-, and 7-year all-cause mortality among patients with CNCP as sensitivity analyses to examine whether the relative short-term mortalities correlated with the long-term opioid use. Additionally, we constructed 17 multivariable Cox regression models for the 10-year disease-specific mortality rates. A variance inflation factor <2·0 was used to confirm that there was no multicollinearity across variables in all models, and the results of Cox regression were presented as hazard ratios (HRs) with 95% CIs. All statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $P<0.05$.

Role of the funding source

No funding received for this study. All authors had full access to all data within the study. The corresponding authors had final responsibility for the decision to submit for publication.

Results

Prevalence of long-term opioid users

The proportions of MSDs between long-term opioid users and opioid-naive patients in the overall cohort from 2010 through 2019 are presented in e-Appendix 4. Figure 2 represents the prevalence of long-term opioid use among patients with CNCP from 2010 to 2019. The prevalence of long-term opioid use was 0.47% (95% CI: 0·46%, 0.48%; 8421/1,808,043) in 2010, which gradually increased to 2.63% (95% CI: 2.61%, 2.66%; 49,846/1,892,913) by 2019. The overall prevalence of long-term opioid use among patients with CNCP over the course of 10 years was 1.78% (95% CI: 1.77%, 1.79%; 333,862/18,770,234).

Cohort in 2010 and long-term opioid use

Table 1 represents the results of the comparison of clinicopathological characteristics between long-term opioid users and opioid-naive patients in the 2010 cohort (N = 1,804,019). The median value of age was higher in the long-term opioid user group at 67 years [IQR: 56, 74 years) than in opioid-naive patients at 44 years (IQR: 33, 56 years). Table 2 demonstrates the results of the multivariable logistic regression model for long-term opioid use among patients with CNCP. Older age (OR: 1.02, 95% CI: 1.02, 1.03; $P<0·001$), underlying mild-to-moderate disability (OR: 1.62, 95% CI: 1.44, 1.81; $P<0.001$), severe disability (OR: 1·94, 95% CI: 1.66, 2.27; $P<0.001$), benzodiazepine use (OR: 2.11, 95% CI: 1.89, 2.36; $P<0.001$), Z-drug use (OR: 1.70, 95% CI: 1.36, 2.12; $P<0.001$), and increased CCI (OR: 1.06, 95% CI: 1.04, 1.08; $P<0.001$) were associated with a high prevalence of long-term opioid use among patients with CNCP. Among MSDs, underlying rheumatoid arthritis (OR: 2.11, 95% CI: 1.89, 2.36; $P<0.001$), osteoarthritis (OR: 2.68, 95% CI: 2.45, 2.93; $P<0.001$), lower back pain (OR: 2.14, 95% CI: 1.95, 2.34; $P<0.001$), and other MSDs (OR: 1.80, 95% CI: 1.64, 1.97; $P<0.001$) were associated with a high prevalence of long-term opioid use among patients with CNCP.

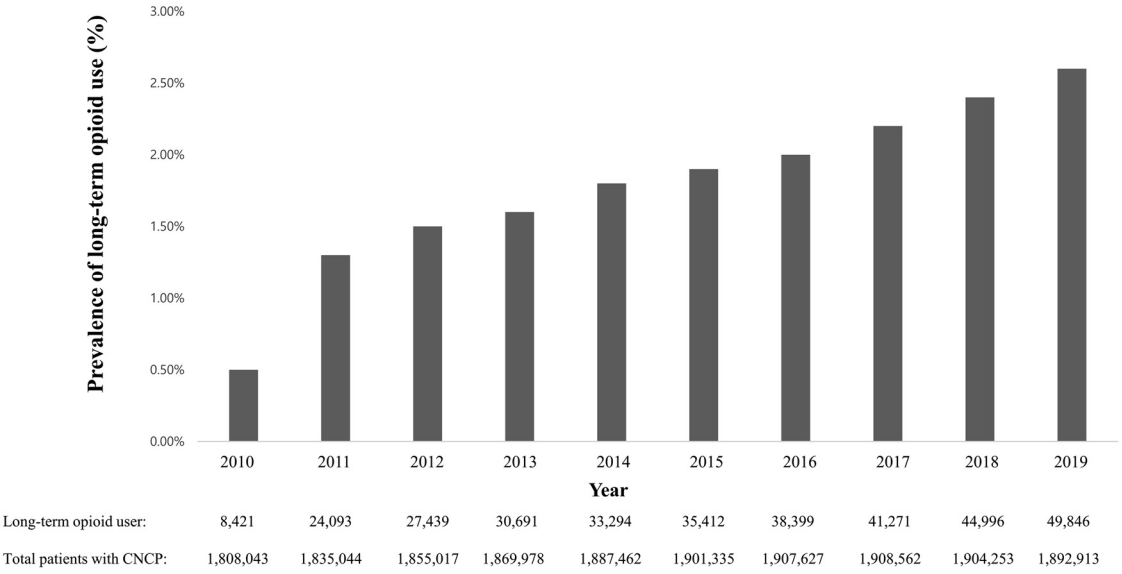

Figure 2. Prevalence of long-term opioid users among patients with chronic non-cancer pain between 2010 and 2019. CNCP, chronic non-cancer pain.

Variable	Long-term opioid user *n* = 8320	Opioid naïve patient *n* = 1,795,699	*P*-value
Age, year	67 [56, 74]	44 [33, 56]	<0.001
Sex, male	5933 (71.3)	922,071 (51.3)	<0.001
Having a Job	3859 (46.4)	954,581 (53.2)	<0.001
Household income level			<0.001
Medical aid program	921 (11.1)	55,367 (3.1)	
Q1 (Lowest)	1420 (17.1)	333,042 (18.5)	
Q2	1212 (14.6)	357,023 (19.9)	
Q3	1795 (21.6)	446,448 (24.9)	
Q4 (Highest)	2702 (32.5)	546,755 (30.4)	
Unknown	270 (3.2)	57,065 (3.2)	
Residence			<0.001
Urban area	3595 (43.2)	834,534 (46.5)	
Rural area	4725 (56.8)	961,165 (53.5)	
Disability			<0.001
Mild to moderate	1329 (16.0)	66,312 (3.7)	
Severe	562 (6.8)	39,131 (2.2)	
CCI, point	2 [1, 3]	0 [0, 1]	<0.001
Benzodiazepine use	1701 (20.4)	37,629 (2.1)	<0.001
Z-drug use	297 (3.6)	7207 (0.4)	<0.001
Other pain medication			
Gabapentin or pregabalin	1012 (12.2)	8298 (0.5)	<0.001
Paracetamol	6325 (76.0)	998 (0.1)	<0.001
NSAIDs	135 (1.6)	1653 (0.1)	<0.001
Underlying MSDs			
RA	1354 (16.3)	33,196 (1.8)	<0.001
OA	6197 (74.5)	285,574 (15.9)	<0.001
LBP	6311 (75.9)	420,639 (23.4)	<0.001
Neck pain	1836 (22.1)	131,571 (7.3)	<0.001
Gout	299 (3.6)	22,729 (1.3)	<0.001
Other MSD	6428 (77.3)	449,545 (25.0)	<0.001

***Table 1*: Comparison of clinicopathological characteristics between long-term opioid users and opioid-naive patients in the 2010 cohort (*N* =1,804,019).**

CCI, Charlson comorbidity index; NSAIDs, Non-steroidal anti-inflammatory drugs; MSD, musculoskeletal disease; RA, rheumatoid arthritis; OA, osteoarthritis; LBP, low back pain.

Variable	OR (95% CI)	*P*-value
Age, year	1.02 (1.02, 1.03)	<0.001
Sex, male	0.93 (0.85, 1.01)	0.064
Having a Job	0.93 (0.86, 1.01)	0.092
Household income level		
Medical aid program	1	
Q1 (Lowest)	1.01 (0.86, 1.19)	0.884
Q2	1.01 (0.85, 1.19)	0.936
Q3	1.00 (0.85, 1.17)	0.987
Q4 (Highest)	0.97 (0.84, 1.13)	0.698
Unknown	1.00 (0.78, 1.27)	0.966
Residence		
Urban area	1	
Rural area	0.84 (0.78, 0.91)	<0.001
Disability		
Mild to moderate	1.62 (1.44, 1.81)	<0.001
Severe	1.94 (1.66, 2.27)	<0.001
CCI, point	1.06 (1.04, 1.08)	<0.001
Benzodiazepine use	2.11 (1.89, 2.36)	<0.001
Z-drug use	1.70 (1.36, 2.12)	<0.001
Other pain medication		
Gabapentin or pregabalin	8.21 (7.23, 9.35)	<0.001
Paracetamol	2371.19 (2172.85, 2587.63)	<0.001
NSAIDs	1.50 (1.04, 2.178)	0.031
Underlying MSDs		
RA	2.11 (1.89, 2.36)	<0.001
OA	2.68 (2.45, 2.93)	<0.001
LBP	2.14 (1.95, 2.34)	<0.001
Neck pain	1.02 (0.92, 1.12)	0.756
Gout	1.08 (0.88, 1.33)	0.442
Other MSD	1.80 (1.64, 1.97)	<0.001

***Table 2*: Multivariable logistic regression model for long-term opioid use among patients with chronic non-cancer pain in 2010.**
OR, odds ratio; CI, confidence interval; CCI, Charlson comorbidity index; NSAIDs, Non-steroidal anti-inflammatory drugs; MSD, musculoskeletal disease; RA, rheumatoid arthritis; OA, osteoarthritis; LBP, low back pain.

Survival analyses

Table 3 represents the results of the survival analyses. In the multivariable Cox regression model, the 10-year all-cause mortality in long-term opioid users was 1·21-fold (HR: 1.21, 95% CI: 1.13, 1.31; $P<0.001$; model 1) higher than that in opioid-naive patients with CNCP. Table 4 shows the results of sensitivity analyses such as multivariable Cox regression models for 3-, 5-, and 7-year all-cause mortalities. Long-term opioid users show 1.24-fold (HR: 1.24, 95% CI: 1.08, 1.43; $P = 0.002$), 1.17-fold (HR: 1.17, 95% CI: 1.05, 1.30; $P = 0.005$), and 1.20-fold (HR: 1.20, 95% CI: 1.09, 1.31; $P = 0.003$) higher 3-, 5-, and 7-year all-cause mortalities, respectively, than opioid-naive patients with CNCP. Table 5 shows the results of survival analyses regarding 10-year disease-specific mortality among patients with CNCP. Among disease-specific mortalities, long-term opioid users showed higher 10-year mortality owing to cancer (HR: 1.19, 95% CI: 1.02, 1.40; $P =0.041$), circulatory disease (HR: 1.26, 95% CI: 1.10, 1.45; $P<0.001$), symptoms, signs, and abnormal clinical and laboratory findings (HR: 1.70, 95% CI: 1.38, 2.06; $P<0.001$) than opioid-naive patients among patients with CNCP.

Discussion

This population-based cohort study demonstrated that the prevalence of long-term opioid use increased from 2010 to 2019 in South Korea among patients with CNCP. Certain factors (old age, underlying disability, comorbid status, use of benzodiazepine or Z-drug, rheumatoid arthritis, osteoarthritis, and low back pain) were associated with an increased prevalence of long-term opioid use among patients with CNCP. In the survival analysis of a 10-year follow up period, long-term opioid use was found to be a potential risk factor for increased 10-year all-cause mortality among patients with CNCP.

In South Korea, the overall prevalence of long-term opioid use among patients with CNCP over the course of 10 years was 1.78% (333,862/18,770,234). This is

Mortality	Event (*n*, %)	Multivariable Cox regression model HR (95% CI)	*P*-value
10-year all-cause mortality (model 1)			
Opioid naïve patient	109,920 (6.1)	1	
Long-term opioid user	1953 (23.5)	1.21 (1.13, 1.31)	<0.001
10-year all-cause mortality (model 2)			
Opioid naïve patient	109,920 (6.1)	1	
Long-term opioid user without BDZ use	1441 (21.8)	1.22 (1.22, 1.31)	<0.001
Long-term opioid user with BDZ use	623 (30.1)	1.32 (1.19, 1.46)	<0.001
10-year all-cause mortality (model 3)			
Opioid naïve patient	109,920 (6.1)	1	
Long-term opioid user without Z drug use	1845 (23.0)	1.21 (1.13, 1.31)	<0.001
Long-term opioid user with Z drug use	108 (36.4)	1.55 (1.28, 1.89)	<0.001
10-year all-cause mortality (model 4)			
Opioid naïve patient	109,920 (6.1)	1	
Long-term opioid user without gabapentin or pregabalin use	1637 (22.4)	1.25 (1.16, 1.35)	<0.001
Long-term opioid user with gabapentin or pregabalin use	316 (31.2)	1.53 (1.36, 1.73)	<0.001

***Table 3*: Survival analyses among patients with chronic non-cancer pain in 2010.**
HR, hazard ratio; CI, confidence interval; BDZ, benzodiazepine.

Mortality	Event (*n*, %)	Multivariable Cox regression model HR (95% CI)	*P*-value
3-year all-cause mortality			
Opioid naïve patient	25,348 (1.4)	1	
Long-term opioid user	520 (6.3)	1.24 (1.08, 1.43)	0.002
5-year all-cause mortality			
Opioid naïve patient	47,144 (2.6)	1	
Long-term opioid user	870 (10.5)	1.17 (1.05, 1.30)	0.005
7-year all-cause mortality			
Opioid naïve patient	70,923 (3.9)	1	
Long-term opioid user	1292 (15.5)	1.20 (1.09, 1.31)	0.003

***Table 4*: Sensitivity analyses among patients with chronic non-cancer pain in 2010.**
HR, hazard ratio; CI, confidence interval.

relatively lower than that in the United States,[12] and Canada.[14] These differences may have resulted from several factors. The prescription of opioids for patients with CNCP in South Korea is presumed to differ from that in Europe and America, and physicians must follow strict prescription guidelines.[22] Moreover, health insurance coverage is applied for up to 30 days per opioid prescription for patients with non-cancer pain, whereas there are no restrictions on health insurance coverage for prescription of any opioids for patients with cancer in South Korea. Therefore, if patients with CNCP in South Korea want an opioid prescribed, they must pay for their own expensive opioid analgesics. This policy was implemented by the South Korean government to reduce the misuse and abuse of opioid analgesics.

The increase of long-term opioid use in patients with CNCP in South Korea should be interpreted meticulously. In South Korea, the prescription of opioid has increased from 2009 to 2019.[23] In a study based on a survey in South Korea, 39.0% of patients with chronic pain did not want an opioid prescription, citing fear of addiction and side effects as the primary reasons.[24] In general, physicians in South Korea have persuaded patients with CNCP about the importance of pain treatment; therefore, the use of opioids has increased accordingly. Moreover, the healthcare utilization among patients with CNCP might have increased in South Korea, which had an effect on the increase of long-term opioid users among patients with CNCP. For example, a recent cohort study reported that healthcare utilization of patients with epicondylitis rose every year from 2010 to 2018.[25]

Among MSDs, rheumatoid arthritis, osteoarthritis, and low back pain were found to be significant risk

Mortality	Event (*n*, %)	Multivariable Cox regression model HR (95% CI)	*P*-value
Infectious mortality			
Opioid naïve patient	3110 (0.2)	1	
Long-term opioid user	62 (0.7)	1.13 (0.75, 1.70)	0.431
Cancer mortality			
Opioid naïve patient	28,207 (1.6)	1	
Long-term opioid user	371 (4.5)	1.19 (1.02, 1.40)	0.041
Blood disease mortality			
Opioid naïve patient	291 (0.0)	1	
Long-term opioid user	1 (0.0)	0.15 (0.03, 1.41)	0.099
Endocrine disease mortality			
Opioid naïve patient	4504 (0.3)	1	
Long-term opioid user	112 (1.3)	1.14 (0.90, 1.47)	0.520
Mental disease mortality			
Opioid naïve patient	2008 (0.1)	1	
Long-term opioid user	37 (0.4)	1.42 (0.87, 2.33)	0.235
Nervous disease mortality			
Opioid naïve patient	4523 (0.3)	1	
Long-term opioid user	86 (1.0)	0.80 (0.55, 1.13)	0.312
Circulatory disease mortality			
Opioid naïve patient	24,862 (1.4)	1	
Long-term opioid user	515 (6.2)	1.26 (1.10, 1.45)	<0.001
Respiratory disease mortality			
Opioid naïve patient	12,097 (0.7)	1	
Long-term opioid user	234 (2.8)	1.15 (0.90, 1.45)	0.274
Digestive disease mortality			
Opioid naïve patient	4648 (0.3)	1	
Long-term opioid user	66 (0.8)	1.35 (0.94, 1.93)	0.210
Skin disease mortality			
Opioid naïve patient	236 (0.0)	1	
Long-term opioid user	4 (0.0)	1.50 (0.40, 5.70)	0.372
Musculoskeletal disease mortality			
Opioid naïve patient	656 (0.0)	1	
Long-term opioid user	24 (0.3)	1.48 (0.70, 2.98)	0.250
Genitourinary disease mortality			
Opioid naïve patient	2872 (0.2)	1	
Long-term opioid user	78 (0.9)	1.05 (0.75, 1.52)	0.842
Mortality due to event during pregnancy, childbirth and the puerperium			
Opioid naïve patient	15 (0.0)	1	
Long-term opioid user	0 (0.0)	0.00 (0.00-)	0.998
Congenital disease mortality			
Opioid naïve patient	48 (0.0)	1	
Long-term opioid user	2 (0.0)	7.05 (0.95, 50.25)	0.098
Mortality associated symptoms, signs and abnormal clinical and laboratory findings			
Opioid naïve patient	10,225 (0.6)	1	
Long-term opioid user	224 (2.7)	1.70 (1.38, 2.06)	<0.001
Mortality due to Injury, poisoning and certain other consequences of external causes			
Opioid naïve patient	10,842 (0.6)	1	
Long-term opioid user	124 (1.5)	1.15 (0.85, 1.52)	0.278
Mortality due to factors influencing health status and contact with health services			
Opioid naïve patient	39 (0.0)	1	
Long-term opioid user	2 (0.0)	6.55 (0.80, 48.75)	0.085

***Table 5*: Survival analyses regarding 10-year disease specific mortality among patients with chronic non-cancer pain in 2010.**
HR, hazard ratio; CI, confidence interval.

factors for long-term opioid use. Rheumatoid arthritis and osteoarthritis are the most common indications for long-term opioid prescription among MSDs.[26,27] Recent studies have reported that up to 40% of patients with rheumatoid arthritis are long-term opioid users,[26] while long-term opioid users among patients with osteoarthritis varied from 8.9% to 26.4%.[28] Low back pain is also one of the most common causes for which patients with CNCP require long-term opioid therapy,[29,30] and the improvement of pain care to reduce opioid therapy in patients with low back pain has recently been clinically emphasized.[30] We demonstrated that the pain management of MSDs, such as rheumatoid arthritis, osteoarthritis, and low back pain, is a major public health challenge that needs to be addressed in order to effectively reduce long-term opioid use.

The results of the survival analyses are notable given that we followed patient outcomes for a 10-year period from 2011 through 2019. Among disease-specific mortalities, long-term opioid sage was associated with an increased prevalence of 10-year mortality due to cancer among patients with CNCP. Similarly, we recently reported that long-term opioid use is associated with an increased risk of development of cancer among patients with CNCP in South Korea.[31] Moreover, 10-year mortality due to circulatory disease was associated with long-term opioid use among patients with CNCP. Recent data suggest that opioid use in patients with chronic pain results in adverse pharmacological outcomes and interferes with cardiovascular medications.[32] Therefore, opioid prescriptions were associated with increased cardiovascular mortality in the United States.[16] However, another cohort study in Denmark reported no statistically significant association between long-term opioid use and both cardiovascular and cancer mortality among patients with CNCP.[33] The impact of long-term opioid use on long-term mortality remains a controversial topic, especially owing to cancer and cardiovascular diseases, and more studies are warranted to confirm these findings.

The increased 10-year circulatory mortality based on the long-term opioid use was a notable finding. Relationship between opioid use and cardiovascular diseases have raised a concern for the public health worldwide,[32] and an overdose could trigger some major adverse cardiovascular events resulting from hemodynamic, vascular, and electrophysiological consequences.[34] In a previous study, morphine administration was associated with higher mortality in patients presenting with non-ST-segment elevation acute coronary syndromes.[35] Moreover, morphine was reported to decreases clopidogrel concentration and effect due to drug interaction, which might lead to treatment failure of patients with myocardial infarction.[36] In these perspectives, our study is the first to report that the long-term use of opioids might affect the increased 10-year circulatory mortality in patients with CNCP.

There is an issue regarding sample size in this study. We found that approximately over five million people visited or got admitted at hospitals for treatment with diagnosis of CNCP in a month in South Korea. Therefore, the sample size of patients with CNCP in South Korea was too large for statistical analysis. Consequently, 2.5% of adult patients were newly extracted using a stratified random sampling technique considering age and sex as exclusive strata. Thus, 1,804,019 patients with CNCP were included in the survival analysis as 2010 cohort. Considering the event rate of 10-year all-cause mortality in the two groups with a 0.05 chance of type 1 error, 4913 in the opioid-naive patients and 23 patients in the long-term opioid users were enough in the justification of sample size. Thus, our sample size has an adequate power for detecting statistical difference in the survival analyses regarding 10-year all-cause mortality.

This study had several limitations. First, we used a 2.5% stratified random sampling technique for data extraction, and there might have been some differences between the sampled patients with CNCP and all patients with CNCP. Second, the severity of each MSD was not considered in the context of this study. For example, the amount, or severity of pain due to each MSD was not measured using pain scale, which might have an impact on the study findings. Third, some important information regarding lifestyle factors, such as alcohol consumption and smoking history, was not reflected in this study because of the lack of information contained in the NHIS database. Fourth, we used opioid prescription information; actual compliance with opioids in patients with CNCP was not reflected in this study, which might also have affected the results. Finally, we excluded patients who were diagnosed with cancer, to focus on the patients with CNCP. However, there might be a selection bias, because some patients with cancer might have suffered from MSDs such as rheumatoid arthritis or osteoarthritis. Moreover, the exclusion of patients who underwent surgery during the period might cause another selection bias, because surgical patients are usually not prescribed opioids three months after surgery.

In conclusion, long-term opioid use increased in patients with CNCP in South Korea from 2010 to 2019. Certain key factors (old age, underlying disability, comorbid status, use of benzodiazepine or Z-drug, rheumatoid arthritis, osteoarthritis, and low back pain) represent potential risk factors predisposing individuals to long-term opioid use. Moreover, long-term opioid use was associated with increased 10-year all-cause mortality among patients with CNCP. This association had a most evident impact on the 10-year mortality rates resulting from cancer and circulatory diseases.

Contributors

TKO and IAS contributed to the study design, analyzed the data, and drafted the first manuscript. HRC contributed to the data acquisition, project administration and

critically revised the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of interests

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101558.

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