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Opioid Prescription and Long-Term Survival Outcomes in Adults: A Nationwide Cohort Study in Korea

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Disclosure

The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: We aimed to investigate the association between short- and long-term opioid use and long-term mortality in Korea.

Methods: In this population-based retrospective cohort study, data were obtained from the National Health Insurance Service of South Korea. The study included all adult individuals who were prescribed opioids in 2016. The control group comprised adults not prescribed opioids in 2016 selected using a 1:1 stratified random sampling technique. Participants were categorized into three groups: non-user, opioid 1–89 days user (short-term), and opioid ≥ 90 days user (long-term) groups. The primary endpoint in this study was 5-year all-cause mortality, evaluated from January 1, 2017 to December 31, 2021.

Results: In total, 4,556,606 adults were included in this study. Of these, 2,070,039 were prescribed opioids at least once. Specifically, 1,592,883 adult individuals were prescribed opioids for 1–89 days, while 477,156 adults were prescribed opioid for ≥ 90 days. In the multivariable Cox regression modelling, the opioid user group had a 28% (hazard ratio [HR], 1.28; 95% confidence interval [95% CI], 1.26–1.29; $P < 0.001$) higher risk of 5-year all-cause mortality than had the non-user group. Moreover, the opioid 1–89 days and opioid ≥ 90 days user groups had 15% (HR, 1.15; 95% CI, 1.14–1.17; $P < 0.001$) and 49% (HR, 1.49; 95% CI, 1.47–1.51; $P < 0.001$) higher risks of 5-year all-cause mortality than had the non-user group, respectively.

Conclusion: Both short and long-term opioid prescriptions were associated with increased long-term mortality among the Korean adult population.

Keywords: Analgesics, Opioid; Population; Cohort Studies; Mortality; Korea

INTRODUCTION

Opioids are among the most common analgesics prescribed as they are potent pain relievers.¹ However, their prescription has been associated with the risk of dependence and addiction,² contributing to the current global opioid epidemic.³ A recent study reported that the risk of opioid abuse and dependence was the highest in six countries, namely Australia, Canada, France, Germany, United Kingdom, and United States,⁴ suggesting that the opioid epidemic is currently one of the most important public health issues.

Author Contributions

Conceptualization: Oh TK, Song IA. Data curation: Oh TK. Formal analysis: Oh TK. Methodology: Song IA. Writing - original draft: Oh TK. Writing - review & editing: Song IA.

Opioid administration can cause a range of side effects, including sedation, dizziness, nausea, vomiting, constipation, and respiratory depression.⁵ Moreover, opioid therapy is known to have an immunosuppressive effect,⁶ which may lead to various adverse health outcomes.⁷ Population-based cohort studies have consistently reported that opioid use is associated with increased mortality,⁸⁻¹⁰ with similar results reported in South Korea.^{11,12} However, these studies have primarily focused on the effect of long-term or chronic opioid use on long-term prognosis using relatively small sample sizes.⁸⁻¹² While both short- and long-term opioid use can affect long-term mortality in the general adult population; the exact nature of this association remains controversial.

Therefore, this study aimed to investigate the association between both short- and long-term opioid use and long-term mortality using a national registration database in South Korea.

METHODS**Study design and ethical statement**

This population-based cohort study followed the requirements of the Strengthening the Reporting of Observational Studies in Epidemiology.¹³

Data source

As South Korea's sole public health insurance system, the NHIS record data on drug prescriptions, medical procedures, and disease diagnosis, all of which are classified using the International Classification of Diseases, 10th Revision (ICD-10) numbers. The NHIS is an obligatory government health-care system in Korea that covers citizens as well as foreigners who have been in the nation for more than six months. Furthermore, the NHIS supplies information on socioeconomic characteristics and fatalities for all individuals in the NHIS database.¹⁴

Study population

We initially requested the extraction of the data of all adult individuals (≥ 20 years old) who received any opioid prescription from medical institutions in 2016. Data were collected for only one day of opioid prescription for each individual. Thus, 2,304,592 adults receiving a prescription of opioids in 2016 were included. Thereafter, using a 1:1 stratified random sampling technique, considering the age and sex, we requested the extraction of data for 2,304,592 adult individuals in the non-user group who did not receive any opioid prescription between January 1, 2016 and December 31, 2016. Therefore, 4,609,184 adults were screened. After excluding 52,578 individuals who died in 2016, 4,556,606 were included in the analysis. Among them, 2,070,039 were prescribed opioids in 2016. Specifically, 1,592,883 individuals were prescribed opioids for 1–89 days while 477,156 individuals were prescribed opioids for ≥ 90 days. The participants were classified into three groups: non-user, opioid 1–89 days user, and opioid ≥ 90 days user groups according to the criteria of classification of short-term and long-term opioid prescription period.¹⁵ To evaluate chronic opioid prescriptions (lasting more than 3 months), data on opioid prescriptions from October 2015 to March 2017 was analysed. This approach was taken to minimize the misclassification of individuals who actually received long-term prescriptions as short-term users due to the relatively brief study period of one year. For instance, patients receiving opioid prescriptions from November 2016 to February 2017 might be inaccurately categorized as short-term users. The selection process for the study population is illustrated in **Fig. 1**.

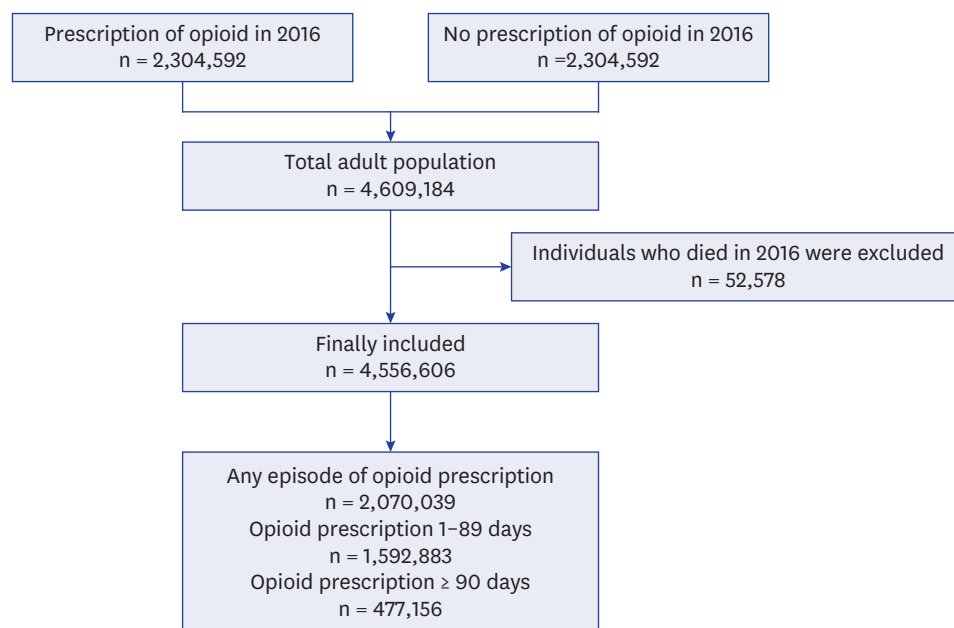


Fig. 1. Flow chart depicting the study participants' selection process.

Study endpoint

The primary endpoint in this study was 5-year all-cause mortality, which was evaluated from January 1, 2017 to December 31, 2021.

Collected covariates

All information regarding the covariates used in the analyses were collected in 2016. Demographic data included age and sex. Socioeconomic status-related information was assessed using household income levels and residences. Regarding household income, individuals who were too poor to pay insurance premiums were classified into the medical aid program group by the NHIS. All other patients were classified into four groups using quartile ratios (Q1 [lowest], Q2, Q3, and Q4 [highest]). Residences were classified into urban (Seoul or other metropolitan cities) and rural (all other areas). Information regarding underlying disabilities was collected as all disabilities must be registered in the NHIS database to be eligible for receiving various benefits from the social welfare systems in South Korea. All disabilities should be determined legally by a specialist doctor based on the criteria of difficulty in maintaining daily life activities due to disability. Underlying disability was categorized according to severity, distinguishing between mild-to-moderate and severe disability. To reflect the comorbid status of patients, 31 underlying diseases in the Elixhauser Comorbidity index were collected.¹⁶ Prescription data for other analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs, gabapentin, and pregabalin were collected. Underlying musculoskeletal diseases such as osteoarthritis, low back pain, neck pain, gout, and other musculoskeletal diseases were collected as covariates because they necessitated opioid prescriptions. The ICD-10 codes of the underlying musculoskeletal diseases are displayed in **Supplementary Data 1**.

Statistical analysis

Percentages and interquartile ranges were used to represent categorical and continuous variables, respectively. Continuous variables were found to have a non-normal distribution,

as indicated by the Kolmogorov-Smirnov test. The Mann-Whitney U Test and χ^2 test were employed to test for the between-group comparisons of continuous and categorical variables, respectively.

We employed a multivariable Cox regression model to examine whether the opioid user group showed higher long-term mortality than the non-user group. All covariates were included in the adjusted model. Moreover, we fitted another multivariable Cox regression model for 5-year all-cause mortality after classifying the opioid user group into two subgroups—the 1–89 days opioid user and ≥ 90 days opioid user groups—to investigate whether the prescription period affects results. All results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and log-log plots were used to confirm that the central assumptions of the Cox proportional hazard models were satisfied. There was no multicollinearity between the variables in the multivariate model, with variance inflation factors below 2.0. All statistical analyses were performed using IBM SPSS for Windows (version 25.0; IBM Corp., Armonk, NY, USA), and a P value < 0.05 was deemed statistically significant.

Ethics statement

Because this investigation used publicly available data, the Institutional Review Board (IRB) waived protocol deliberation (IRB number: X-2307-840-903). The National Health Insurance Service (NHIS) authorized the study protocol (NHIS approval number: NHIS-2023-1-115) and permitted data access. The IRB waived the necessity for informed consent because the study used retrospectively collected anonymised data.

RESULTS

Study population

Fig. 1 shows a flowchart depicting the participant selection process in this study. The NHIS initially screened 2,304,592 adult individuals who were prescribed opioids in 2016 and extracted 2,304,592 controlled individuals as the non-user group. Thus, a total of 4,609,184 adult individuals were screened in 2016. After excluding 52,578 individuals who died in 2016, 4,556,606 adults were included in the study. Of these, 2,070,039 patients were prescribed opioids at least once. Specifically, 1,592,883 adult individuals were prescribed opioid for 1 day to 89 days, while 477,156 adults were prescribed opioids for 90 days or more. Table 1 shows the clinicopathological characteristics of the study population.

Opioid use and mortality

Table 2 shows the comparison of clinicopathological characteristics between opioid users and non-users. The 5-year all-cause mortality rate was higher in the non-user group (6.1%; 151,130/2,486,567) than in the opioid user group (5.6%; 115,216/2,070,039). However, as depicted in Table 3, after covariate adjustment, multivariable Cox regression model 1 showed that the opioid user group was associated with a 28% (HR, 1.28; 95% CI, 1.26–1.29; $P < 0.001$) higher risk of 5-year all-cause mortality than the non-user group. Moreover, the multivariable Cox regression model 2 showed that the opioid 1–89 days user group and opioid ≥ 90 days user group were associated with 15% (HR, 1.15; 95% CI, 1.14–1.17; $P < 0.001$) and 49% (HR, 1.49; 95% CI, 1.47–1.51; $P < 0.001$) higher risk of 5-year all-cause mortality, respectively, compared with the non-user group. All HRs with 95% CIs of the other covariates included in multivariable Model 1 are presented in Table 4. Old age (HR, 1.11; 95% CI, 1.11–1.11; $P < 0.001$), male sex (vs. female sex HR, 1.60; 95% CI, 1.59–1.61; $P < 0.001$), living in rural area (vs. urban area;

Table 1. Clinicopathological characteristics of the study population (N = 4,556,606)

Variables	Values
Age, yr	57.0 [44.0–68.0]
Sex, male	2,115,980 (46.4)
Household income level	
Medical aid program group	192,806 (4.2)
Q1 in quartile (lowest)	827,964 (18.2)
Q2 in quartile	889,905 (19.5)
Q3 in quartile	1,090,853 (23.9)
Q4 in quartile (highest)	1,478,018 (32.4)
Unknown	77,060 (1.7)
Residence	
Urban area	1,975,151 (43.3)
Rural area	2,581,455 (56.7)
Underlying disability	
Mild to moderate	266,466 (5.8)
Severe	127,325 (2.8)
Underlying comorbidity	
Congestive heart failure	200,149 (4.4)
Cardiac arrhythmias	172,593 (3.8)
Valvular disease	23,761 (0.5)
Pulmonary circulation disorders	12,893 (0.3)
Peripheral vascular disorders	538,161 (11.8)
Hypertension, uncomplicated	1,467,173 (32.2)
Hypertension, complicated	158,857 (3.5)
Paralysis	37,848 (0.8)
Other neurological disorders	195,909 (4.3)
Chronic pulmonary disease	1,239,793 (27.2)
Diabetes, uncomplicated	760,143 (16.7)
Diabetes, complicated	390,968 (8.6)
Hypothyroidism	218,182 (4.8)
Renal failure	73,103 (1.6)
Liver disease	971,674 (21.3)
Peptic ulcer disease, excluding bleeding	779,330 (17.1)
AIDS/HIV	2,586 (0.1)
Lymphoma	7,243 (0.2)
Metastatic cancer	35,586 (0.8)
Solid tumor without metastasis	290,745 (6.4)
Rheumatoid arthritis/collagen vascular diseases	237,796 (5.2)
Coagulopathy	48,892 (1.1)
Obesity	5,230 (0.1)
Weight loss	36,163 (0.8)
Fluid and electrolyte disorders	224,926 (4.9)
Blood loss anemia	10,055 (0.2)
Deficiency anemia	242,680 (5.3)
Alcohol abuse	82,568 (1.8)
Drug abuse	1,972 (0.0)
Psychoses	48,135 (1.1)
Depression	460,661 (10.1)
Prescription of other analgesics	
Paracetamol	263,333 (5.8)
NSAIDs	1,267,814 (27.8)
Gabapentin or pregabalin	263,333 (5.8)
Underlying MSDs	
Osteoarthritis	1,658,176 (36.4)
Low back pain	2,123,876 (46.6)
Neck pain	598,821 (13.1)
Gout	192,110 (4.2)
Other MSDs	1,974,681 (43.3)

Values are presented as median [interquartile range] or number (%).

AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, NSAID = nonsteroidal anti-inflammatory drug, MSD = musculoskeletal disease.

Table 2. Comparison of clinicopathological characteristics between opioid users and non-users

Variables	Opioid user (n = 2,070,039)	Non-user (n = 2,486,567)	P value
Age, yr	57.0 [44.0–68.0]	57.0 [44.0–69.0]	< 0.001
Sex, male	951,502 (46.0)	1,164,478 (46.8)	< 0.001
Household income level			< 0.001
Medical aid program group	104,209 (5.0)	88,597 (3.6)	
Q1 in quartile (lowest)	380,087 (18.4)	447,877 (18.0)	
Q2 in quartile	412,561 (19.9)	477,344 (19.2)	
Q3 in quartile	502,497 (24.3)	588,356 (23.7)	
Q4 in quartile (highest)	637,009 (30.8)	841,009 (33.8)	
Unknown	33,676 (1.6)	43,384 (1.7)	
Residence			< 0.001
Urban area	845,794 (40.9)	1,129,357 (45.4)	
Rural area	1,224,245 (59.1)	1,357,210 (54.6)	
Underlying disability			< 0.001
Mild to moderate	143,220 (6.9)	123,246 (5.0)	
Severe	53,056 (2.6)	74,269 (3.0)	
Underlying comorbidity			
Congestive heart failure	102,801 (5.0)	97,348 (3.9)	< 0.001
Cardiac arrhythmias	88,067 (4.3)	84,526 (3.4)	< 0.001
Valvular disease	11,331 (0.5)	12,430 (0.5)	< 0.001
Pulmonary circulation disorders	6,810 (0.3)	6,083 (0.2)	< 0.001
Peripheral vascular disorders	319,354 (15.4)	218,807 (8.8)	< 0.001
Hypertension, uncomplicated	724,080 (35.0)	743,093 (29.9)	< 0.001
Hypertension, complicated	80,027 (3.9)	78,830 (3.2)	< 0.001
Paralysis	14,413 (0.7)	23,435 (0.9)	< 0.001
Other neurological disorders	103,553 (5.0)	92,356 (3.7)	< 0.001
Chronic pulmonary disease	690,375 (33.4)	549,418 (22.1)	< 0.001
Diabetes, uncomplicated	390,707 (18.9)	369,436 (14.9)	< 0.001
Diabetes, complicated	201,361 (9.7)	189,607 (7.6)	< 0.001
Hypothyroidism	112,985 (5.5)	105,197 (4.2)	< 0.001
Renal failure	33,733 (1.6)	39,370 (1.6)	< 0.001
Liver disease	523,363 (25.3)	448,311 (18.0)	< 0.001
Peptic ulcer disease, excluding bleeding	460,524 (22.2)	318,806 (12.8)	< 0.001
AIDS/HIV	1,291 (0.1)	1,295 (0.1)	< 0.001
Lymphoma	3,574 (0.2)	3,669 (0.1)	< 0.001
Metastatic cancer	17,861 (0.9)	17,725 (0.7)	< 0.001
Solid tumor without metastasis	139,331 (6.7)	151,414 (6.1)	< 0.001
Rheumatoid arthritis/collagen vascular diseases	158,824 (7.7)	78,972 (3.2)	< 0.001
Coagulopathy	25,227 (1.2)	23,665 (1.0)	< 0.001
Obesity	3,153 (0.2)	2,077 (0.1)	< 0.001
Weight loss	18,111 (0.9)	18,052 (0.7)	< 0.001
Fluid and electrolyte disorders	123,819 (6.0)	101,107 (4.1)	< 0.001
Blood loss anemia	5,254 (0.3)	4,801 (0.2)	< 0.001
Deficiency anemia	127,428 (6.2)	115,252 (4.6)	< 0.001
Alcohol abuse	44,317 (2.1)	38,251 (1.5)	< 0.001
Drug abuse	1,162 (0.1)	810 (0.0)	< 0.001
Psychoses	19,719 (1.0)	28,416 (1.1)	< 0.001
Depression	274,357 (13.3)	186,304 (7.5)	< 0.001
Prescription of other analgesics			
Paracetamol	2,054,093 (99.2)	1,024,258 (41.2)	< 0.001
NSAIDs	704,240 (34.0)	563,574 (22.7)	< 0.001
Gabapentin or pregabalin	203,574 (9.8)	59,759 (2.4)	< 0.001
Underlying MSDs			
Osteoarthritis	1,060,467 (51.2)	597,709 (24.0)	< 0.001
Low back pain	1,375,985 (66.5)	747,891 (30.1)	< 0.001
Neck pain	417,497 (20.2)	181,324 (7.3)	< 0.001
Gout	119,910 (5.8)	72,200 (2.9)	< 0.001
Other MSDs	1,237,029 (59.8)	737,652 (29.7)	< 0.001
5-year all-cause mortality	115,216 (5.6)	151,130 (6.1)	< 0.001

Values are presented as median [interquartile range] or number (%).

AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, NSAID = nonsteroidal anti-inflammatory drug, MSD = musculoskeletal disease.

Table 3. Multivariable cox regression model for 5-year all-cause mortality (event N = 266,177, 5.8%)

Variables	HR (95% CI)	P value
Multivariable model 1		
Non-users	1	
Opioid users	1.28 (1.26–1.29)	< 0.001
Multivariable model 2		
Non-users	1	
Opioid prescription 1–89 days	1.15 (1.14–1.17)	< 0.001
Opioid prescription ≥ 90 days	1.49 (1.47–1.51)	< 0.001

HR = hazard ratio, CI = confidence interval.

HR, 1.08; 95% CI, 1.07–1.09; $P < 0.001$), mild to moderate disability (HR, 1.19; 95% CI, 1.18–1.21; $P < 0.001$), severe disability (HR, 1.79; 95% CI, 1.76–1.81; $P < 0.001$) and various underlying comorbidities were associated with an increased risk of 5-year all-cause mortality.

DISCUSSION

This population-based cohort study showed that opioid prescriptions are associated with increased long-term mortality within the adult population of South Korea. Moreover, this association was significantly evident in both short- and long-term opioid prescription periods. These findings suggest that both long-term and short-term opioid use could contribute to a worsened long-term prognosis among adults.

Long-term opioid therapy poses many risks and is a major public health concern, as it can lead to dependence, addiction, misuse, and overdose.¹⁷ In the United States, death due to opioid-related overdoses have tripled, increasing from 2006 to 2016, and health care costs, criminal justice expenses, and productivity losses associated with opioid misuse were estimated to total \$78.5 billion.^{18,19} Moreover, cohort studies in Korea have reported that the number of opioid users in the general population has increased and that opioid use is associated with increased mortality,^{11,12,20} suggesting that long-term opioid use is becoming a major public health concern that cannot be ignored in Korea.

As a direct effect, long-term opioid therapy can cause various medical problems,²¹ which could be related to increased long-term mortality. The most common cause of mortality from an opioid overdose or misuse is opioid-induced respiratory depression.²² Opioid-induced respiratory depression could be linked to obstructive sleep apnoea because opioids impair upper airway function and disrupt respiratory control, resulting in central apnoea, upper airway obstruction, and hypoxemia during sleep.²³ Long-term opioid therapy may induce immune system alterations, which can be elucidated by modifications in both the innate and adaptive immune systems.²⁴ The immunosuppression associated with opioid prescription was linked to an increased risk of infection such as pneumonia²⁵ and cancer through carcinogenesis due to long-term opioid therapy.²⁶ Moreover, chronic opioid therapy was related to an elevated incidence rate ratio of 2.66 (95% CI, 2.30–3.08) for myocardial infarction compared with that in the general population.²⁷ This is because chronic opioid use was associated with alterations in the serum concentrations of triglycerides and total high-density lipoprotein and low-density lipoprotein cholesterol,²⁸ which could elevate risk of myocardial infarction.²⁴

The exact physical condition that warranted opioid prescription could have also affected the results of this study. It was well reported that patients with chronic pain had higher prevalence

Table 4. All HRs with 95% CIs of the other covariates included in multivariable model 1

Variables	HR (95% CI)	P value
Age, yr	1.11 (1.11–1.11)	< 0.001
Sex, male	1.60 (1.59–1.61)	< 0.001
Household income level		
Medical aid program group	1.33 (1.32–1.35)	< 0.001
Q1 in quartile (lowest)	1	
Q2 in quartile	1.00 (0.99–1.01)	0.887
Q3 in quartile	0.91 (0.90–0.93)	< 0.001
Q4 in quartile (highest)	0.81 (0.80–0.82)	< 0.001
Unknown	0.89 (0.86–0.92)	< 0.001
Residence		
Urban area	1	
Rural area	1.08 (1.07–1.09)	< 0.001
Underlying disability		
Mild to moderate	1.19 (1.18–1.21)	< 0.001
Severe	1.79 (1.76–1.81)	< 0.001
Underlying comorbidity		
Congestive heart failure	1.31 (1.29–1.33)	< 0.001
Cardiac arrhythmias	1.12 (1.11–1.14)	< 0.001
Valvular disease	1.29 (1.25–1.33)	< 0.001
Pulmonary circulation disorders	1.43 (1.39–1.48)	< 0.001
Peripheral vascular disorders	0.93 (0.92–0.94)	< 0.001
Hypertension–uncomplicated	1.00 (1.00–1.01)	0.393
Hypertension–complicated	0.92 (0.90–0.93)	< 0.001
Paralysis	1.80 (1.76–1.83)	< 0.001
Other neurological disorders	1.42 (1.41–1.44)	< 0.001
Chronic pulmonary disease	1.11 (1.10–1.12)	< 0.001
Diabetes–uncomplicated	1.11 (1.10–1.12)	< 0.001
Diabetes–complicated	1.20 (1.19–1.21)	< 0.001
Hypothyroidism	0.84 (0.82–0.85)	< 0.001
Renal failure	1.38 (1.36–1.40)	< 0.001
Liver disease	0.98 (0.97–0.99)	< 0.001
Peptic ulcer disease–excluding bleeding	0.95 (0.94–0.96)	< 0.001
AIDS/HIV	0.85 (0.74–0.97)	0.018
Lymphoma	2.05 (1.96–2.14)	< 0.001
Metastatic cancer	3.65 (3.58–3.72)	< 0.001
Solid tumor without metastasis	1.56 (1.54–1.57)	< 0.001
Rheumatoid arthritis/collagen vascular diseases	0.99 (0.98–1.01)	0.365
Coagulopathy	1.22 (1.19–1.24)	< 0.001
Obesity	0.71 (0.58–0.87)	0.001
Weight loss	1.45 (1.42–1.47)	< 0.001
Fluid and electrolyte disorders	1.45 (1.43–1.46)	< 0.001
Blood loss anemia	1.24 (1.18–1.31)	< 0.001
Deficiency anemia	1.32 (1.30–1.33)	< 0.001
Alcohol abuse	1.79 (1.76–1.83)	< 0.001
Drug abuse	1.41 (1.27–1.57)	< 0.001
Psychoses	1.57 (1.53–1.60)	< 0.001
Depression	1.21 (1.19–1.22)	< 0.001
Prescription of other analgesics		
Paracetamol	0.69 (0.68–0.70)	< 0.001
NSAIDs	0.80 (0.79–0.80)	< 0.001
Gabapentin or pregabalin	1.06 (1.04–1.07)	< 0.001
Underlying MSDs		
Osteoarthritis	0.88 (0.87–0.89)	< 0.001
Low back pain	0.92 (0.91–0.93)	< 0.001
Neck pain	0.82 (0.82–0.83)	< 0.001
Gout	0.98 (0.97–1.00)	0.052
Other MSDs	0.82 (0.82–0.83)	< 0.001

HR = hazard ratio, CI = confidence interval, AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, NSAID = nonsteroidal anti-inflammatory drug, MSD = musculoskeletal disease.

of all comorbidities than those without chronic pain.²⁹ In patients with knee osteoarthritis, comorbid hypertension, gastrointestinal disease, and depressed mood were independently associated with opioid use.³⁰ In this study, as shown in **Table 2**, the opioid user group shows a higher proportion of 26 medical illnesses with regard to the Elixhauser Comorbidity index than the non-user group. Thus, the physical conditions related to opioid prescription may increase the 5-year all-cause mortality rate in the opioid user groups in this study.

Although the adverse effects of long-term opioid therapy are well established, the effect of short-term opioid therapy on long-term mortality remains to be identified. We included patients who were prescribed opioids for 1–89 days in 2016 and analysed their impact on 5-year all-cause mortality using large sample sizes. Short-term opioid users are at risk of progressing to long-term opioid use,¹⁵ which may worsen long-term survival outcomes. However, the corresponding clinical significance could be questionable in this study as the risk among short-term opioid users was low with an HR of 1.15 (95% CI, 1.14–1.17) based on a sample size of 4,556,606 individuals. Therefore, further studies to identify the impact of both short- and long-term opioid use on long-term mortality are warranted.

Additional important findings regarding 5-year all-cause mortality were depicted among the covariates in multivariable modelling, regardless of opioid use. Poor household income (medical aid program group) was a significant risk factor for increased 5-year all-cause mortality, whereas the high household income group (Q3 and Q4) was associated with decreased 5-year all-cause mortality. Income inequality was associated with mortality in the United States,³¹ which was also observed in South Korea in the present study. Living in rural areas was also associated with an increased 5-year all-cause mortality compared to those living in urban areas. Indeed, it has been reported that accessibility to healthcare services could significantly affect mortality,³² and those living in rural areas have limited access to healthcare service centres compared with those living in urban areas, which may have affected the results of this study. Moreover, we included underlying disabilities in addition to the 31 underlying diseases calculated using the Elixhauser comorbidity index. Therefore, our findings were derived from a robust analysis using several covariates.

This study had several limitations. First, opioid dosage was not considered in this study. Second, some important variables such as body mass index, smoking history, and alcohol consumption were not included as covariates because of the lack of information in the NHIS database. Third, because our study used South Korean data from a nationwide registration database, generalizability to other countries may be limited. Finally, residual or unmeasured confounders may have affected the results.

In conclusion, this population-based cohort study showed that opioid prescriptions are associated with increased long-term mortality in adults. Moreover, this association was significantly evident in both short- and long-term opioid users. Future studies to confirm the mechanism between opioid prescriptions and long-term mortality, considering the duration, dosage, and potency of opioid prescriptions, are warranted.

SUPPLEMENTARY MATERIAL

Supplementary Data 1

ICD-10 codes of musculoskeletal disease

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