Observational Study

Medicine

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Prevalence of and risk factors associated with chronic opioid use after traumatic injury

A historical cohort study using the Korean National Health Insurance Service sample cohort data

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Abstract

Chronic opioid use (COU) after traumatic injuries is a global health concern. COU after trauma delays recovery and increases the risk of long-term drug dependence. However, the population-prevalence and factors associated with COU after traumatic injury in South Korea remain unclear. We aimed to estimate the prevalence of COU and associated risk factors in patients after trauma in South Korea. A historical cohort study using the population-representative database including 1,103,405 South Korean subjects, patients admitted due to a newly diagnosed trauma (n = 65,444) or nontraumatic etiologies (n = 338,321) from January 1, 2003, to June 30, 2015, were analyzed. COU was defined as the prescription of opioid in the first 3 to 6 months from the index date. Prevalence of COU was summarized. A multivariable logistic regression analysis was conducted to investigate association of COU with traumatic injuries, accounting for a priori sociodemographic and clinical risk factors. A total of 13.5% and 12.6% of patients were found to be chronic opioid users in the trauma and the control group, respectively. The adjusted odds ratio (aOR) (95% CI) of COU in the injured compared to the noninjured was 1.13 (1.01 to 1.16), when controlling for age group, sex, calendar year, area of residence, previous opioid use, comorbidity, surgery during the index admission and intensive care unit care. Risk factors included being aged 65 to 74 years (aOR = 2.87; 95% CI = 2.73 to 3.01), aged ≥ 75 years (aOR = 2.48; 95% CI = 2.35 to 2.62), and history of previous opioid use (aOR = 3.27; 95% CI = 3.21 to 3.34) were the most significant risk factors of COU, independent of injury. COU was prevalent both in the injured and noninjured patients, with slightly increased risk of COU in those sustaining traumatic injury compared to those who were noninjured. Further stud y to address prevalent COU in South Korea is required to avoid opioid-related harms.

Abbreviations: AIS = abbreviated injury scale, aOR = adjusted odds ratio, ATC = anatomical therapeutic chemical, CCI = charlson comorbidity index, CI = confidence intervals, CONSORT = the consortium to study opioid risks and trends, COU = chronic opioid use, DALY = disease-adjusted life years, ICD = international classification of diseases, ICISS = the international classification of disease 10th edition-based injury severity score, ICU = intensive care unit, IQR = interquartile range, IRB = institutional review board, KNHIS = Korean National Health Insurance Service, OR = odds ratio, PAG = periacueductal gray, US = United States.

Keywords: chronic opioid use, cohort study, injury, risk factor, trauma

1. Introduction

Traumatic injuries are the leading cause of global burden of disease-adjusted life years (DALY) in people aged 10 to 49 years and seventh most common cause across all ages, accounting for 8.8% of global deaths in 2019.[1] Traumatic injuries increase the risk of developing chronic pain and chronic opioid

Kun Hyung Kim was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. NRF-2020R1F1A1075181). The funding body had no role in the study design and did not play any role during its execution, analyses, interpretation of data, or decision to submit the report for publication.

The author(s) of this work have nothing to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

The study was carried out with the relevant principles of the Declaration of Helsinki.

The Ethics board of Pusan National University Korean Medicine Hospital (PNUKH IRB-2020009-017) and the London School of Hygiene and Tropical Medicine (MSc Ethics Ref: 21716) approved the research. Individual participants' consents were exempted as the dataset was anonymized and managed by the Korean Government.

Supplemental Digital Content is available for this article.

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How to cite this article: Kim KH, MacLeod D, Cho H, Kim SH. Prevalence of and risk factors associated with chronic opioid use after traumatic injury: A historical cohort study using the Korean National Health Insurance Service sample cohort data. Medicine 2024;103:48(e40664).

Received: 14 July 2024 / Received in final form: 1 November 2024 / Accepted: 6 November 2024

http://dx.doi.org/10.1097/MD.0000000000040664

use (COU),[2,3] which also both significantly delay recovery, increase mortality and impose personal as well as economic burdens.[4–9]

Currently, several sociodemographic and clinical factors have been reported as being associated with COU.[10–14] However, a recent systematic review revealed that prevalence of COU substantially differed between studies depending on study characteristics and methodology used, with estimates ranging from 0.1% to 88.1%.[15] Other evidence also reported that information on prevalence and risk factors of COU is highly inconsistent,[10–16] which should be acknowledged when designing future studies. Heterogeneity in terms of prevalence and associated risk factors of COU after traumatic injuries calls for more high-quality evidence to better understand the burden of chronic pain management, help clinicians plan adequate opioid prescription and inform appropriate interventions to tackle COU.

Recent historical cohort studies using a nationally representative cohort dataset from South Korea investigated COU, associated factors and health outcomes in the general population,[8] in cancer surgery patients[17] and in those with chronic noncancer pain.[18] As little information is available for patients after traumatic injuries, we aimed to investigate the population-level prevalence of COU and explore risk factors associated with COU after traumatic injuries in South Korea.

2. Methods

2.1. Study design and data collection

This was a historical cohort study using the sample cohort database of the Korean National Health Insurance Service (KNHIS)[19] between 2002 and 2015 among adult patients (aged ≥ 18 years) with a first diagnosis of traumatic injury requiring hospital admission. KNHIS is a national, population-based cohort established in South Korea with systematic stratified random samples of approximately 1-million participants to represent the wider population of 46 million individuals in the 2002 National Health Information Database.[20] Cohort participants in the KNHIS database were followed for 14 years, from 2002 to 2015. The data were validated by triangulating information with another public database from Statistics Korea that offers services of overall planning and coordination of national statistics.[8]

2.2. Study population

The study population consisted of adult patients aged over 18 years who had no record of hospital admission due to trauma (defined as absence of any S00 to T79 codes in International Classification of Diseases 10th revision) and no history of cancer diagnosis (defined as absence of C code and D37, D38, D39, and D4 codes) 1 year prior to the start of follow-up. All eligible subjects were selected if they had survived and were discharged from the hospital within 3 months of their injury, to minimize the competing risk of death or prolonged hospitalization (Fig. 1).

2.3. Main exposure and control group

The main exposure was traumatic injury, ascertained as a record of the first injury that required hospital admission during the observation period. For both the exposure and control group, a record of hospital admission with ICU care was prioritized over those without ICU care whenever available. The unexposed control group was defined as people who were first admitted to the hospital due to nontraumatic etiologies during the same observation period (Fig. 1 for eligibility criteria for the exposure and control group).

2.4. Index date and follow-up

The index date was defined as the first day of the hospital admission due to a newly diagnosed traumatic injury in the exposure group or a nontraumatic diagnosis in the control group during the follow-up period. If there was a hospital admission requiring intensive care unit (ICU) care, the first day of that admission, whether due to trauma in the exposure group or a nontraumatic diagnosis in the control group, was regarded as the index date, to reflect the more severe condition in the analysis. If there were multiple hospital admissions with ICU care, the first admission during the follow-up was selected. Diagnosis codes for ascertaining traumatic injury included S00 to T19 codes referring to injuries of various body parts. Codes related to foreign body entrance, burns, frostbite, poisoning and unspecified or complication of trauma (i.e., T20 to T98) were excluded. A 1 year period prior to the index date was necessary to measure clinical covariates (i.e., diagnosis of comorbidities and prior opioid use). To ensure the trauma was newly diagnosed (i.e., no trauma history within 1 year prior to the index date) and to allow for outcome measurement, the index date of patients with trauma was set between January 1, 2003, and July 30, 2015. All follow-up was truncated at the 1 year from the index date.

2.5. Research ethics

The Ethics board of Pusan National University Korean Medicine Hospital (IRB-2020009-017) and the London School of Hygiene and Tropical Medicine (MSc Ethics Ref: 21716) approved the research. Individual participants' consents were exempted as the dataset was anonymised and managed by the Korean government.

2.6. Potential confounders and effect modifiers

Age in years was stratified into 10-year age bands (i.e., 18–24, 25–34, 35–44, 45–54, 55–65, 65–74, and ≥75 years at the index date). Other variables included sex, level of income, calendar year of the index date, Charlson comorbidity index (i.e., 0, 1, and ≥2), history of any surgery that occurred during the index admission, ICU care during the index hospital admission, the ICD 10th edition-based injury severity score (ICISS) which can range score of 0 (i.e., worst survival probability) to 1 (i.e., the best survival probability) and provides estimation of the injury-severity.[21] These factors were regarded as potential a priori confounders. Sex was considered as a priori effect modifier as previous evidence indicated that females are more likely to experience persistent post-operative pain and/or the delayed opioid cessation.[14,22–24] A full list of covariates and their categorization is provided in Appendix 1, Supplemental Digital Content, http://links.lww.com/MD/O37.

2.7. Primary and secondary outcomes

The primary outcome was COU, classified as having at least 1 opioid prescription record in the first 90 to 180 days after a traumatic injury in the exposed group, or after the first hospital admission due to nontraumatic etiologies in the unexposed control group.[14,25] As a secondary outcome persistent opioid use was defined as an opioid prescription record that started in the first 90 days and lasting at least 90 days within 1 year from the index date.[25] The adapted definition of COU by the Consortium to Study Opioid Risks and Trends (CONSORT) criteria was also used. It classifies COU as episodes of opioid prescription lasting at least 90 days and either at least 120 days of opioid supply or 10 or more separate prescription of opioids within 1 year from the index date.[25,26]

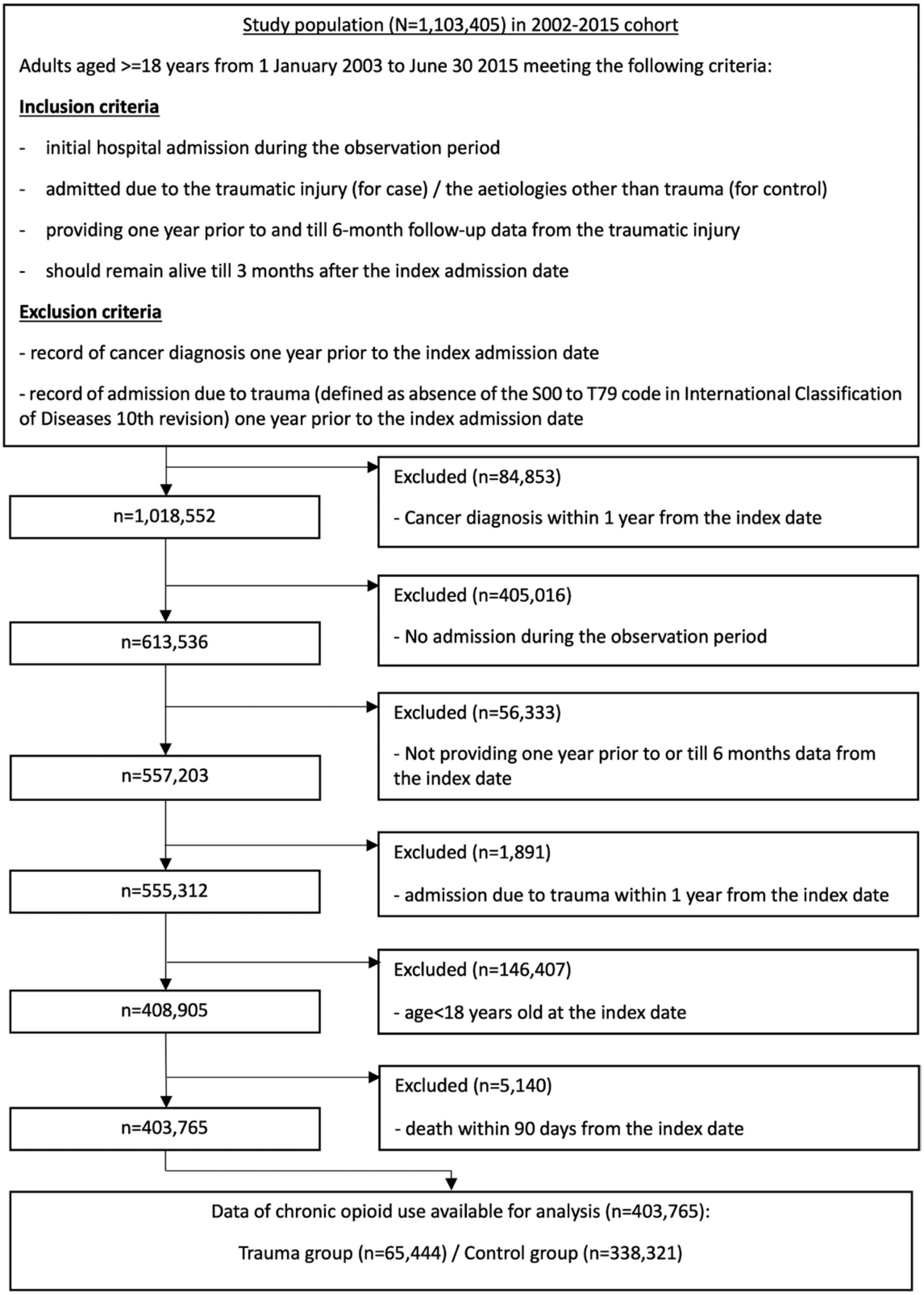

Figure 1. Study flowchart.

2.8. Types of opioids

Opioid prescriptions were identified using the Korean national medication code, which corresponds to the Anatomical Therapeutic Chemical (ATC) code of opioid medications in the dataset.[27] Opioids included codeine, dihydrocodeine, hydrocodone, tramadol, tapentadol, pethidine, fentanyl, morphine, oxycodone, hydromorphone, pentazocine, and buphrenorphine.[8,28] The full list of codes is provided in Appendix 2, Supplemental Digital Content, http://links.lww.com/MD/O37.[28] Previous opioid use was identified as any record of opioid prescription within 1 year before the index date.

2.9. Statistical analysis

Baseline demographic, socioeconomic, and clinical characteristics were descriptively summarized. Frequency counts and percentages were calculated for categorical variables. Continuous variables were presented using means with standard deviation or medians with interquartile range (IQR), according to the normality of distribution. Chi-square tests were performed to assess whether distribution of each characteristic differ according to the exposure status. The prevalence of COU, frequency, and proportion of chronic opioid user among them were illustrated.

The crude odds ratio (OR) and 95% confidence intervals (CI) comparing COU among patients exposed to trauma and the unexposed control group were calculated. Mantel-Haenszel stratification method was used to estimate the crude OR and 95% CI for COU. Multivariable logistic regression analysis was used to estimate the association between trauma and COU, adjusted for confounders, as OR and 95% CIs. Age and sex adjusted, and fully adjusted analysis including all predetermined confounders was performed. Due to the 4.3% missing values, the level of income was excluded from the final multivariable analysis. Likelihood ratio tests were performed to compare the fitness of models with different confounders. Multicollinearity issue was considered among confounders by monitoring whether the standard error of the ORs and its 95% CI substantially changed when variables were included in the existing model. Missing values were not imputed. Data management and statistical analyses were performed using Stata 17.0 (Stata Corp, Texas, US).

2.10. Sensitivity analysis

The following sensitivity analyses were conducted:

- restriction of analysis to patients with ICU care, to check whether the severity of condition affected estimations;
- restriction of analysis to patients with trauma, to explore factors associated with COU after traumatic injury;
- use of ICISS rather than ICU care as an indicator of injury severity amongst patients with traumatic injury, to reflect the severity of injury more accurately;
- impact of excluding the income level variable in the final adjusted model on the estimates of association between trauma and COU.

3. Findings

Amongst the total KNHIS database containing 1103,405 subjects, patients with traumatic injury (n = 65,444, 16.2%) and the noninjured control (n = 338,321, 83.8%), were deemed eligible and analyzed (Fig. 1). Trauma patients were more likely to be male and less likely to have comorbid conditions. Other sociodemographic and clinical characteristics are provided in Table 1 and Appendix 3, Supplemental Digital Content, http://links.lww.com/MD/O37. The distribution of missing data for income level is tabulated in Appendix 4, Supplemental Digital Content, http://links.lww.com/MD/O37, showing a slightly higher proportion of missingness in trauma patients (4.6%) than in the control group (4.2%). The most common sites of injuries in the trauma group included the abdomen, lower back or lumbar spine/pelvis (n = 20,033; 30.6%), wrist and hand (n = 18,915; 28.9%) and knee and lower leg (n = 18,248; 27.9%) (Table 2).

There were 8848 (13.5%) chronic opioid users in the trauma group and 42,715 (12.6%) in the control group, respectively. Persistent opioid use was found in 84 (0.13%) of the trauma patients and 409 (0.12%) of the control patients, respectively. Patients meeting the CONSORT criteria of opioid use were 68 (0.10%) in the trauma group and 320 (0.09%) in the control group, respectively (Table 3).

Tramadol was the most commonly prescribed opioid (93.7% in the trauma group and 91.2% in the control group, respectively) amongst chronic opioid users (n = 51,563) (Appendices 5 and 6, Supplemental Digital Content, http://links.lww.com/MD/O37). There was a slight increase in COU over time, with an overall similar trend, from 10.0% in 2003 to 11.3% in 2015 (Appendix 7, Supplemental Digital Content, http://links.lww.com/MD/O37).

The crude odds of COU were estimated to be 1.08 times higher (95% CI = 1.06 to 1.10) in trauma patients compared to non-trauma patients. After controlling for age group and sex, the association between trauma and COU remained similar (aOR = 1.13; 95% CI = 1.10 to 1.16). After adjusting for all potential confounders, the estimate remained unchanged (aOR = 1.13; 95% CI = 1.01 to 1.16) (Table 4). When adjusted for all potential confounders, the higher magnitude with increased uncertainty was observed both for persistent opioid use (aOR = 1.32; 95% CI = 1.04 to 1.68) and CONSORT-based opioid use (aOR = 1.37; 95% CI = 1.05 to 1.80).

After adjusting for trauma and all other factors, older age, women, living in metropolitan cities (not Seoul) or other areas, previous opioid use and a CCI score of above 0 were associated with higher odds of COU (Table 4). Previous opioid use (aOR = 3.27; 95% CI = 3.21 to 3.34; $P < .001$) showed the largest magnitude of association, followed by the age group of 65 to 74 years (aOR = 2.87; 95% CI = 2.73 to 3.01; $P < .001$). Surgery during the index admission showed a small protective association with COU (aOR = 0.94; 95% CI = 0.92 to 0.96; $P < .001$). There was no evidence of effect modification by sex (Appendix 8, Supplemental Digital Content, http://links.lww.com/MD/O37).

In sensitivity analyses, restricting the analysis only to patients with ICU care (i.e., having more severe condition; n = 26,630) did not change the estimates (aOR = 1.12; 95% CI = 1.01 to 1.24). Amongst patients with traumatic injuries (n = 65,444), older age, female sex, calendar years other than 2015, previous opioid use, CCI score and area of residence were associated with COU, while ICU care was not (Appendix 9, Supplemental Digital Content, http://links.lww.com/MD/O37). Surgery during the index admission showed small protective effects on COU (aOR = 0.90; 95% CI = 0.86 to 0.95; $P < .001$). Use of the ICD 10th edition-based injury severity score (ICISS) rather than ICU in the model restricted to the trauma patients showed similar results (Appendix 10, Supplemental Digital Content, http://links.lww.com/MD/O37). Including income level, despite some missing data, in the fully adjusted regression model did not change the primary analysis results (Appendix 11, Supplemental Digital Content, http://links.lww.com/MD/O37).

4. Discussion

Prevalence of COU 3 to 6 months after hospital admission due to trauma in South Korea was 13.5%, compared to 12.6 % in noninjured control patients over the period from 2003 to 2015. Tramadol was the most prescribed opioid amongst the chronic opioid users. Patients after trauma were at almost similar but increased risk which might not be clinically important, at 1.13 times higher odds of COU than those without trauma, when adjusted for age group, sex, area of residence, calendar year, comorbidity, previous opioid use, surgery and ICU care. Previous opioid use and older age group were the most prominent risk factors for increased risk of COU.

The proportion of chronic opioid users both in the trauma and noninjured control group were higher than findings in the historical cohort study using the same data source by Oh (2019) which reported rates of 1.0% (95% CI = 1.01% to 1.05%) in 2002, rising to 9.6% (95% CI = 9.56% to 9.69%) by 2015.[8] Similarly, Oh study reported opioid use prevalence of 0.5% in 2010 rising to 2.6% in 2019 amongst in chronic noncancer pain patients in South Korea[18] Difference of classification in COU may partially explain the observed discrepancy in the estimated prevalence of COU. Previous Korean studies have defined COU as a continuous supply of opioid over ≥ 90 days,[8,18] whereas in

Table 1

Characteristics of the study population by trauma status.

Characteristic	Category	Trauma (N, %)	Control (N, %)	Total (N, %)	*P*-value*
Total, n		65,444 (16.21)	338,321 (83.79)	403,765 (100.0)	
Age (yr)					
	18 to 24	7824 (11.96)	30,753 (9.09)	38,577 (9.55)	<.001
	25 to 34	11,815 (18.05)	86,957 (25.70)	98,772 (24.46)	
	35 to 44	13,412 (20.49)	60,902 (18.00)	74,314 (18.41)	
	45 to 54	14,293 (21.84)	63,160 (18.67)	77,453 (19.18)	
	55 to 64	8938 (13.66)	43,861 (12.96)	52,799 (13.08)	
	65 to 74	5339 (8.16)	33,280 (9.84)	38,619 (9.56)	
	≥75	3823 (5.84)	19,408 (5.74)	23,231 (5.75)	
Sex					
	Male	40,508 (61.91)	138,421 (40.91)	178,929 (44.32)	<.001
	Female	24,936 (38.10)	199,900 (59.09)	224,836 (55.68)	
Calendar year					
	2003	3869 (5.91)	28,587 (8.45)	32,456 (8.04)	<.001
	2004	4531 (6.92)	28,362 (8.38)	32,893 (8.15)	
	2005	5341 (8.16)	29,099 (8.60)	34,440 (8.53)	
	2006	5833 (8.91)	30,653 (9.06)	36,486 (9.04)	
	2007	5751 (8.79)	29,803 (8.81)	35,554 (8.81)	
	2008	5892 (9.00)	28,307 (8.37)	34,199 (8.47)	
	2009	6076 (9.28)	28,020 (8.28)	34,096 (8.44)	
	2010	5976 (9.13)	26,649 (7.88)	32,625 (8.08)	
	2011	5345 (8.17)	25,750 (7.61)	31,095 (7.70)	
	2012	5078 (7.76)	25,192 (7.45)	30,270 (7.50)	
	2013	4934 (7.54)	23,873 (7.06)	28,807 (7.13)	
	2014	4577 (6.99)	22,869 (6.76)	27,446 (6.80)	
	2015	2241 (3.42)	11,157 (3.30)	13,398 (3.32)	
Income level (decile)					
	1st (affluent)	5115 (7.82)	26,251 (7.76)	31,366 (7.77)	<.001
	2nd	5089 (7.78)	23,556 (6.96)	28,645 (7.09)	
	3rd	5310 (8.11)	24,940 (7.37)	30,250 (7.49)	
	4th	6013 (9.19)	28,945 (8.56)	34,958 (8.66)	
	5th	6371 (9.74)	31,675 (9.36)	38,046 (9.42)	
	6th	6316 (9.65)	33,619 (9.94)	39,935 (9.89)	
	7th	6948 (10.62)	37,672 (11.13)	44,620 (11.05)	
	8th	6874 (10.50)	36,595 (10.82)	43,469 (10.77)	
	9th	7464 (11.41)	39,400 (11.65)	46,864 (11.61)	
	10th (deprived)	6953 (10.62)	41,630 (12.23)	48,313 (11.97)	
	Missing	2991 (4.57)	14,308 (4.23)	17,299 (4.28)	
Total, n		65,444 (16.21)	338,321 (83.79)	403,765 (100.0)	
Area of residence					
Urban city (Seoul)	11,018 (16.84)	67,461 (19.94)	78,479 (19.44)	<0.001	
Metropolitan cities (other than Seoul)	16,824 (25.71)	88,129 (26.05)	104,953 (25.99)		
	Others	37,602 (57.46)	182,731 (54.01)	220,333 (54.57)	
Previous opioid use					
	No	43,917 (67.11)	234,719 (69.38)	278,636 (69.01)	<.001
	Yes	21,527 (32.89)	103,602 (30.62)	125,129 (30.99)	
ICU care					
	No	62,245 (95.11)	314,890 (93.07)	377,135 (93.40)	<.001
	Yes	3199 (4.89)	23,431 (6.94)	26,630 (6.60)	
Surgery					
	No	28,475 (43.51)	129,273 (28.21)	157,748 (39.07)	<.001
	Yes	36,969 (56.49)	209,048 (61.79)	246,017 (60.93)	
ICISS†					
	Median (IQR)	0.988 (0.959, 0.995)	–	–	–
	≥0.9	59,002 (90.16)	–	–	
	<0.9	6442 (9.84)	–	–	
CCI score					
	0	41,454 (63.34)	172,316 (50.93)	213,770 (52.94)	<.001
	1	14,866 (22.72)	85,334 (25.22)	100,200 (24.82)	
	≥2	9124 (13.94)	80,671 (23.84)	89,795 (22.24)	

Abbreviations: CCI = charlson comorbidity index, ICISS = international classification of disease-10 based injury severity score, ICU = intensive care unit, IQR = interquartile range.

**P*-values were from the chi-square tests.

†ICISS scores were calculated only for patients with traumatic injury.

this study, COU was defined by at least 1 prescription of opioid use between days 91 and 180 after the index date regardless of the continuity of the prescription. Similar trends were observed in the US studies. In a US State healthcare claims database dataset including the 191,130 adults with a newly diagnosed injury during 2015 to 2017, prevalence of COU defined as ≥90 days of prescription was 3.0% (5855 patients),[29] whereas, in another nationally representative US study, which ascertained the opioid use as having at least 1 prescription of opioid, the estimated prevalence of persistent opioid use was 15.6%.[30] A

Table 2

ICD-10 Diagnosis code for traumatic injuries included in the study.

Type of injuries	Diagnosis codes	N = 65,444
Injuries to the head	S00 to S09	15,014 (22.94%)
Injuries to the neck	S10 to S19	7901 (12.07%)
Injuries to the thorax	S20 to S29	10,813 (16.52%)
Injuries to the abdomen, lower back, lumbar spine and pelvis	S30 to S39	20,003 (30.57%)
Injuries to the shoulder and upper arm	S40 to S49	9510 (14.53%)
Injuries to the elbow and forearm	S50 to S59	8323 (12.72%)
Injuries to the wrist and hand	S60 to S69	18,915 (28.90%)
Injuries to the hip and thigh	S70 to S79	5025 (7.68%)
Injuries to the knee and lower leg	S80 to S89	18,248 (27.88%)
Injuries to the ankle and foot	S90 to S99	13,737 (20.99%)
Injuries involving multiple body regions	T00 to T07	488 (0.75%)
Injuries to the unspecified part of trunk, limb or body region	T08 to T14	1698 (2.59%)

Abbreviation: ICD = international classification of disease.

Table 3

Risk of chronic opioid use by trauma status.

	Chronic opioid use	Persistent opioid use	CONSORT definition of chronic opioid use
Trauma (n = 65,444)	8848 (13.52%)	84 (0.13%)	68 (0.10%)
Control (n = 338,321)	42,715 (12.63%)	409 (0.12%)	320 (0.09%)
Total (n = 403,765)	51,563 (12.77%)	493 (0.12%)	388 (0.10%)

Abbreviation: CONSORT = consortium to study opioid risks and trend.

recent systematic review found significant heterogeneity in the classification methods of COU after surgery which was also associated with a wide variation in prevalence of COU from 0.01% to 14.7%.[31] Other sources of the heterogeneity, such as difference in clinical context, population characteristics and policy associated with opioid prescription might exist, which should be speculated in further studies.

Other studies have reported an increasing trend in COU in South Korea.[8,18,32] Kim et al (2020) found that the prescription of tramadol, considered a weak opioid, has steeply increased from 2003 (19.9%) to 2013 (33.3%), which can be partially explained by the market availability of generic formulations of tramadol and tramadol/acetaminophen combinations products in South Korea in 2008.[33] In our study, proportion of chronic opioid users remained over 10% during observation periods with majority of them being prescribed with tramadol regardless of being injured or not. Such high use might be due to its perceived analgesic benefits and assumption that it would be safer and less addictive than other opioid drugs.[25] However, factors associated with and perceptions of the relevant stakeholders including physicians, patients and policymakers on its use need to be further investigated to elucidate potential role of tramadol in COU after traumatic injury.

Older age and female sex were risk factors for COU, consistent with previous findings.[18,24,30,34,35] Ageing might be associated with susceptibility of developing chronic pain and compromised physiological recovery process.[36,37] Preclinical evidence suggests biological differences in pain signaling in the central nervous system between sexes, including differences in the descending pathway from the periaqueductal gray (PAG) to the spinal cord, activation of the PAG by inflammatory pain and the role of gonadal hormones on opioid receptor activation, opioid metabolism and the PAG responses to pain.[38] Sociocultural background which may affect pain experience of women and drug prescribing pattern of physicians who encounter women with chronic pain might also be important,[39] and role of sex and gender difference in COU after trauma warrants further research. We found no association between level of income and COU, which has been observed in previous population-representative cohort studies in South Korea[18,35] thus contradicts with evidence in other settings. In the UK Biobank study of 466,486 participants, the highest rates of regular opioid use were observed in people with lower socioeconomic status.[40] Musich et al (2019) found that low income was associated with 1.5 times higher odds of COU in opioid-naïve patients in a sample of 180, 498 US Medicare beneficiaries aged 65 or over.[41] Possible explanations for the absence of association in this study may include misclassification of income level, as it was measured indirectly by decile of national healthcare reimbursement fees rather direct income measurement. The role of socioeconomic status on the COU in nontraumatic conditions with different underlying etiology and clinical context may differ from those in traumatized patients. Income may not have affected the relatively short-term (i.e., 3–6 months after trauma) opioid prescription patterns after trauma in South Korea, although this hypothesis should be clarified in further analyses. Living either in metropolitan city other than Seoul and other non-urban areas was associated with higher risk of COU, which is consistent with previous evidence.[42,43] Nevertheless, risk of misclassification in area of residence should not be excluded, as a total of 282 clustered area codes were merged into 3 area groups (i.e., Seoul, metropolitan cities other than Seoul, and others) in the analysis which might ignore regional variations within each area group. In the study by Lee et al (2016) which investigated regional distribution of unmet healthcare needs across 17 provinces comprised of 253 districts in South Korea, there was substantial variation of unmet healthcare needs across districts within each province ranging from 2.6% to 26.2%, which may support the potential risk of misclassification introduced by categorizing the region information in the analysis.[44]

Both previous opioid use and comorbid conditions in the recent year before traumatic injuries were significantly associated with COU, which is consistent with previous evidence.[10,14,18,45,46] The findings might be of clinical relevance, as information on prior clinical history may help physicians ascertain people who are at an increased risk of COU and provide advice and intervention to avoid or reduce long-term opioid use. A recent pilot study enrolled traumatized patients with history of substance abuse and mental disorders as a high risk group for COU and randomized into a specific opioid-tapering program

Table 4

Univariable and multivariable logistic regression analysis of factors associated with chronic opioid use in South Korea (n = 403,765).

Characteristics	Unadjusted	*P*-value*	Adjusted for age and sex	*P*-value*	Fully adjusted†	*P*-value*
Trauma						
No	1.00 (Ref)	.001	1.00 (Ref)	<.001	1.00 (Ref)	<.001
Yes	1.08 (1.06, 1.10)		1.13 (1.10, 1.16)		1.13 (1.01, 1.16)	
Age at trauma (yr)						
18 to 25	1.00 (Ref)	<.001	1.00 (Ref)	<.001	1.00 (Ref)	<.001
25 to 34	1.10 (1.05, 1.15)		1.06 (1.01, 1.11)		1.13 (1.08, 1.18)	
35 to 44	1.59 (1.51, 1.66)		1.60 (1.53, 1.68)		1.41 (1.34, 1.48)	
45 to 54	2.21 (2.11, 2.31)		2.21 (2.11, 2.31)		1.73 (1.65, 1.81)	
55 to 64	3.14 (3.00, 3.29)		3.13 (2.99, 3.28)		2.21 (2.11, 2.32)	
65 to 74	4.62 (4.41, 4.84)		4.50 (4.30, 4.72)		2.87 (2.73, 3.01)	
≥75	4.06 (3.86, 4.27)		3.81 (3.62, 4.01)		2.48 (2.35, 2.62)	
Sex						
Male	1.00 (Ref)	<.001	1.00 (Ref)	<.001	1.00 (Ref)	<.001
Female	1.39 (1.36, 1.41)		1.40 (1.37, 1.43)		1.30 (1.28, 1.33)	
Calendar yr at trauma						
2003	1.00 (Ref)	<.001	–	–	1.00 (Ref)	<.001
2004	1.15 (1.09, 1.20)		–		1.09 (1.04, 1.15)	
2005	1.28 (1.22, 1.35)		–		1.16 (1.10, 1.22)	
2006	1.33 (1.27, 1.40)		–		1.14 (1.08, 1.19)	
2007	1.36 (1.30, 1.43)		–		1.14 (1.09, 1.20)	
2008	1.36 (1.29, 1.42)		–		1.11 (1.05, 1.17)	
2009	1.40 (1.33, 1.46)		–		1.17 (1.11, 1.23)	
2010	1.42 (1.35, 1.49)		–		1.16 (1.10, 1.22)	
2011	1.43 (1.36, 1.50)		–		1.17 (1.11, 1.23)	
2012	1.42 (1.36, 1.50)		–		1.15 (1.09, 1.21)	
2013	1.36 (1.29, 1.43)		–		1.11 (1.05, 1.17)	
2014	1.33 (1.27, 1.40)		–		1.09 (1.03, 1.15)	
2015	1.14 (1.07, 1.22)		–		0.92 (0.86, 0.99)	
Income level at trauma (decile)§						
1st	1.00 (Ref)	<.001	–	–	–	–
2nd	0.91 (0.87, 0.95)		–		–	
3rd	0.88 (0.84, 0.92)		–		–	
4th	0.86 (0.82, 0.90)		–		–	
5th	0.83 (0.80, 0.86)		–		–	
6th	0.86 (0.82, 0.90)		–		–	
7th	0.89 (0.85, 0.93)		–		–	
8th	0.94 (0.90, 0.98)		–		–	
9th	0.97 (0.93, 1.01)		–		–	
10th	0.91 (0.87, 0.95)		–		–	
Area of residence						
Urban city (Seoul)	1.00 (Ref)	<.001	–	–	1.00 (Ref)	<.001
Metropolitan cities (other than Seoul)	1.54 (1.50, 1.59)		–		1.37 (1.33, 1.42)	
Others	1.67 (1.63, 1.71)		–		1.42 (1.38, 1.46)	
Previous opioid use						
No	1.00 (Ref)	<.001	–	–	1.00 (Ref)	<.001
Yes	4.17 (4.09, 4.25)		–		3.27 (3.21, 3.34)	
CCI score						
0	1.00 (Ref)	<.001	–	–	1.00 (Ref)	<.001
1	1.66 (1.62, 1.70)		–		1.18 (1.15, 1.21)	
≥2	2.32 (2.27, 2.38)		–		1.38 (1.35, 1.42)	
Surgery						
No	1.00 (Ref)	<.001	–	–	1.00 (Ref)	<.001
Yes	0.81 (0.80, 0.83)		–		0.94 (0.92, 0.96)	
ICU care						
No	1.00 (Ref)	<.001	–	–	1.00 (Ref)	.1724
Yes	1.55 (1.50, 1.61)		–		0.98 (0.94, 1.01)	

Abbreviations: CCI = charlson comorbidity index, ICISS = international classification of disease-10 based injury severity score, ICU = intensive care unit.

*P-values were from the Wald tests.

†Adjusted for age group, sex, calendar year, area of residence, previous opioid use, CCI score and ICU care.

§Level of income was not included in the full model due to the missingness of data.

or educational leaflet intervention, showing the feasibility of conducting trial but no evidence of the proposed intervention's benefit.[47] Evidence of benefits regarding physician awareness of prior health condition on change of opioid prescription pattern and health outcomes remains largely unclear. The link between specific comorbidities, or their duration and severity, with COU after traumatic injuries in South Korea remains poorly understood and needs further investigation. Indicators of severity of condition (i.e., ICU care and surgery during the index admission) showed null or negligible association with COU, contradicting studies showing significant association with injury severity measured by trauma-specific scales, such as Abbreviated Injury scale (AIS)[14] or Injury Severity Score (ISS).[48] Misclassification of trauma severity might exist, although use of ICISS (≥0.9) which is a diagnosis code based trauma severity classification system, instead of ICU care in the model restricted to the traumatized patients did not change the estimation. These findings need to be investigated further using different datasets such as trauma registry and prospective cohort studies with valid trauma severity indicators.

4.1. Strengths and limitations

This study investigated the association between traumatic injury and COU, controlling for age, sex, sociodemographic and clinical factors, using the large nationally representative sample of healthcare use database in South Korea. Long-term observations from 2003 to 2015 revealed a constant trend of COU in the study population. Exposure status, outcomes and confounders were ascertained through the large-scale electrical healthcare database, thus were not prone to recall or reporting bias. Subjects who survived to 3 months after trauma or the corresponding index admission were analyzed to avoid competing risk.

Limitations of this study are as follows. Firstly, subjects were from a large-scale representative sample cohort of people who have visited or been referred to the healthcare facilities. People who had been admitted to hospitals may have been systematically different in terms of sociodemographic and clinical characteristics from those who did not seek or could not access hospital care, which can introduce selection bias although the direction and the magnitude of bias seem hard to determine. Secondly, traumatic injury was ascertained using diagnosis codes in the healthcare administration dataset for reimbursement purposes, thus the risk of upcoding for diagnosis of trauma cannot be completely excluded. Possibility of upcoding has been raised in previous studies of other diseases using the same dataset,[49,50] although upcoding behavior for trauma patients is not well known. Thirdly, the use of surgery or ICU care as proxies for severity of the condition might not correctly reflect the actual severity of the injury and might have introduced misclassification bias. Fourth, unmeasured confounders such as smoking, alcohol consumption, level of education, subjective pain severity which are all associated with development of chronic pain or long-term opioid use might have biased the coefficient estimates. Fifth, the potential discrepancy between the prescription data and actual intake of the prescribed opioids as well as the arbitrary classification of COU using cutoff values of 90 to 180 days may have led to risk of misclassification bias, although the magnitude and the direction of bias are unclear. Finally, the findings cannot be generalized to the population in other countries as healthcare system and clinical contexts may differ from South Korea.

4.2. Implications for clinical practice and public health

The findings may inform healthcare professionals, patients, and caregivers about the overall prognosis after traumatic injury with respect to COU and associated risk factors. The overall prevalence of COU among patients with trauma might inform the development of acute and long-term care after injury, to reduce the burden of COU in this population. Patients who have used opioids before injury might need particular attention as being at higher risk of COU, and further care to reduce COU might be considered. Further surveillance focusing on the opioid prescription pattern for traumatized patients and associated factors may be needed to address whether temporal trends of chronic opioid user change over time.

4.3. Recommendations for future research

Several aspects of COU, including dose and continuity of prescription, and long-term prognosis including mortality and patient-reported outcomes need to be further investigated. Clinical, psychological, and behavioral risk factors which were unmeasured in this study need to be addressed in future studies whenever available. Sources of heterogeneity and inconsistent findings between studies need to be considered when designing future studies investigating prevalence and risk factors of COU after traumatic injuries.

5. Conclusion

Chronic opioid use was prevalent both in the injured and noninjured patients in South Korea. Traumatic injuries requiring hospital admission increased odds of COU to 1.13 times compared to those admitted due to nontraumatic etiologies, when adjusted for the effects of age, sex, calendar year, area of residence, previous opioid use and ICU care. Older age, female sex, previous opioid use, having comorbid conditions were independent risk factor for higher odds of COU. Future investigations on the association between traumatic injury and COU as well as risk factors of recovery or poor prognosis after traumatic injury in various contexts are warranted.

Acknowledgments

This study is a part of Master degree thesis of Epidemiology of KHK in London School of Hygiene and Tropical Medicine, UK. Authors are thankful to Professor Yongjoo Kim, KMD, ScD, PhD, MPH who provided helpful comments for the article.

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