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# Association of Acute Myocardial Infarction with Ossification of the Posterior Longitudinal Ligament in Korea: A Nationwide Longitudinal Cohort Study

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**Objective:** This nationally matched longitudinal study aimed to investigate the relationship between acute myocardial infarction (AMI) and ossification of the posterior longitudinal ligament (OPLL) in Korea.

**Methods:** We collected patient data from January 1, 2004 to December 31, 2015 from the National Health Insurance Service Health Screening Cohort. Patients with OPLL were defined as patients with the International Classification of Diseases, Tenth Revision code M48.8 (other specified spondylopathies) and were newly diagnosed through computed tomography imaging. The OPLL group had a total of 1,289 patients. The control group included 6,445 people. Utilizing the Kaplan-Meier technique, The incidence of AMI in both groups was estimated. A Cox proportional-hazards regression analysis was used to compute the AMI hazard ratio.

**Results:** After controlling for age and sex, the hazard ratio of AMI in the OPLL group was 2.065 (95% confidence interval [CI], 1.228–3.474). The adjusted hazard ratio in the OPLL group was 2.209 after restricting the sample for demographics and concomitant medical conditions (95% CI, 1.311–3.721). In a subgroup analysis, the incidence of AMI was substantially greater in the OPLL group, which included women younger than 65 years and without hypertension, diabetes, or dyslipidemia.

**Conclusion:** This nationwide longitudinal study found that patients with OPLL were at higher risk of AMI.

**Keywords:** Epidemiology; Longitudinal ligaments; Myocardial Infarction; Population; Risk factors

## INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL) is a rare pathologic process of lamellar bone deposition that can result in spinal cord compression[2]. The prevalence of OPLL has been estimated to be 0.6% to 4.6% in South Korea[14,16,29]. OPLL is a multifactorial disease caused by genetic and environmental factors[20], but the pathogenesis remains poorly understood. OPLL is often found on multiple levels rather than on a single level, and in many cases, it occurs together with ossification of the anterior longitudinal ligament, ossification of the ligamentum flavum[30], or diffuse idiopathic skeletal hyperostosis (DISH)[28]. Therefore, it may be considered as part of a systemic disease rather than a disease of a single lesion[27].

In previous studies, the incidence of acute myocardial infarction (AMI) was higher in patients with acute infections[17,26], and another study found that patients with pyogenic spondylitis had a higher risk of developing AMI[13]. We considered the possibility of a relationship between AMI and other spinal diseases, and OPLL was selected as the target.

Given the paucity of studies demonstrating an association between OPLL and AMI, we conducted a national longitudinal study to investigate whether there were significant changes in the incidence of AMI in patients with OPLL.

## MATERIALS AND METHODS

### 1. Data Source

We conducted the study based on data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) between 2004 and 2015. South Korea provides a single-payer health insurance system supervised and managed by the NHIS. The NHIS conducts health examinations every 2 years for citizens aged 40 and older and annually for non-office workers. The NHIS collects data on sociodemographic parameters (age, sex, average insurance premium, residential area, and presence of disability), clinical information (comorbidities, number of outpatient visits, and hospitalization records), and the results from a national health screening program. This collected information is stored in the National Health Information Database (NHID)[10,24], and the data is accessible to the public for research purposes.

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of our study (IRB No. 2020-01-011).

### 2. Study Design and Establishment

This sex-/age-matched cohort study aimed to determine the potential risk of AMI in individuals with OPLL. The study population included an OPLL group and a control group. For the OPLL group, patients corresponding to the International Classification of Diseases, Tenth Revision (ICD-10) codes 'M48.8' and 'M48.80' to 'M48.83' and those newly diagnosed by computed tomography were selected. The NHIS-HEALS cohort population consisted of the total number of patients enrolled between January 1, 2002, and December 31, 2003, which was 514,557; This accounts for about 10% of Koreans over 40 who underwent national examinations during this period. The selected population was followed up for 12 years from January 2004 to December 2015.

From the NHIS-HEALS cohort population of 514,557 individuals, we screened 3,405 individuals corresponding to ICD-10 codes 'M48.8' and 'M48.80' to 'M48.83'. Excluding 1,977 patients who had not undergone CT imaging, 1,428 patients diagnosed with OPLL according to a CT scan were selected. After excluding 139 patients diagnosed with OPLL before January 1, 2004, 1,289 patients were finally selected for the study (Fig. 1). Through 1:5 age- and sex-stratified matching (without replacement) using a greedy-matching algorithm with the R package 'MatchIT' software, 6,445 individuals were chosen as controls[7,8].

The criteria for the selection of the patients with AMI are as follows: (1) ICD-10 codes (I21, I22); (2) brain CT or MRI; and (3) hospitalization, as used in the previous studies[15,22,23]. The NHIS-HEALS database was used to obtain information about underlying comorbidities, such as hypertension, diabetes, and dyslipidemia. Patients in this study were followed from the first episode of AMI until death or the end of the follow-up period.

### 3. Statistical Analysis

Mean differences in demographic variables between the OPLL and control groups were investigated using the $\chi^2$ and Student's *t*-test. The Kaplan-Meier technique was used to evaluate the survival rate without AMI in both groups. The differences in the rates of surviving disease-free between the groups were compared using the Wilcoxon's log-rank test.

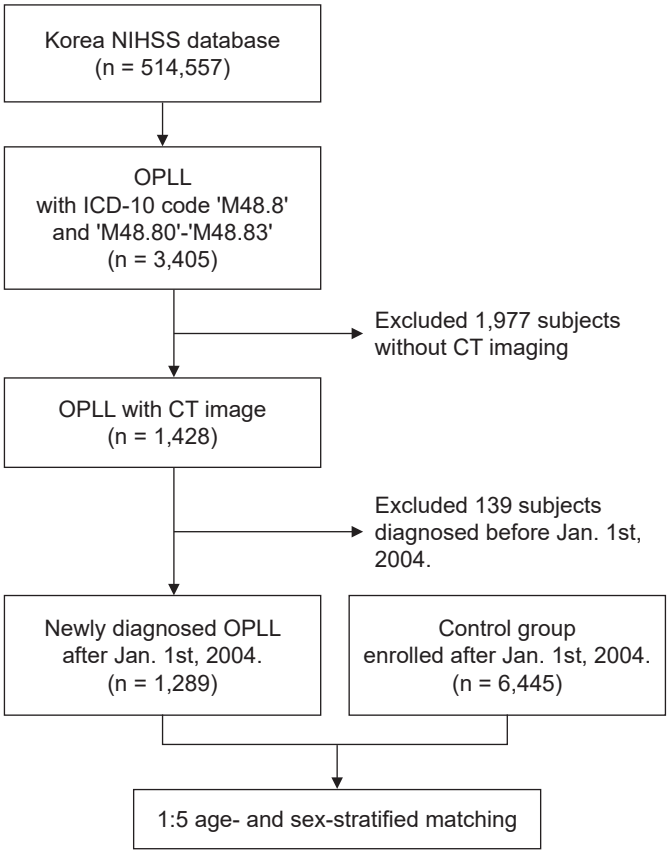


Fig. 1. A flow diagram depicting the cohort formation process. The National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) was used in this 12-year longitudinal cohort study. NIHSS: the National Institutes of Health Stroke Scale; OPLL: ossification of the posterior longitudinal ligament; ICD-10: International Classification of Diseases, Tenth Revision; CT: computed tomography.

Multivariate studies employing a Cox proportional hazard regression model were used to evaluate the impact of OPLL on the subsequent occurrence of each event. Two Cox proportional hazards regression models were employed; Model 1 was adjusted for age and sex, and Model 2 was adjusted for the lowest quintile of income, age, sex, and accompanying comorbidities. Subgroup analyses were also performed using Cox proportional hazards regression models to estimate the effects of OPLL on the risk of each event. Data analysis was performed using R software (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Characteristics of the OPLL and control groups

| Variables | OPLL (n = 1,289) | Control (n = 6,445) | p-value |
|---|---|---|---|
| Sex (male) | 623 (48.33%) | 3,115 (48.33%) | |
| Age | 57.4 ± 9.65 | 57.4 ± 9.65 | |
| Age ≥ 65 | 339 (26.30%) | 1.695 (26.30%) | |
| Low income | 314 (24.36%) | 1,687 (26.18%) | 0.186 |
| Diabetes | 127 (9.85%) | 841 (13.05%) | 0.002 |
| Hypertension | 470 (36.46%) | 2,691 (41.75%) | <0.001 |
| Dyslipidemia | 187 (14.51%) | 1,122 (17.41%) | 0.013 |

The data is presented as number (%) or mean ± standard deviation.
OPLL: ossification of the posterior longitudinal ligament.

## RESULTS

### 1. Characteristics of the OPLL and Control Groups

During the study period, 1,289 patients were newly diagnosed with OPLL. Males accounted for 48.33%. The average age was 57.4±9.65 years, and the population aged 65 years or older accounted for 26.30%. Among the patients with OPLL, 314 (24.36%) were in the low-income quintile. In addition, 127 (9.85%), 470 (36.46%), and 187 (14.51%) patients had comorbidities such as diabetes, hypertension, and dyslipidemia, respectively (Table 1).

### 2. AMI in the OPLL and Control Groups

The OPLL group had a significantly higher incidence of AMI than the control group (p<0.01). The Kaplan-Meier curve of the cumulative incidence of AMI indicated that the risk of developing AMI was higher in the OPLL group than in the control group (Fig. 2). In multivariate analyses using the Cox proportional hazards regression model, the risks of AMI was higher in the OPLL group compared to the control group; The hazard ratio of AMI in the OPLL group was 2.065 (95% confidence interval [CI], 1.228–3.474) in Model 1, while it was 2.209 (95% CI, 1.311–3.721) in Model 2 (Table 2).

### 3. Subgroup Analysis of AMI Incidence Rate

When analyzing the subgroups of the OPLL group and the control group, the incidence rate of AMI was substantially higher in females in both the OPLL group and the control group (95% CI, 1.620–7.317; Table 3). The incidence rate of AMI showed a significant increase in both the OPLL group and the control in the under-age-65 subgroup (95% CI, 1.486–5.252; Table 3), the non-diabetic subgroup (95% CI, 1.116–3.639; Table 3), the non-hypertensive subgroup (95%

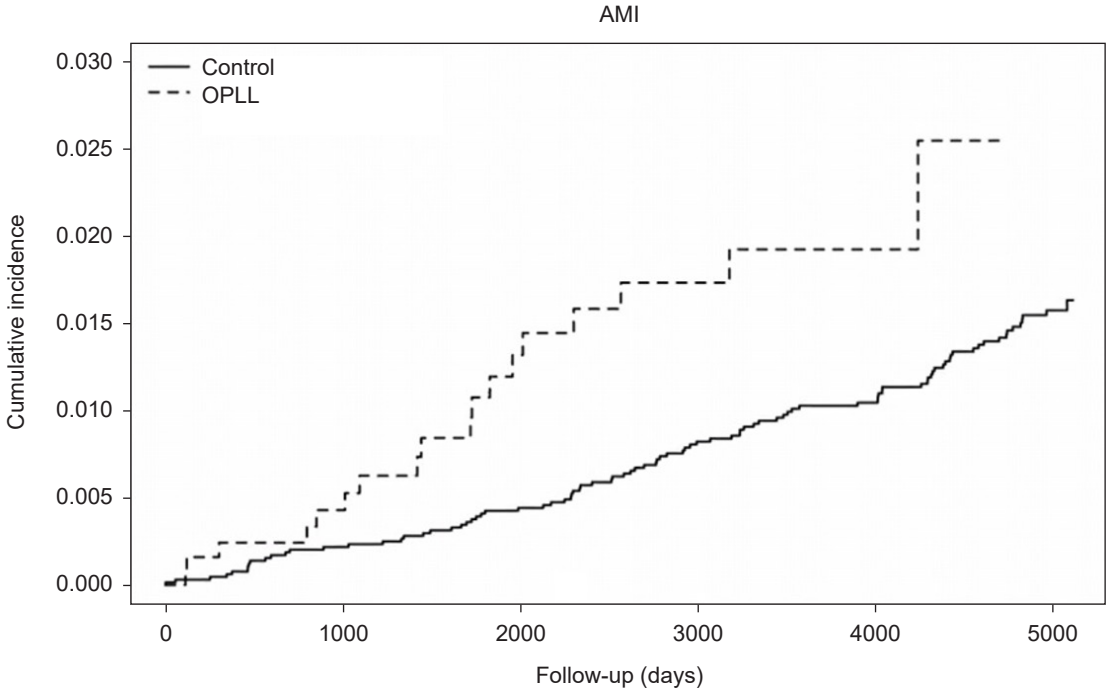


**Fig. 2.** The cumulative incidence rates of acute myocardial infarction (AMI) in the ossification of the posterior longitudinal ligament (OPLL) and control groups were compared. The Kaplan-Meier curves for increasing AMI risk were contrasted between the OPLL and control groups.

**Table 2.** Adjusted hazard ratio for AMI in the OPLL and control groups

| Group | n | Event | Duration (days) | Duration (years) | Incidence rate (%) | HR (95% CI) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Model 1* | Model 2† |
| AMI | | | | | | | |
| Control | 6,445 | 92 | 29,585,869 | 81,057.175 | 1.135 | 1 | 1 |
| OPLL | 1,289 | 18 | 3,215,056 | 8,808.373 | 2.044 | 2.065 (1.228, 3.474) | 2.209 (1.311, 3.721) |

P-values were 0.006 and 0.003 for model 1 and model 2, respectively.
AMI: acute myocardial infarction; OPLL: ossification of the posterior longitudinal ligament; HR: hazard ratio; CI: confidence interval.
*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, income, diabetes, hypertension, and dyslipidemia.

CI, 1.089–4.523; Table 3), and the non-dyslipidemia subgroup (95% CI, 1.556-4.583; Table 3).

## DISCUSSION

Our findings show a higher incidence of AMI in patients with OPLL. This was a significant result in several models that were adjusted considering not only sex and age but also the patient's economic status and comorbidities, in this case hypertension, diabetes, and dyslipidemia; The hazard ratio of AMI occurrence was 2.065 in model 1 and 2.209 in model 2 (Table 2).

There are no known studies of the association between OPLL and AMI, and there is no definitively established theory of the pathophysiology of OPLL. In addition, given that OPLL is known to be an idiopathic or multifactorial disease determined by environmental factors, it is difficult to identify a clear pathological cause. However, relatively recent human leukocyte antigen haplotype analyses and genetic studies have revealed that several genetic loci affect OPLL susceptibility[12,18,19,33]. Genes for collagen, nucleotide pyrophosphatase, transforming growth factors (TGF), and the vitamin

**Table 3.** Subgroup analyses between the OPLL and control groups

| Variables | OPLL | | Control | | HR (95% CI) |
|---|---|---|---|---|---|
| | n | Incidence rate (%) | n | Incidence rate (%) | |
| Sex | | | | | |
| Male | 8 | 20.412 | 66 | 1.752 | 1.460 (0.688, 3.096) |
| Female | 10 | 2.049 | 26 | 0.599 | **3.443 (1.620, 7.317)** |
| Age | | | | | |
| <65 | 13 | 2.036 | 53 | 0.868 | **2.793 (1.486, 5.252)** |
| ≥65 | 5 | 2.062 | 39 | 1.953 | 1.175 (0.456, 3.025) |
| Diabetes | | | | | |
| N | 14 | 1.755 | 70 | 0.990 | **2.015 (1.116, 3.639)** |
| Y | 4 | 4.807 | 22 | 2.130 | 2.733 (0.913, 8.186) |
| Hypertension | | | | | |
| N | 10 | 1.783 | 43 | 0.899 | **2.219 (1.089, 4.523)** |
| Y | 8 | 2.500 | 49 | 1.474 | 1.992 (0.926, 4.286) |
| Dyslipidemia | | | | | |
| vN | 18 | 2.392 | 65 | 0.973 | **2.671 (1.556, 4.583)** |
| Y | 0 | 0.000 | 27 | 1.891 | - |

OPLL: ossification of the posterior longitudinal ligament; HR: hazard ratio; CI: confidence interval.

D receptor have all been implicated[31], and mutations in collagen genes and the TGF-β superfamily genes have been proposed as genetic markers for OPLL[9,11,12,33]. Myocardial infarction is associated with the induction of several members of the superfamily, including TGF-β1, TGF-β2, TGF-β3, bone morphogenetic protein (BMP)-2, BMP-4, BMP-10, growth differentiation factor (GDF)-8, GDF-11 and activin A[5,6]. In addition, the TGF-β superfamily is involved in the regulation of cardiac fibrosis after cardiac fibrosis following myocardial infarction, and researchers are examining myocardial infarction treatments using this signaling pathway[3,4,34]. Bai et al.[1] induced myocardial infarction in rats by inhibiting the TGF-β1 gene through RNA manipulation. Therefore, if studies of OPLL and various genes (especially the TGF-β superfamily) are conducted, similarities with AMI may be found based on genetics.

According to subgroup analyses, the association between OPLL and AMI was more likely in women younger than 65 without hypertension, diabetes, or dyslipidemia (Table 3). Hypertension and diabetes are widely recognized as strong risk factors for AMI and are also risk factors for OPLL. Shin et al.[25] found through a nationwide population-based case-control study that hypertension, diabetes, ischemic stroke, hypothyroidism, and osteoporosis were risk factors for OPLL. Oshima et al.[21] showed that carotid arteriosclerosis is a risk factor for OPLL. Therefore, the risks of both OPLL and AMI may be increased in patients with underlying diseases. This suggests that the association between OPLL and AMI can be maximized in patients without underlying diseases such as hypertension, diabetes, and dyslipidemia, which is consistent with the subgroup analyses in this study.

The limitations of this study, which we considered, include the following. First, The severity and trend of the diseases were not considered in this study. Clinically, AMI is diagnosed with elevated cardiac enzyme, new electrocardiographic change, symptoms of ischemia, and angiographic evidence of thrombus. Given the inability to access individual patient's data in the NHIS database, many researchers including cardiologists used "ICD code (I21, I22) and hospitalization ≥1" as the definition of AMI in South Korea. In addition, initially, our study plan included studying the change in association according to affected areas and the number of levels of involvement, but this was not possible due to data access limitations. Second, as is widely known, the causes of AMI are various, such as carotid artery occlusive disease, arrhythmia, and embolism. In the data we collected, none of these comorbidities were utilized, and heterogeneous patient populations could have negatively affected our results. Third, when explaining the association between OPLL and AMI in the genetic background, non-atherosclerotic AMI was not considered. Atherosclerosis has the most important pathological role of AMI, but non-atherosclerotic processes

are also contributors to AMI[32]. In this study, there were limitations in distinguishing the pathogenesis of AMI. This may have negatively impacted study results when comparing associations from a genetic perspective.

Despite some limitations, this nationwide cohort study is the first to demonstrate a higher incidence of AMI in patients with OPLL. This study suggests the potential contribution of OPLL to the incidence of AMI.

## CONCLUSION

Our nationwide longitudinal cohort analysis shows that patients with OPLL have an elevated risk of AMI.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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