Research Article

Evidence-Based Cutoff Threshold Values from Receiver Operating Characteristic Curve Analysis for Knee Osteoarthritis in the 50-Year-Old Korean Population: Analysis of Big Data from the National Health Insurance Sharing Service

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We aimed to investigate the characteristics of patients with osteoarthritis (OA), using the data of all Koreans registered in the National Health Insurance Sharing Service Database (NHISS DB), and to provide ideal alternative cutoff thresholds for alleviating OA symptoms. Patients with OA (codes M17 and M17.1–M17.9 in the Korean Standard Classification of Disease and Causes of Death) were analyzed using SAS software. Optimal cutoff thresholds were determined using receiver operating characteristic curve analysis. The 50-year age group was the most OA pathogenic group (among 40–70 years, n = 2088). All exercise types affected the change of body mass index (p < 0.05) and the sex difference in blood pressure (BP) (p < 0.01). All types of exercise positively affected the loss of waist circumference and the balance test (standing time on one leg in seconds) (p < 0.01). The cutoff threshold for the time in seconds from standing up from a chair to walking 3 m and returning to the same chair was 8.25 (80% sensitivity and 100% specificity). By using the exercise modalities, categorized multiple variables, and the cutoff threshold, an optimal alternative exercise program can be designed for alleviating OA symptoms in the 50-year age group.

1. Introduction

According to the database (DB) of the Health Insurance Review and Assessment Service, the proportion of patients with diseases of the musculoskeletal system was 50% in 2003 and 71% in 2013. In particular, knee diseases were the 10th most common cause of hospitalization, involving costs of about 2500 USD per person and ranking second in terms of total medical expenses (http://www.hira.or.kr). In addition, medical treatments take an average of 8 days to complete. Furthermore, the number of patients with OA increases steadily and OA pathogenesis shows a pattern of occurring even in younger age groups, which necessitates the establishment of prognostic and treatment programs for knee OA.

Several trials to identify multiple causes of knee OA have been performed to establish individualized and specific treatments for curing OA symptoms [1, 2].

As many cases have an unspecified etiology (causality; i.e., OA has multiple causes such as knee anterior cruciate ligament, meniscus damage, and quadriceps muscle weakness), providing individualized solutions for OA is difficult [3–5]. Because the causality between knee damage and OA cannot be clearly identified and it is difficult to find solutions for OA (many factors lead to aggravation of knee OA), prevention of OA is considered the ideal option [6]. To reach a reasonable solution to this issue, understanding the various characteristics of OA from diverse aspects is important to determine related factors affecting the pathogenesis of the
Table I: Characteristics of the NHISS DB-based population older than 40 years.

| Parameters               | Men       | Values       | Women      |
|--------------------------|-----------|--------------|------------|
| Total analyzed population| 279,125   | 2002–2013    | 235,740    |
| Average age (years)      | 56.66     |              | 58.36      |
| Follow-up years (years)  | 23.99     |              | 23.99      |
| BMI (kg/m\(^2\))        | 196.47    |              | 203.08     |
| Total cholesterol (mg/dL)| 28.36     |              | 24.66      |
| SGOT_AST (U/L)           | 29.11     |              | 21.72      |
| SGPT_ALT (U/L)           | 52.04     |              | 22.86      |

The total analyzed population from the NHISS DB showed sex differences in demographic characteristics. NHISS DB, National Health Insurance Sharing Service database; BMI, body mass index; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamic pyruvic transaminase and alanine aminotransaminase; Gamma_GTP, gamma glutamyl transpeptidase.

disease and to decide appropriate optimal cutoff threshold points for improving prognostic programs (e.g., exercise prescriptions).

Big data analysis of health information is possible, as health-care providers mandatorily register their patient’s injury or disease information through the National Health Insurance Sharing Service (NHISS) for reimbursement of medical service costs in Korea. The NHISS DB provides standardized health and medical information from unilateral medical check records of the entire Korean population. This DB was electronically organized, digitalized, and formatted from 2002 to 2013.

To address the above-mentioned issues and provide beneficial information about patients with OA for ameliorating OA symptoms from various aspects by using NHISS big data, we first set the following research objectives.

In this study, we aimed to examine the most prevalent ages of patients with OA among the elderly Korean population and characterize various features of OA according to four different exercise types, in order to provide evidence-based proper cutoff points for ameliorating OA pathogenesis. We examined three hypotheses in this study, as follows:

1. There would be specific age ranges of pathogenic OA in the elderly Korean population.
2. Variables related to comprehensive and physical function will show the overall characteristics of OA in relation to different exercise modalities.
3. There are appropriate cutoff thresholds for variables of pathogenic OA, and these can provide beneficial information for designing a reasonable prognostic program for improving OA symptoms.

2. Materials and Methods

2.1. Study Design. This study is a retrospective cohort study of data from the NHISS DB. Korean Standard Classification of Disease and Causes of Death- (KSCDCD-) designated OA-related codes (M17 and M17.1–17.9) were used to identify patients with OA aged > 40 years from the NHISS DB. These patients were categorized into four age groups with increments of 10 years (40–49, 50–59, 60–69, and 70–79 years) to examine which age groups have a high risk of OA. The demographic, exercise, and functional test characteristics of each age group were subsequently investigated. The flow of the study is described in Figure 1.

2.2. Data Source and Subject Population. A total of 514,866 patients (approximately 10% of the whole population aged >40 years from the NHISS DB pool) were randomly selected from patients registered in the NHISS. After the age of 40 years, Korean adults mandatorily need to undergo life cycle-based health checks, and the NHISS DB stores their data including exercise information and basic physiological health screening data (Table 1). An individualized design based on the NHISS data of patients aged > 40 years was used because OA-related symptoms with clinical evidence were observed at this age [7]. Patients with OA codes M17 and M17.1–M17.9 in the KSCDCD (http://kssc.kostat.go.kr/ksscNew_web/index.jsp) were extracted by using SAS software (Table 2). The KSCDCD defines M17 and M17.1 to M17.9 as indicating arthrosis of the knee. The study was approved by the institutional review board of Yonsei University (1040917-201603-HRB-152-01E).

2.3. Categorization of Variables. Nineteen variables were divided into three categories. The first category comprised four exercise-related variables (Exerci_Freq_RSPS_CD: frequency of moderate-intensity exercise per week, Mov20_Wek_Freq_ID: frequency of 20 min intensive exercise per week, Mov30_Wek_Freq_ID: frequency of 30 min moderate-intensity exercise per week, and WLK30_Wek_Freq_ID: frequency of 30 min walking per week). The second category comprised 10 comprehensive variables including sex difference, body mass index (BMI, kg/m\(^2\)), high blood pressure (BP_high, mm Hg), low blood pressure (BP_LWST, mm Hg), total cholesterol (TOT_CHOLE, mg/dl), serum glutamic oxaloacetic transaminase and aspartate aminotransferase (SGOT_AST, U/L), serum glutamic pyruvic transaminase and alanine aminotransaminase (SGPT_ALT, U/L), gamma glutamyl transpeptidase (Gamma_GTP, U/L), disease history (HCHK_PMH_CD2), and waist circumference (WAIST, cm). The third category comprised physical function-related variables such as lower-limb function test results for 66-year-old
Patients registered in NHISS DB (N = 514,866)

Patients were extracted using OA codes M17 and M17.1–M17.9 of KSCDCD

Analysis of the frequency of OA by age group (age range 40–79 years; n = 2088, 4.06‰)

The 50–59-year-old age group was found to have the highest rate of OA

Two-way ANOVA for variable comparisons in 50–59-year-old patients with OA

Five independent variables:
- Walk30_Wek_Freq_ID
- Mov20_Wek_Freq_ID
- Mov30_Wek_Freq_ID
- Exerci_Freq_RSPS_CD
- sex difference

Sixteen dependent variables:
- BMI
- BP_High
- BP_LWST
- TOT_CHOLE
- SGOT_AST
- SGPT_ALT
- Gamma_GTP
- HCHK_PMH_CD1
- HCHK_PMH_CD2
- HCHK_PMH_CD3
- WAIST
- ELD_LLFX_SEC
- ELD_LLFX_YN
- ELD_STF_SEC
- ELD_STFX_MTHD
- FALL

Cutoff thresholds of variables obtained from ROC analysis in 50–59-year-old patients

2.4. Statistical Analysis. All data are presented as mean ± standard deviation. In the most OA pathogenic group, reciprocal effects and interactions were investigated by analyzing the established independent and dependent variables to understand the characteristics of OA. Statistically ideal cutoff thresholds of statically examined variables of OA (hypothesis (3)) in the most OA pathogenic age group (hypothesis (1)).
well-defined variables were then selected to provide the optimal cutoff thresholds in the most OA pathogenic patient group. As described in the *Categorization of Variables* section, the four exercise types were indicated as independent variables, and the 10 comprehensive and 5 physical function-related variables were considered dependent variables. Each of the four exercise types was tested for its effectiveness and interaction with the 15 dependent variables by using two-way univariate analysis of variance (ANOVA) in the 50-year OA group (to verify hypothesis (2)). By using logistic regression between patients with and without OA in the 50-year age group, risk factors according to the existence of OA were found and these variables were analyzed by using receiver operating characteristic (ROC) curve analysis to determine the cutoff points for the optimal threshold for avoiding OA pathogenesis (to examine hypothesis (3)). SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 18.0 were used for all statistical analyses. A value of \( p < 0.05 \) was considered to indicate a statistically significant difference in all analyses.

### 3. Results

#### 3.1. Subject Characteristics

All Koreans are mandatorily registered in the NHISS for their health check. A total of 514,886 randomly selected subjects from the NHISS DB pool were used to represent the entire population aged > 40 years, which was estimated to comprise about 5 million Koreans. By using the provided NHISS DB, sex-different demographic characteristics were identified and the values (men versus women) were as follows: total analyzed population, 279,125 versus 235,740; average age, 54.51 versus 54.73 years; BMI, 24.42 versus 25.50; Total cholesterol (mg/dL), 199.84 versus 211.37; SGOT_AST (U/L), 31.06 versus 25.81; SGPT_ALT (U/L), 29.97 versus 23.83; Gamma_GTP (U/L), 63.85 versus 23.21. Patients with KSCDCD-derived codes M17 and M17.1–M17.9 were extracted from the NHISS DB. NHISS DB, National Health Insurance Sharing Service database; KSCDCD, Korean Standard Classification of Disease and Causes of Death; OA, osteoarthritis; BMI, body mass index; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamic pyruvic transaminase and alanine aminotransaminase; Gamma_GTP, gamma glutamyl transpeptidase.

### 3.2. Pathogenesis of OA in Each Age Group

The subjects, aged from their 40s to 70s, were divided into four age groups with increments of 10 years (40–49, 50–59, 60–69, and 70–79 years). The linear function graph was verified to comparatively investigate the frequency of OA pathogenesis in each group (Figure 2). The angle of the graph for the 40–49- and 50–59-year age groups was 7.4° and 8.9°, respectively, and these groups showed an increasing OA pathogenesis pattern; however, the 60–69-year (angle, −3.6°) and 70–79-year (angle, −17.7°) age groups showed reversely decreasing values to patient numbers. Thus, we clarified our first hypothesis based on the observation that OA pathogenesis occurred most frequently in the 50-year age group.

### 3.3. Four Independent Variables (Exercise Modalities) on Comprehensive Variables

A sex difference was observed only in Walk30_Wek_Freq_ID according to age difference within 50–59-year age group (\( p < 0.01 \)). All exercise types significantly affected the change of BMI; however, Walk30 showed a sex difference (\( p < 0.05 \)). The interaction between sex difference and different exercise types was effective in changing BMI (\( p < 0.01 \)). Sex difference affected BP in all exercise types (\( p < 0.01 \)); however, exercise frequency did not seem to affect the change of BP in all exercise types. The four exercise types seemed more related to hypertension, cardiopathy, stroke, diabetes, cancer, and others than to tuberculosis, hepatitis, and hepatitis in HCHK_PMH_CD2. Higher frequencies of exercise did not seem to affect the change of disease history; however, it depended more on the type of exercise (\( p < 0.01 \)).

Male patients with OA aged 50–59 years had higher values of SGOT_AST and SGPT_ALT than female patients with OA. Higher frequency of exercise showed lower values of SGOT_AST and SGPT_ALT. Significant differences of sex and exercise type and interactions between sex difference and exercise type were found in SGOT_AST and SGPT_ALT (\( p < 0.01 \)). The highest value of SGOT_AST was seen with the least frequency of male exercise. TOT_CHOLE in men

### Table 2: Characteristics of the NHISS DB-derived population with OA.

| Parameters                              | Men    | Values | Women  |
|-----------------------------------------|--------|--------|--------|
| Total patients with OA                  | 723    |        | 1365   |
| Average age (years)                     | 54.51  |        | 54.73  |
| BMI (kg/m²)                             | 24.42  |        | 25.50  |
| Total cholesterol (mg/dL)               | 199.84 |        | 211.37 |
| SGOT_AST (U/L)                          | 31.06  |        | 25.81  |
| SGPT_ALT (U/L)                          | 29.97  |        | 23.83  |
| Gamma_GTP (U/L)                         | 63.85  |        | 23.21  |

Patients with KSCDCD-derived codes M17 and M17.1–M17.9 were extracted from the NHISS DB. NHISS DB, National Health Insurance Sharing Service database; KSCDCD, Korean Standard Classification of Disease and Causes of Death; OA, osteoarthritis; BMI, body mass index; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamic pyruvic transaminase and alanine aminotransaminase; Gamma_GTP, gamma glutamyl transpeptidase.
Table 3: Logistic regression and ROC curve analyses for patients with OA.

| Parameter          | OR   | AUC | p value | Cutoff values | Sensitivity (%) | Specificity (%) |
|--------------------|------|-----|---------|---------------|-----------------|-----------------|
| Sex                | 1.973| 0.559| <0.01   | N/A           | N/A             | N/A             |
| Age (years)        | 0.895| 0.265| <0.01   | 18.75         | 88%             | 85%             |
| SGOT_AST (U/L)     | 1.014| 0.463| <0.01   | 14.75         | 75%             | 100%            |
| ELD_STF_SEC (s)    | 0.189| 0.022| <0.01   | N/A           | N/A             | N/A             |
| Fall               | 0.963| 0.895| <0.01   | 8.25          | 80%             | 100%            |
| ELD_LLFX_SEC (s)   | 0.478| 0.861| <0.01   | N/A           | N/A             | N/A             |

Variables with significant $p$ values were selected via logistic regression analysis, and then other factors such as AUC, $p$ value, and sensitivity and specificity of the cutoff points were considered to finally select the cutoff threshold values of the significant variables. ROC, receiver operating characteristic; OA, osteoarthritis; OR, odds ratio; AUC, area under the curve; N/A, not applicable; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; ELD_STF_SEC, standing time on one leg in seconds; ELD_LLFX_SEC, time in seconds from standing up from a chair to walking 3 m and returning to the same chair.

Figures 3(a) and 3(b) show representative variables among 10 variables that had clearly common patterns according to the relationship to sex difference in Exerci_Freq.

3.4. Physical Function-Related Variables according to Independent Variables (Four Exercise Types). All exercise types affected the changes in ELD_LLFX_SEC ($p < 0.01$), with patterns showing that daily exercise seemed to decrease the time in ELD_LLFX_SEC (Figure 3(c)). In ELD_LLFX_YN (presence or absence of gait disability), patients with OA with gait disability did not exercise at all, whereas all patients with OA without gait disability performed exercise. Sex difference was seen in all types of exercise ($p < 0.01$) except Mov20_Wek_freq. The balance test ELD_STF_SEC was affected by all exercise types ($p < 0.01$). Another balance test, ELD_STFX_MTHD, showed a significant difference in the effect of all exercise types ($p < 0.05$). Sex difference, exercise type, and the interaction between sex difference and exercise type had significant differences in FALL ($p < 0.01$). Figure 3(d) shows that female patients with less exercise experienced falls more frequently, and this difference showed a decreasing tendency as the women exercised more (Figure 3(d)). A clear difference was observed between the daily exercise and less exercise groups (Figure 3(d)).

Panels (c) and (d) of Figure 3 represent similar patterns of each variable in the four exercise types.

We thus examined hypothesis (2) and concluded that there are specific high-risk dependent variables with the effect of exercise modalities in the incidence of OA.

3.5. Which Variables Affect OA Pathogenesis and What Are the Evidence-Based Optimal Cutoff Points of the Variables for Preventing and Alleviating OA Symptoms? Randomly selected patients without OA registered in the NHISS were compared with patients with OA for logistic regression analysis. Among the variables, we found that FALL ($p < 0.05$) and ELD_LLFX_SEC ($p < 0.01$) significantly affected the pathogenesis of OA (Table 3). For 50-year-old patients with OA, ROC curve analysis provided ideal cutoff values for ELD_LLFX_SEC as 8.25 s (80% sensitivity and 100% specificity, area under the curve 0.861) (Figure 4). FALL did not have a meaning for the cutoff value because the responses for FALL were 1 (no experience of falls) or 2 (with experience of falls).
4. Discussion

We obtained the following OA-related results from patients registered in the NHIS by clustering the retrospective cohort of Koreans aged > 40 years.

Hypothesis (3) was also clearly examined by using these results.

(1) OA pathogenesis was found most frequently in the 50-year age group.

(2) The four analyzed exercise types affected the change of BMI ($p < 0.05$) and affected BP with a sex difference ($p < 0.01$); however, exercise frequency did not affect the change of BP. Exercise type and exercise frequency were important for SGOT and SGPT.
4.2. Individualized Exercise Prescription for Reducing the Incidence of OA. A specific exercise prescriptive program based on these data can be designed. BP, cholesterol, and HCHK,PMH showed a pattern that is more related to the specific intensity, time, and frequency of exercise. The results showed that tailor-made exercise prescriptions are possible, and thus this study evidences that the DB can be an indispensable tool for improving the symptoms of OA. Our results comprehensively include microlevel to macrolevel data, from blood tests to physical function tests. Most modernized countries have emerging issues about experiences of falls in the aging society [9]. In Korea, 13% of 828 urban and 32% of 2295 rural elderly dwellers experienced falls in 1 year [9, 10]. The socioeconomic cost from fall injuries was calculated to be 343,614,988,000 Korean won [11]. To relieve this socioeconomic and individual burden, a more specially individualized exercise prescription can be an ideal option. According to this study, falls more often occurred in 50-year-old women with OA than in 50-year-old men with OA; thus, performing any kind of exercise on a daily basis can be an ideal option for improving fall symptoms in patients with OA.

4.3. Optimal Cutoff Threshold for OA Pathogenesis. The finding that OA occurred most frequently in the 50-year age group was used in further analysis to identify factors influencing the pathogenesis of the disease. We found that FALL and ELD_LLFX_SEC (p < 0.01) were associated with the occurrence of OA in the 50-year age group, and we suggest that this is associated with the muscle strength of the lower limb [12] (Table 3).

In conclusion, we obtained the following multifaceted results from the large-scale analysis of the NHISS DB, which can help in developing evidence-based OA preventive methods such as individualized exercise prescription programs.

(1) Pathogenic OA was found most frequently in the 50-year age group.

(2) All four exercise types investigated affected the change of BMI (p < 0.05) and had a sex-different effect on BP (p < 0.01); however, exercise frequency did not affect the change of BP. Exercise type and exercise frequency were important for SGOT and SGPT. Exerci_Freq only did not affect the change of cholesterol (p < 0.01), and all exercise types affected loss of WAIST (p < 0.01). All types of exercise positively affected the balance test result (p < 0.01).

(3) The optimal cutoff threshold for SGOT_AST and ELD_STFX_SEC was 18.75 (88% sensitivity and 85% specificity) and 14.75 (75% sensitivity and 100% specificity), respectively.
This large-scale DB study may be indispensable in describing the risk factors affecting the aggravation of knee damage, for example, from anterior cruciate ligament to OA, and may lead to the development of standard and individualized prognostic OA interventions in the most OA pathogenic period of life.

Conflicts of Interest

The authors have no conflicts of interest.

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