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ORIGINAL ARTICLE

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Risk factors for total knee arthroplasty in rheumatoid arthritis

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Abstract We conducted a study to assess the predictive factors for total knee arthroplasty (TKA) in a cohort of rheumatoid arthritis (RA) patients recruited and followed prospectively for 5 years. A linked registry study using information from a large observational cohort of RA patients followed at the Institute of Rheumatology, Tokyo Women's Medical University (IORRA) was done. Baseline routine clinical and laboratory assessments were recorded. The data were analyzed using the multivariate piecewise-linear Cox (PL-Cox) regression model; the model initially included variables such as gender, age, duration of the disease, visual analog scale (VAS) generated by physicians (VAS-physician), patient-reported VAS for pain (VAS-pain), VAS for general health (VAS-GH), disability level using the Japanese version of the Health Assessment Questionnaire (J-HAQ), C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor (RF), and hemoglobin. Of the 3945 patients registered at baseline, 955 (24.2%) had pain or tenderness in their knee joints, and 114 (11.9%) had TKA surgery in one or both knee joints. On PL-Cox regression, the variables with positive coefficients were J-HAQ, VAS-pain, VAS-physician, and RF positive; advanced age was associated with a reduced risk of TKA. The hazard ratios were: 0.920 for age >60 years; 2.64 for J-HAQ <1.5; 1.01 for J-HAQ >1.5; 1.47 for VAS-pain >6 (cm); 1.20 for VAS-physician >4 (cm); and 2.08 for RF positive. The consistently predictive factors for TKA in RA were age, J-HAQ, VAS-pain, VAS-physician, and RF positive. Age greater than 60 years was associated with a decreased risk of TKA, while J-HAQ from 0 to 1.5, VAS-pain >6 (cm), and VAS-physician >4 (cm) were associated with an increased risk for TKA surgery. These results suggest that, when treating RA patients, physicians should pay particular attention to pain complaints, the patient's daily activity level, and the RF factor status.

Key words Orthopedic surgery · Outcome · Rheumatoid arthritis · Risk factors · Total knee arthroplasty

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Introduction

The course of rheumatoid arthritis (RA) varies greatly from mild disease to a severe, destructive variant progressing rapidly over a few years. Despite aggressive treatment, progressive destruction of joints continues to occur in a subgroup of RA patients who eventually require joint surgery. Orthopedic procedures have substantially improved RA patients' overall function and quality of life.[1] However, the need for orthopedic surgery is considered to be a marker of disease severity,[1–3] since orthopedic surgery may indicate failure of medical therapy and a poor prognosis.[3] Therefore, this paper reports the predictors for total knee arthroplasty (TKA) among RA patients undergoing orthopedic surgery.

Total knee arthroplasty was selected from among all of the possible orthopedic procedures because it has been proven to be one of the most successful surgical interventions that reduces pain and enhances physical function of RA patients.[4] Moreover, primary TKA is the most frequent procedure of all orthopedic interventions done for any other joint in RA patients.[2] As well, it is generally agreed that the knee joint is one of the most important joints in the lower extremity. The performance of TKA means that there is severe destructive arthritis in the knee joint due to the failure of medical therapy.

The aim of the present study was to identify the risk factors for TKA in a cohort of RA patients recruited and followed prospectively for 5 years. The identification of the disease-associated risk factors for TKA provides important insights into the course of the disease and its impact on patients, as well as the potential consequences for health care resource utilization planning.

Materials and methods

Patients and study design

In this study, possible risk factors related to TKA were assessed over a 5-year period as part of a large cohort study. In 2000, a large observational cohort of RA patients was established at the Institute of Rheumatology, Tokyo Women's Medical University (IORRA). This cohort database is a powerful resource not only for clinical research, but also for extensively evaluating therapeutic strategies under real-life conditions.[5,6] All patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA.[7] More than 98% of the RA patients in our Institute have been registered in this study. Patient information is collected biannually and then used to construct the database. This database consists of three domains: evaluation data generated by trained physicians, information from patients, and results of laboratory investigations.

The datasets from IORRA that we used in this study were age, age of RA onset, RA duration, the number of tender and swollen joints (TJC, SJC) out of 68 joints,[8,9] visual analog scale (VAS) generated by physicians (VAS-physician), patient-reported VAS for pain (VAS-pain), patient-reported VAS for general health (VAS-GH), the disability index of the modified Stanford Health Assessment Questionnaire (HAQ),[10] disability level using the Japanese version of the Health Assessment Questionnaire (J-HAQ),[11] height (Height), body weight (Weight), the patient's dosage of methotrexate (MTX dose) and glucocorticoid (Steroid dose), C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) (either positive or negative), and hemoglobin (Hb) level.

Patients who had pain or tenderness in their knee joints and did not have a previous TKA before October 2000 were included in this study. These patients were followed until the TKA event occurred, for up to 5 years, ending October 2005. Survival analysis was conducted to find the predictive factors for TKA.

Statistical analysis

Patients' baseline characteristics are reported as median values and interquartile range. The total observation period was determined using the person-year method, and the crude incidence of TKA was calculated. The Kaplan–Meier estimator was used to describe the survival rates at the first, second, and fifth years.

To determine the predictive factors for TKA, and to study their effects, we analyzed the data using the Cox proportional hazards model. At first, we did a univariate analysis. However, given the nonrandom nature of an observational study, such as IORRA, a multivariate analysis adjusting for the effects of potential confounders was required. Therefore, we constructed two models in this study. The first model was the time-dependent Cox proportional hazards model, which initially included the following variables: gender, age, duration of the disease, J-HAQ, VAS-GH, VAS-pain, VAS-physician, CRP, ESR, RF, and Hb. Variable selection to determine the predictive factors for TKA was done using the stepwise method based on AIC, and only significant variables (significance level, $P < 0.05$) based on the Wald test were included. The second model was constructed using a piecewise-linear Cox (PL-Cox) model.[12,13] This model is capable of discovering other predictive risk factors that the first model could not detect, since it can deal with non-linear log-relative hazard functions. Four or five piecewise points were set for each variable: for age, from 30 to 70 years, at 10-year intervals; for duration of disease, at 1, 2, 10, and 20 years; for J-HAQ, from 0.5 to 2.5 by steps of 0.5; for VAS-GH, VAS-pain, VAS-physician, from 2 to 8 by steps of 2; for CRP, at 1, 2, 4, and 10; for ESR, at 15, 50, and 150; for Hb, at 10, 12, and 14. These points were set to ensure that multicollinearity did not occur. To compare the results of two models, we plotted the relative risk against the median value for the variables that both models identified as predictive factors.

Results

Patients' characteristics

Of the 3945 patients registered in October 2000, 955 (24.2%) patients (131 men, 13.7%; 824 women, 86.3%) had pain or tenderness in their knee joints. Table 1 shows the baseline

Table 1. Baseline patient characteristics

	Median, frequency	IQR
Gender (female%)	86.3%	
Onset age of RA (years)	48	39–57
Age (years)	58	51–66
RA duration (years)	8	3–14
Height (cm)	155	151–160
Weight (kg)	50	46–57
BMI (m^2/kg)	21.1	19.2–23.1
DAS28	4.63	3.94–5.46
J-HAQ	1	0.375–1.5
TJC	4	2–8
SJC	3	2–7
VAS-pain (cm)	4.2	2.2–6.2
VAS-physician (cm)	4.7	2.4–5.9
VAS-GH (cm)	3.4	2–5.1
CRP (mg/dl)	1.3	0.5–3.1
ESR (mm/h)	42.8	26.3–64.1
RF	67	24.5–149.5
RF (positive %)	84.6%	
Hemoglobin	12	11.1–12.9
MTX users (%)	42.9%	
DMARDs users (%)	86.2%	
Steroid users (%)	58.8%	
MTX dose (mg/week)	5	4–7.5
PSL dose (mg/day)	5	3.5–6

For continuous variables, median values and interquartile range (IQR) are shown; for dichotomous variables, frequency (%) is used
RA, rheumatoid arthritis; BMI, body mass index; DAS28, 28-joint disease activity score; J-HAQ, Japanese version of Health Assessment Questionnaire; TJC, tender joint count; SJC, swollen joint count; VAS, Visual Analog Scale; GH, general health; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; PSL, prednisolone

Table 2. Results of the time-dependent Cox regression to determine the risk factors for total knee arthroplasty

	Coefficient	HR	95% CI	*P* value
Age (years)	–0.0231	0.977	0.961–0.993	0.0054
Functional disability, J-HAQ	0.462	1.59	1.20–2.10	0.0013
VAS-pain	0.211	1.23	1.13–1.34	0.000001
Rheumatoid factor	0.784	2.19	1.14–4.21	0.019

HR, hazard ratio; 95% CI, 95% confidence interval
P value = Wald test for each variable

Table 3. Results of the analysis using time-dependent piecewise-linear Cox model

	Value range	Risk region	Coefficient	HR	*P* value
Age (years)	18–87	60–	–0.0826	0.921	0.0019
Functional disability, J-HAQ	0–3	0–1.5	0.972	2.64	0.00014
		1.5–3	–0.962	1.01	0.036
VAS-pain (cm)	0–10	6–	0.384	1.47	0.00001
VAS-physician (cm)	0–10	4–	0.1864	1.2	0.033
Rheumatoid factor	Negative (0) or Positive (1)	–	0.732	2.08	0.028

Each hazard ratio (HR) corresponds only to the corresponding risk range. For example, the HR for age, 0.921, corresponds to age greater than 60 years
P value = Wald test for each variable

characteristics of the patients included in the present study.

TKA events

During the 5 years of follow-up, 114 (11.9%) patients (11 men, 9.6%; 103 women, 90.4%) had TKA of one or both knee joints. The observation times were: total, 3090.25 person-years (py); men, 428 py (13.9%); and women 2662.25 py (86.1%). Therefore, the crude prevalences of TKA were: total, 0.0369; men, 0.0257; and women, 0.0387. The estimated survival rates with a 95% confidence interval (CI) based on a Kaplan–Meier estimator were 0.976 (95% CI 0.966–0.986) at the first year, 0.937 (95% CI 0.920–0.953) at the second year, and 0.831 (95% CI 0.802–0.861) at the fifth year.

Cox regression

Table 2 shows the results of the time-dependent Cox model. The variables with positive coefficients (associated with a greater risk as the values increase) were J-HAQ, VAS-pain, and RF positive; increasing age reduced the risk for TKA.

Table 3 shows the results of the PL-Cox model. In addition to the variables identified by the time-dependent Cox model, VAS-physician was identified as a predictive factor for TKA. The hazard ratio (HR) of RF positive was 2.08, which was consistent with the value derived from the time-dependent Cox model, 2.19. The HR for age greater than 60 was 0.921, for J-HAQ below 1.5 it was 2.64, for J-HAQ greater than 1.5 it was 1.01, for VAS-pain more than 6 (cm) it was 1.47, and for VAS-physician more than 4 (cm) it was 1.20. The relative risks for age, J-HAQ, and VAS-pain are shown in Fig. 1.

Discussion

In our IORRA cohort study, the percentage of patients needing surgery was 19%. This result is in line with other studies, one of which was also performed in a similar cohort.[2,3,14]

The decision to have joint surgery is complex and does not simply reflect joint damage and attendant loss of function. However, the need for orthopedic surgery is considered to be a marker of disease severity,[1–3] as has been reported mainly by a few observational studies.[15–17]

There are many orthopedic procedures that are used to treat RA patients. Among them, primary total joint arthroplasties are frequently done, and the knee is the joint on which surgery is most frequently done for RA-related disease.[2] Furthermore, TKA has proven to be the most successful surgical intervention in patients with arthritis.[4] In our institute, TKA is the most common surgical procedure for RA; it represents about 33% of RA-related surgery. Therefore, in this study we focused only on TKA as representative of the need for surgery in RA patients. In our institute the same experienced orthopedic surgeons were making the determination that surgery was needed.

There are no other directly comparable studies of TKA done in RA patients. However, there are some reports that assessed the risk factors of the need for orthopedic surgery, including total replacement surgery in RA patients.[3,14] To decrease the eventual need for TKA procedures, the therapeutic target in RA is the suppression of disease activity. We analyzed the following factors as measures: age, age of RA onset, RA duration, TJC, SJC, VAS-physician, VAS-pain, VAS-GH, HAQ, J-HAQ, height, weight, MTX dose, steroid dose, CRP, ESR, RF, and Hb.

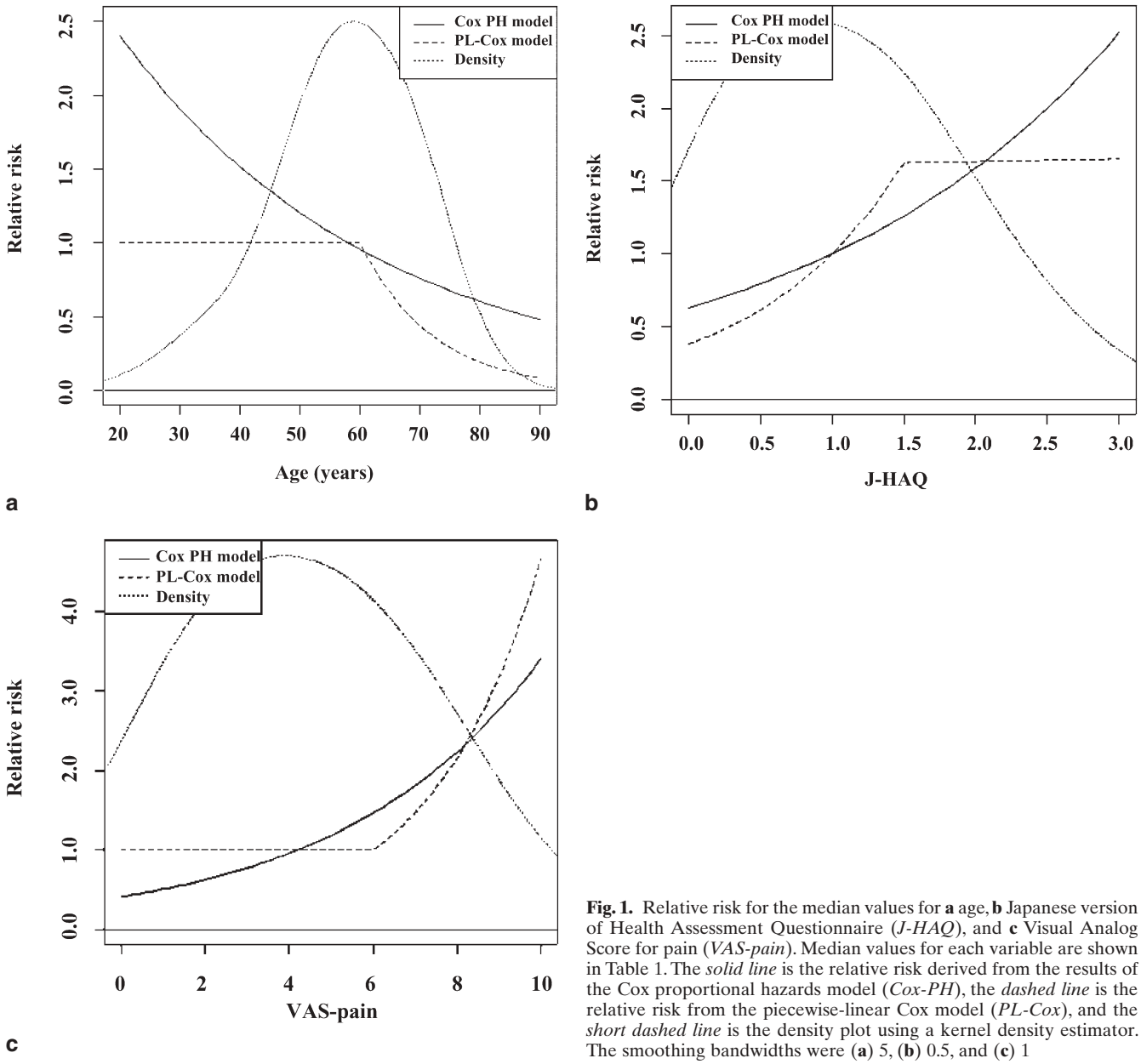

Fig. 1. Relative risk for the median values for **a** age, **b** Japanese version of Health Assessment Questionnaire (*J-HAQ*), and **c** Visual Analog Score for pain (*VAS-pain*). Median values for each variable are shown in Table 1. The *solid line* is the relative risk derived from the results of the Cox proportional hazards model (*Cox-PH*), the *dashed line* is the relative risk from the piecewise-linear Cox model (*PL-Cox*), and the *short dashed line* is the density plot using a kernel density estimator. The smoothing bandwidths were (**a**) 5, (**b**) 0.5, and (**c**) 1

At first, we analyzed the factors using the univariate Cox proportional hazards model. Based on this analysis, the risk factors for TKA were ESR, RF, VAS-GH, VAS-pain, VAS-physician, J-HAQ, and HAQ (data not shown). We also evaluated whether the use of glucocorticoids or disease-modifying antirheumatic drugs had an influence on the risk for TKA on univariate Cox proportional analysis (data not shown). The use of MTX was proven to be a risk factor for TKA. It is possible that patients with high disease activity were treated with MTX, and this explains why the use of MTX is a risk factor for TKA.

However, univariate analysis does not deal with confounding among covariates. Therefore, we evaluated the data using multivariate analysis. In this study, we constructed two regression models. The first model was the time-dependent Cox proportional hazards model, and the second one was the PL-Cox model. To model the effects of the drugs appropriately, we adopted the time-dependent model, in which the covariate values were updated.

In the multivariate time-dependent model, age, J-HAQ, VAS-pain, and RF positive were useful prognostic factors for TKA. We did not identify age as a risk factor on univariate analysis. From the data of the time-dependent model, aging decreases the risk for TKA, while J-HAQ, VAS-pain, and RF positive increase the risk for TKA surgery. These results suggest that, when treating RA patients, physicians should pay particular attention to pain complaints, the patient's daily activity level, and the RF factor status.

In addition to the risk factors identified using the time-dependent Cox model, the PL-Cox model also identified VAS-physician as a predictive factor of TKA. Using the PL-Cox model, the nonlinear log relative hazards function

could be modeled. Compared with the frequently used categorization method that uses dummy variables, the PL-Cox model was flexible because it could represent any relative risk shape. The PL-Cox model showed that age greater than 60 years decreased the risk for TKA while age less than 60 years was not associated with requiring TKA. To the best of our knowledge, there are no previous reports that identified age as a risk factor for surgical intervention.

Functional disability has often been shown to be a predictor of unfavorable outcome measures, such as for joint replacement.[3,16,18] However, Verstappen et al. reported that functional disability was excluded from multivariate analyses.[14] Based on our study, a value of J-HAQ from 0 to 1.5 increases the risk for TKA surgery, while a value of J-HAQ from 1.5 to 3 has almost the same hazard ratio. VAS-pain with a value less than 6 (cm) and VAS-physician with a value less than 4 (cm) was associated with no risk for TKA, while VAS-pain with a value greater than 6 (cm) and VAS-physician with a value greater than 4 (cm) increased the risk for TKA.

There are few predictive tests of long-term outcome in RA, although recently both ESR and the HLA-DRB1 RA shared epitope have been reported to be clinically useful prognostic markers for major joint replacement.[17] James et al. reported that baseline risk factors for large joint replacement surgery were low Hb concentration, high ESR, and high scores for DAS and Larsen X-rays; the HLA-DRB1 RA shared epitope was associated with the need for any type of orthopedic surgery.[3]

The mechanism by which the need for joint surgeries in RA patients could be affected by changes in various therapeutic agents is unclear. However, patients diagnosed with RA who are treated according to current therapeutic concepts may require less disease-related joint surgery. Surgical outcomes could be used to compare conventional drug regimens. Recently, biological agents used in RA have improved short-term efficacy, but at a considerable cost. This circumstance highlights the need to have information on the proportion of RA patients who fail conventional drug therapy and require surgery.

In summary, we found that 955 (24.2%) of the 3945 patients registered in October 2000 had pain or tenderness in their knee joints, and 114 (11.9%) patients had TKA surgery for one or both knee joints within 5 years. The factors that were consistent predictors for TKA were age, J-HAQ, VAS-pain, VAS-physician, and RF positive. Based on the time-dependent PL-Cox regression model, age greater than 60 years decreased the risk for TKA, while J-HAQ from 0 to 1.5, VAS-pain greater than 6 (cm), and VAS-physician greater than 4 (cm) increased the risk for TKA surgery. Further work is required to determine the clinical utility of these prognostic markers.

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