ORIGINAL ARTICLE

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Impact of socioeconomic status on biologics utilization in rheumatoid arthritis: revealing inequalities and healthcare efficiency

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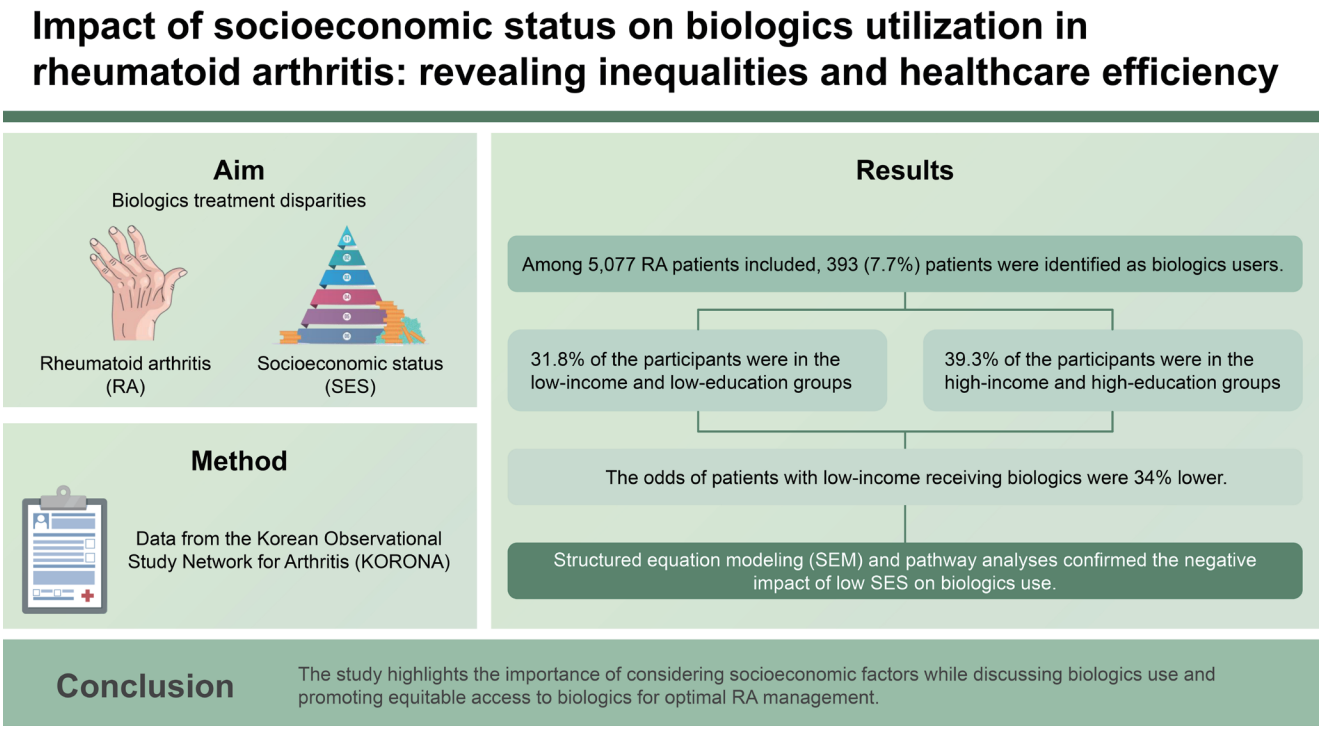

Background/Aims: This cross-sectional study aimed to investigate biologics treatment disparities in rheumatoid arthritis (RA) patients based on socioeconomic status (SES).

Methods: Data from the KOrean Observational Study Network for Arthritis (KORONA) database were analyzed to assess various factors associated with SES, health behaviors, and biologics use. Logistic regression and structured equation modeling (SEM) were utilized for data analysis.

Results: Among 5,077 RA patients included, 393 (7.7%) patients were identified as biologics users. Within the entire co-

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hort, 31.8% of the participants were in the low-income and low-education groups, and 39.3% of the participants were in the high-income and high-education groups. Despite the patients with low income or low education experienced higher disease activity at diagnosis, had more comorbidities, exhibited higher medication compliance, underwent more check-ups, and had more hospital admissions than their counterparts, the odds of patients with low-income receiving biologics were 34% lower (adjusted odds ratio = 0.76, 95% confidence interval: 0.60–0.96, p = 0.021) after adjustment for demographics and comorbidities. SEM and pathway analyses confirmed the negative impact of low SES on biologics use.

Conclusions: The findings suggest that SES plays a significant role in biologics use among RA patients, indicating potential healthcare inefficiencies for low SES patients. Moreover, adverse healthcare habits negatively affect biologics use in RA patients. The study highlights the importance of considering socioeconomic factors while discussing biologics use and promoting equitable access to biologics for optimal RA management.

Keywords: Rheumatoid arthritis; Low socioeconomic status; Biologic drug

INTRODUCTION

Biologics have demonstrated notable efficacy in reducing disease activity, impeding radiographic progression, and enhancing physical functions in individuals diagnosed with rheumatoid arthritis (RA) [1]. In the era of biologics, remarkable advancements have been made in the therapeutic management of RA, leading to a substantial improvement in the quality of life and work participation of RA patients [2]. However, not all RA patients benefit equally from biologics, as health inequality remains a pervasive issue within the RA population. Previous studies demonstrated that patients with low socioeconomic status (SES) had limited access to biologics [3-6]. However, the mechanisms underlying the disparity in biologics use among RA patients with low SES are undetermined.

Patients with lower SES have higher RA activity [6], worse physical and mental health, reduced quality of life [7], and an increased risk of poor RA prognosis compared with those with higher SES [8]. These disparities suggest potential treatment inequality between RA patients with low SES and those with high SES, and this is attributable to various factors. One possible reason for this treatment inequality is the unaffordability of high-cost treatments due to limited income [9]. Moreover, patients with lower education levels have lower expectations or compliance with advanced treatments [10]. The higher risk of incident comorbidities associated with low SES can complicate RA treatment decisions for rheumatologists, as the development or worsening of underlying comorbidities, such as heart failure or tuberculosis, may be a concern when considering biologics use for RA treatment [11,12]. Limited access to health resources and suboptimal health behaviors are additional reasons for treatment inequality observed in low SES patients [13,14]. Despite the crucial role of SES in the RA treatment course, biologics use and its association with SES have been underreported [15].

The KORean Observational study Network for Arthritis (KORONA) is a nationwide multicenter, prospective, observational cohort comprising Korean RA patients [16]. This study utilized a prospective protocol and standardized data collection instruments. The KORONA registry provides comprehensive data of RA patients, including high-quality, well-documented SES factors, such as monthly household income, health insurance coverage, family type, marital status, lifestyle, and healthcare habits. Leveraging this extensive dataset from the RA cohort, our objective was to investigate whether various factors, including SES status, comorbidities, lifestyle, and healthcare habits, are associated with the use of biologic therapies in RA patients.

METHODS

Study population

The KORONA registry was established in 2009 by the Clinical Research Center for RA at Hanyang University, South Korea, with funding from the Ministry of Health and Welfare. It comprises a cohort of 5,077 patients diagnosed with RA who were recruited from 23 institutions across the country. All RA patients were aged ≥ 18 years and satisfied the 1987 American College of Rheumatology criteria for RA [17].

Upon enrollment, all patients completed an initial questionnaire capturing their demographic information, medical history, and disease-specific outcomes. Patient-related variables included age, sex, comorbidities, marital status, mean annual household income, education, and insurance type. Disease-related variables encompassed disease onset and diagnosis dates; disease activity measures; laboratory test results; and prescription information for disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, glucocorticoids, and biologics. Disease activity was assessed using the Disease Activity Score (DAS) 28-joint count erythrocyte sedimentation rate, EuroQol-5 dimensions (EQ-5D) with an additional depression dimension, a health assessment questionnaire (HAQ), and the physician's visual analog scale, and joint assessments were performed by the patient's rheumatologists and well-trained medical staff. Patient self-evaluation data were integrated into the database and updated during annual follow-up visits.

Data regarding body mass index, and health behaviors such as smoking, exercise, alcohol consumption, and healthcare utilization within the past 2 years, including hospitalization and various medical check-ups were collected. Medication compliance, and use of alternative medicines and supplemental medicines were also recorded. All items were assessed at enrollment and at annual follow-up visits. However, only baseline data were used for the current study. All data were anonymized, transferred to the Korean Society of Rheumatology for approval, and provided to the researchers. Hospitalization was defined as admissions to the hospital for RA-related reasons, excluding surgeries and normal delivery, within the past 2 years. Medication compliance was measured on a scale from 1 to 5, with 1 indicating the highest compliance level, representing patients who consistently took their medication within a 6-month period. Skipped medication refers to the number of days patients skipped medication, with 1 indicating that they took all of the medication, 2 indicating that they skipped 5 or fewer days, 3 indicating 6–15 skipped days, 4 indicating 16–30 skipped days, and 5 indicating more than 31 skipped days. Check-up represents whether patients underwent the following tests within 2 years: chest X-ray, mammography, abdominal sonography, dual-energy X-ray absorptiometry, electrocardiogram, echocardiogram, computed tomography, magnetic resonance imaging, positron emission tomography, endoscopy, fluoroscopy, and others. Alternative medicine within a year was scored as 1 for herbal medication, 2 for acupuncture, 3 for moxibustion or cupping therapy, 4 for pharmaco-acupuncture, 5 for bee venom acupuncture, and 6 for others. We also recorded the use of the following supplements within a year: glucosamine, chondroitin, omega-3, vitamins, calcium, iron, ginseng, and others.

Socioeconomic determinants

Socioeconomic determinants included educational attainment and annual household income. Income was recorded in Korean Won and dichotomized as ≤ 2,000,000 Won or > 2,000,000 Won for data analysis (1 USD = 1,094 Won, 1,000,000 Won = 914 USD in 2013 currency). Education was recorded in years and dichotomized as < 10 years or ≥ 10 years for data analysis.

Ethics statement

The KORONA protocol was approved by the Institutional Review Boards of Hanyang University Hospital and all participating hospitals. Informed consent was obtained from all patients before registration. The study protocol complied with the Declaration of Helsinki and was fully approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number: X 1812-510-906).

Statistical analysis

The baseline characteristics of patients who had ever used biologics before enrollment (ever-users) and those who had never used biologics during the study period (never-users) were analyzed. The categorical and continuous variables are presented as frequencies and percentages, and means and standard deviations, respectively. Unadjusted associations between the covariates and the primary outcome were assessed using the chi-square test for categorical data and Student's t-test or Mann–Whitney U test for continuous data. Similar analyses were conducted after stratifying the data based on income and education. Pairwise deletion was used to handle missing data, including data of monthly household income for 2 participants. This allowed the use of all available data while only removing data points missing from any analyses. Multivariable logistic regression analysis was performed to identify the factors associated with biologics use after adjusting for income, education, healthcare habits, and comorbidities. To determine additive risks resulting from the interaction between education and income, we determined Relative Excess Risk due to Interaction (RERI),

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attributable proportion (AP) due to interaction, and synergistic index (SI) [18]. In brief, RERI quantifies the degree of additive interaction between two risk factors. If an interaction between risk factor A and risk factor B is present, the combined effect of A and B is greater or smaller than the sum of the individual effects of A and B. A RERI value of 0 indicates no interaction or exact additivity, a RERI value of > 0 indicates positive interaction or more than additivity, and a RERI value of < 0 indicates a negative interaction. AP represents the proportion of disease in the doubly exposed group that is attributable to the interaction. The SI was computed as the ratio between the combined effect and the sum of the individual effects. When an additive interaction effect is absent, AP equals 0 and SI equals 1.

To comprehensively analyze the underlying mechanism, we employed structured equation modeling (SEM) to simultaneously examine multiple factors. SEM allows for the consideration of both the independent and dependent effects of these factors. The measured items for latent variables are presented in Supplementary Table 1. For example, the latent variable of SES included observed variables such as income, education, insurance, and marital status. Our developed model included a direct pathway between SES and biologics use, as well as indirect pathways through latent variables, such as comorbidity, lifestyle, and healthcare habits. Goodness-of-fit indices, including chi-square, comparative fit index (CFI), incremental fit index (IFI), Tucker–Lewis coefficient (TLI), normed fit index (NFI), and relative fit index (RFI), were used to assess the model's fit. $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using R (version 4.1.0, R Foundation for Statistical Computing Platform) or IBM® SPSS® Amos™, version 23 statistical software (IBM Corp., Armonk, NY, USA).

RESULTS

The study enrolled 5,077 participants. Of them, 31.8% were in the low SES (low income, low education) group, 39.3% were in the high SES (high income, high education) group, and the remaining participants belonged to mixed category (mixed group) (Supplementary Table 2).

Table 1 offers a comprehensive overview of patient characteristics. Of the patients, 92.3% were classified as "never-users" (4,684 patients) and 7.7% as "ever-users" (393 patients). Notable findings include a statistically significant age difference between the two groups ($p = 0.002$), with "ever-users" having a lower average age. Other variables, such as gender and familial history of RA showed no statistically significant differences between the two groups. Regarding disease activities at study enrollment, no discernible disparities were noted between the two groups, except for a higher prevalence of rheumatoid factor positivity in the never-user group. Both income and education significantly influenced biologics use. Among patients who have ever been prescribed biologics, a considerably higher proportion of patients exhibited a high income level (41.7% vs. 58.3%). Similarly, a significantly higher percentage of patients with high educational attainment used biologics (39.7% vs. 60.3%) (Table 1). By contrast, health insurance (National Health Insurance [NHI], or medical aid and others), family type, and marital status exhibited no statistically significant differences. A trend toward a longer time lag to biologics initiation was noted in medical aid enrollees compared with NHI enrollees (7.8 ± 6.6 yr vs. 11.6 ± 9.3 yr, $p = 0.068$) (data not shown in the table). Health risk habits such as alcohol consumption (5.8% vs. 8.5%, $p = 0.001$) and smoking were more prevalent in the never-user group (5.3% vs. 8.1%, $p = 0.007$). This indicates that smoking and alcohol consumption were significantly associated with lower biologics use. By contrast, health-promoting habits including medication compliance were more prevalent in the ever-user group (Supplementary Fig. 1).

Assessment of biologics use according to income and education

We investigated the mechanisms underlying the influence of SES on biologics use. Table 2 presents the RA patients categorized based on income and education levels and a description of their insurance coverages. Comparative analyses of biologics usage and the time to initiation of biologics were conducted. We also analyzed disease activity and healthcare utilization habits. Regarding biologics use, the percentage of ever-users was statistically significantly lower in both the low-income and low-education groups than in the high-income and high-education counterparts (6.8% vs. 8.6%, $p = 0.014$, 6.9% vs. 8.5%, $p = 0.04$, Supplementary Fig. 1). Although the time to initiate biologics, which is measured as the interval between the date of RA diagnosis and the first biologics treatment, exhibited no statistically significant differences regardless of income or education levels.

RA patients with lower income or lower education ex-

Table 1. Characteristics of the study patients

Variable	All	Never-user	Ever-user	*p* value
Total	5,077 (100.0)	4,684 (92.3)	393 (7.7)	
Demographics				
Age (yr)	62.8 ± 12.2	63.0 ± 12.2	61.0 ± 12.6	0.002
Sex				
Female	4,327 (85.2)	3,987 (85.1)	340 (86.5)	0.500
Male	750 (14.8)	697 (14.9)	53 (13.5)	
Body mass index (kg/m^2)	22.7 ± 3.2	22.7 ± 3.2	22.9 ± 3.1	0.181
Familial history of RA	699 (13.8)	650 (13.9)	49 (12.5)	0.172
Socioeconomic determinants				
Monthly household income (10,000 Won)				0.014
≤ 200	2,425 (47.8)	2,261 (48.3)	164 (41.7)	
> 200	2,650 (52.2)	2,421 (51.7)	229 (58.3)	
Education				0.040
Low (< 10 yr)	2,273 (44.8)	2,117 (45.2)	156 (39.7)	
High (≥ 10 yr)	2,804 (55.2)	2,567 (54.8)	237 (60.3)	
Health insurance				0.883
National health insurance	4,804 (94.6)	4,431 (94.6)	373 (94.9)	
Medical aid and others	273 (5.4)	253 (5.4)	20 (5.1)	
Number of family members	3.0 ± 1.3	3.0 ± 1.3	3.0 ± 1.2	0.257
Family type				0.113
Single	535 (10.5)	501 (10.7)	34 (8.7)	
Couple	1,327 (26.1)	1,207 (25.8)	120 (30.5)	
Nuclear	2,687 (52.9)	2,483 (53.0)	204 (51.9)	
Extended	471 (9.3)	437 (9.3)	34 (8.7)	
Other	54 (1.1)	53 (1.1)	1 (0.3)	
Marital status				
Ever married	4,744 (93.4)	4,374 (93.4)	370 (94.1)	0.629
Currently married	3,944 (77.7)	3,627 (77.4)	317 (80.7)	0.158
Lifestyle habits and healthcare utilization				
Alcohol	1,460 (28.8)	1,376 (29.5)	84 (21.5)	0.001
Smoking	796 (15.7)	754 (16.1)	42 (10.8)	0.005
Exercise	2,232 (44.0)	2,051 (43.8)	181 (46.2)	0.364
Hospitalization (within 2 yr)	1,367 (26.9)	1,247 (26.6)	120 (30.5)	0.107
Medication compliance (Likert scale)	1.4 ± 0.9	1.4 ± 0.9	1.3 ± 0.7	0.034
Skipped medication (Likert scale)	1.5 ± 0.9	1.5 ± 1.0	1.4 ± 0.8	0.021
Check-up (within 2 yr)	4,878 (96.1)	4,507 (96.2)	371 (94.4)	0.099
Alternative medicine	3,474 (68.4)	3,215(68.7)	259 (65.9)	0.282
Supplements	2,415 (47.6)	2,229 (47.6)	186 (47.3)	0.963

Values are presented as number (%) or mean ± standard deviation.
DAS28-ESR, disease activity score 28-joint count erythrocyte sedimentation rate; EQ-5D, EuroQol-5 dimensions; HAQ, health assessment questionnaire; VAS, visual analog scale.

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hibited higher levels of disease activity, poorer physical and mental health, and a reduced quality of life compared with their higher income or higher education counterparts (Table 2, Supplementary Table 3). Specifically, RA patients with lower income had higher baseline disease activity (DAS 28: 3.6 ± 1.7 vs. 3.4 ± 1.5, $p = 0.001$), lower EQ-5D scores, higher HAQ scores, and greater physician assessment scores than those with higher incomes. Similarly, disease activity was higher in RA patients with lower education than in those with higher education. Overall, despite the trend of higher disease activity in patients with lower income or lower education, we paradoxically found lower biologics use in those groups.

We further explored the relationship between income and education with healthcare utilization and health behaviors. There were no significant differences in alcohol consumption, smoking habits, or exercise frequency based on income and education. However, in terms of medication compliance and skipped medication, individuals in the low-income, low-education group showed lower scores compared to their counterparts, which indicates better medication adherence. Moreover, the consumption of supplementary healthcare products incurring additional costs was found to be higher among those in the high-income, high-education group. Moreover, the low-education and low-income patients were more likely to have higher hospitalization rates, and patients with lower education levels were more inclined to undergo health check-ups, indicating that the NHI system is effective in providing healthcare to low SES patients in Korea.

Table 2. Characteristics of rheumatoid arthritis patients by income and education level

Socioeconomic determinants	Monthly household income (10,000 Won)			Education		
	≤ 200	> 200	*p* value	Low (< 10 yr)	High (≥ 10 yr)	*p* value
Total	2,425	2,650		2,273	2,804	
Insurance coverage			< 0.001			< 0.001
National health insurance	2,172 (89.6)	2,631 (99.3)		2,100 (92.4)	2,704 (96.4)	
Medical aid and others	253 (10.4)	19 (0.7)		173 (7.6)	100 (3.6)	
Biologics use						
Biologics ever use	164 (6.8)	229 (8.6)	0.014	156 (6.9)	237 (8.5)	0.040
Time to biologics initiation for only users (yr)	8.8 ± 8.1	7.6 ± 5.9	0.131	8.7 ± 7.8	7.8 ± 6.4	0.306
Disease activity						
DAS28-ESR	3.6 ± 1.7	3.4 ± 1.5	0.001	3.6 ± 1.7	3.4 ± 1.5	< 0.001
EQ-5D	0.6 ± 0.3	0.7 ± 0.2	< 0.001	0.6 ± 0.3	0.7 ± 0.2	< 0.001
HAQ	0.8 ± 0.7	0.6 ± 0.6	< 0.001	0.9 ± 0.7	0.5 ± 0.6	< 0.001
Physician VAS	27.0 ± 19.0	25.0 ± 18.4	< 0.001	27.7 ± 19.0	24.5 ± 18.4	< 0.001
Lifestyle habits and healthcare utilization						
Alcohol	701 (29.0)	759 (28.7)	0.826	646 (28.5)	814 (29.1)	0.665
Smoking	391(16.2)	405 (15.3)	0.434	380 (16.8)	416 (14.9)	0.074
Exercise	1,068 (44.1)	1,163 (43.9)	0.923	998 (43.9)	1,234 (44.0)	0.958
Medication compliance (Likert scale)	1.4 ± 0.8	1.4 ± 0.9	0.001	1.3 ± 0.8	1.5 ± 0.9	< 0.001
Skipped medication (Likert scale)	1.5 ± 0.9	1.6 ± 1.0	< 0.001	1.4 ± 0.9	1.6 ± 1.0	< 0.001
Check-up	2,334 (96.2)	2,542 (95.9)	0.603	2,200 (96.8)	2,678 (95.5)	0.023
Hospitalization	762 (31.4)	605 (22.8)	< 0.001	730 (32.1)	637 (22.7)	< 0.001
Alternative medicine	1,653 (68.2)	1,821 (68.7)	0.680	1,527 (67.2)	1,947 (69.5)	0.084
Supplements	1,062 (43.8)	1,353 (51.1)	< 0.001	939 (41.3)	1,476 (52.6)	< 0.001

DAS28-ESR, disease activity score 28-joint count erythrocyte sedimentation rate; EQ-5D, EuroQol-5 dimensions; HAQ, health assessment questionnaire; VAS, visual analog scale.

Furthermore, we analyzed comorbidities based on income and education levels. Patients with low income and low education had a higher prevalence of heart failure, hypertension, asthma, hepatitis, diabetes, bone fractures, and osteoporosis (Supplementary Table 4).

Univariate and multivariate analyses for biologics use adjusted for SES and comorbidity index values

As presented in Model 1 of Table 3, univariate logistic regression analysis revealed associations between an increase in biologics use and factors such as age, low income, low education, and positive rheumatoid factor. Conversely, alcohol consumption and smoking were associated with a decrease in biologics use. Rheumatoid factor positivity and smoking did not reach statistical significance in the multivariate analysis.

Since comorbidity itself may directly affect biologics use, a multivariable logistic regression analysis was conducted to identify biologics use-associated factors while adjusting for comorbidities (Models 2 and 3 of Table 3). Instead of including all comorbidities in the model, we used the age-adjusted Charlson comorbidity index (CCI) [19]. Due to the correlation between lower income and low education, we separately assessed regression models with income and education to eliminate the collinearity effect. Following the adjustment for all covariates, older age (OR = 0.98, 95% CI: 0.97–0.99, $p < 0.001$ in both models), low education (OR = 0.77, 95% CI: 0.65–0.98, $p = 0.032$) in the education model, and low income (OR = 0.76, 95% CI: 0.60–0.96, $p = 0.021$) in the income model were significant.

Interaction analysis between income and education for biologics use

While both low income and low education individually showed associations with lower biologics utilization, we further investigated the additive risks resulting from their interaction by using RERI (Supplementary Table 5). Income and education exhibited a significant additive interaction for biologics use. Notably, among low-income patients, biologics use increased by 11% if they had high education. Similarly, among low-education patients, biologics use increased by 9% if they had a high income. When both high income and high education were present (high-income, high-education group, biologics use increased significantly by 68%, indicating that these patients had 68% higher odds of using bio-

Table 3. Univariate and multivariate analyses for biologics use adjusted for socioeconomic determinants and comorbidity index values

Variable	Model 1 Univariate OR	95% CI	*p* value	Model 2 Low education model	95% CI	*p* value	Model 3 Low-income model	95% CI	*p* value
Age	0.99	0.98–0.99	0.002	0.98	0.97–0.99	< 0.001	0.98	0.97–0.99	< 0.001
Sex	1.12	0.84–1.53	0.454	1.12	0.82–1.58	0.488	1.12	0.81–1.57	0.5
Disease duration	1.00	0.99–1.02	0.745	1.00	0.99–1.02	0.614	1.00	0.99–1.02	0.612
Low income	0.77	0.62–0.94	0.013	-	-	-	0.76	0.60–0.96	0.021
Low education	0.80	0.65–0.98	0.035	0.77	0.61–0.98	0.032	-	-	-
Alcohol	0.66	0.51–0.84	0.001	0.63	0.47–0.84	0.002	0.63	0.47–0.85	0.002
Smoking	0.63	0.45–0.86	0.006	0.91	0.61–1.31	0.614	0.90	0.61–1.30	0.582
Erosion on X-ray	1.04	0.84–1.28	0.738	1.01	0.79–1.27	0.965	1.01	0.80–1.28	0.947
Positive rheumatoid factor	0.69	0.53–0.91	0.007	0.74	0.55–1.01	0.052	0.74	0.55–1.01	0.054
Age-adjusted Charlson comorbidity index >3	1.08	0.86–1.35	0.502	1.10	0.84–1.42	0.472	1.10	0.85–1.42	0.465

CI, confidence interval; OR, odds ratio.
DAS28-ESR scores were excluded from the analysis considering that the dataset only contained DAS28-ESR scores at the time of enrollment, which does not accurately reflect the disease activity at the start of biologics use.

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Table 4. Structural and measurement outcomes of structural equation modeling

Path	Coefficient	Standard errors	Critical ratio	Probability
H1: Comorbidity ← SES	-0.054	0.003	-17.248	0.000**
H2: Lifestyle and health habit ← comorbidity	0.016	0.029	5.731	0.000**
H3: Lifestyle and health habit ← SES	0.032	0.007	4.830	0.000**
H4: Biologics ← Disease activity	0.001	0.000	2.600	0.009**
H5: Biologics ← Comorbidity	0.031	0.032	0.980	0.327
H6: Biologics ← Age	0.000	0.000	-2.211	0.027*
H7: Biologics ← SES	0.034	0.007	4.603	0.000**
H8: Biologics ← Lifestyle and health habits	0.006	0.016	0.374	0.708

SES, socioeconomic status.
The items used to measure latent variables are presented in Supplementary Table 1. Briefly, the latent variable of socioeconomic status was comprised of observed variables such as income, education, insurance, and marital status. Comorbidity included age-adjusted Charlson comorbidity index values as well as other conditions.
*$p < 0.05$; **$p < 0.01$.

logics than those with both low income and low education. This suggests a disparity in biologics use based on education and income. RERI was 0.98, indicating a positive additive interaction of income and education. Furthermore, AP was 0.92 (95% confidence interval [CI]: 0.62–1.22), indicating that 92% of the odds ratio (OR) for biologics use in patients with both high income and high education could be attributed to the additive interaction. The OR for biologics utilization in individuals with high income and high education was 3.27 (SI, 3.27, 95% CI: 0.19–57.09) times higher than the sum of the risks in the patients with low-income or low-education alone. This indicates a synergistic effect of high education and high income, which increased biologics use 3.3-fold when both were present.

Structural and measurement results of the SEM model

Supplementary Figure 2 presents the structural and measurement results of the SEM model. Despite a chi-square value for the SEM model fit of 53.507 with 4 degrees of freedom, which does not support a good model fit, the *p* value for probability was considerably substantial (> 0.05), indicating support for the proposition that the overall model fitted the data. The other standardized fit indices demonstrated that the model had a satisfactory fit (CFI = 0.999, IFI = 0.999, TLI = 0.995, RFI = 0.994, and NFI = 0.999).

On examining the direct structural effects of the variables (Table 4), several significant findings were noted. First, SES significantly and negatively affected comorbidity (β = -0.054, $p < 0.001$, critical ratio = -17.248), suggesting that patients with higher SES have lower comorbidity rates. Second, both comorbidity (β = 0.016, $p < 0.001$, critical ratio = 5.731) and SES (β = 0.032, $p < 0.001$, critical ratio = 4.830) positively affected lifestyle and healthcare habits, suggesting that patients with comorbidities and those with higher SES show more favorable lifestyle and healthcare behaviors. Third, disease activity had a positive effect on the use of biologics (β = 0.001, $p = 0.009$, critical ratio = 2.600), whereas age exhibited a negative effect on biologics use (β = 0.000, $p = 0.027$, critical ratio = -2.211). SES had a positive effect on biologics use (β = 0.034, $p = 0.007$, critical ratio = 4.603). These findings collectively suggest that patients with higher disease activity, younger age, and higher SES are more likely to use biologics for their RA treatment. The mediation analysis revealed that age and disease activity partially mediates the association between SES and biologics use. However, no mediating effect of comorbidities, lifestyle, or healthcare habits was noted in the linkage between SES and biologics. In the pathway analyses, several factors were identified as significant predictors of biologics use (Supplementary Table 6 [H117-153]). Alcohol consumption, smoking, and the use of alternative medicine significantly and negatively affected biologics use. Additionally, older age and comorbidities measured on the basis of age-adjusted CCI were associated with a lower likelihood of biologics use. By contrast, higher disease activity, longer disease duration, hospitalization, good medication compliance, higher income, and higher education significantly and positively affected biologics use.

These findings highlight the complex interplay between various factors that influence biologics use.

DISCUSSION

Using nationally representative data, this study demonstrates that low SES have a significant impact on the limited utilization of biologics use. To comprehensively examine the underlying mechanisms, a multidimensional evaluation of biologic use, encompassing the factors of income, education, insurance level, marital status, disease activities, comorbidities, and health behaviors, was conducted. Additionally, an SEM approach was used to examine these factors simultaneously and assess the intricate relationships among them. Both low income and low education independently and synergistically had negative impacts on biologics use. Although lifestyle, healthcare habits, and comorbidities were closely associated with SES, they did not mediate the relationship with biologics use. Independent of old age or high disease activity, SES exerted a direct positive effect on biologics use. These findings facilitate a deeper understanding of the intricate interplay between SES and biologics use.

Despite the higher disease activity observed in patients with lower income or lower education levels, we paradoxically found a lower rate of biologics use in those groups. Although lower SES has been consistently linked to increased disease activity [20], evidence regarding the mechanism underlying its association with biologics use is limited. The METEOR registry study reported that low SES is associated with higher disease activity and lower biologics usage, but this result was demonstrated at a country level rather than at an individual level [21]. Factors such as lack of information, lifestyle choices, comorbidities, poor medication adherence, increased levels of chronic pain and fatigue, overall well-being, and barriers to optimal treatment as recommended by guidelines may contribute to lower biologics use [20]. Our SEM analysis confirmed the direct effect of SES on biologics usage, alongside with high disease activity. We suspect that SES may exert a direct effect on biologics usage, surpassing the impact of disease activity. Considering the intricate relationship between SES, RA disease activity, and outcomes, we believe that further research can provide deeper insights.

In this study, RA patients with low SES had a higher prevalence of certain comorbidities. Moreover, our findings indicated that comorbidities, such as heart failure and malignancy, were associated with lower biologics use, possibly because of their negative impact of RA treatment decisions by rheumatologists prescribing biologics [2]. However, while comorbidities may have some effect, our adjusted multivariable analysis revealed that they had no significant association with biologics use. Furthermore, in our SEM analysis, comorbidities had no mediating effect on biologics use, suggesting limited supporting evidence for biologics use in relation to comorbidities.

We here explored whether the low usage of biologics among patients with low SES was associated with the high-cost factor. However, the KORONA dataset lacks specific cost-related information or underlying reasons for the limited adoption of biologics among this demographic. To indirectly address this point, patients' health insurance type was investigated as a proxy for SES. Korea provides mandatory social health insurance coverage with varying copayment structures based on an individual's income. Medical aid program supports poor people in need of medical assistance. Medical aid beneficiaries are not required to provide copayments for any medical utilization or they have minimum copayment rates of up to 15%. Surprisingly, our analysis reported no significant difference in biologics use rates between NHI beneficiaries and medical aid recipients. The finding that medical aid recipients did not exhibit a significantly higher biologics usage rate suggests that factors other than financial costs likely influence the decision-making process regarding biologics use among low SES patients. A study conducted in Canada, where all patients receive identical health insurance coverage, found that factors such as rural residence, greater distance to prescribers, and the unavailability of rheumatologists had a negative impact on biologics use [3]. This suggests that physician's discretion plays a larger role than patients' affordability or biologics cost. While these factors warrant consideration in the context of our study in South Korea, it is important to clarify that our current research did not encompass an investigation into this specific aspect.

We also determined whether the inconvenience of hospital visits for injectable biologics could explain low biologics usage among low SES patients. Accordingly, we investigated surrogate markers including hospitalization, check-ups, and medication compliance for healthcare utilization habits. Surprisingly, patients with a low income or low education exhibited health conscious behaviors with more hospitalizations, better medication compliance, and more frequent

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check-ups than those with a high income or high education. While low SES patients with RA in Korea seem adequately or even excessively use healthcare services based on their health coverage level [22,23], inconvenience of hospital visits does not appear to be the primary reason for the lack of biologics use among low SES patients. Interestingly, healthcare utilization, such as increased hospitalizations and better medication compliance, positively affected biologics use. However, in our SEM model, these conscious lifestyle habits and healthcare utilization did not serve as mediators of the effect on biologics usage, indicating lack of sufficient supporting evidence for a direct relationship.

Notably, health risk behaviors such as alcohol consumption, smoking, and medication non-compliance exhibited associations with lower biologics use among patients. These associations were independent of income and education levels. Indeed, never-users had a higher prevalence of alcohol and smoking consumption than ever-users. Nonetheless, patients with lower income and low education levels did not exhibit significantly higher rates of alcohol and smoking use. This observation is indeed noteworthy as it deviates from the expected patterns typically associated with lower individuals who often exhibit higher rates of health risk behaviors such as smoking, alcohol consumption, and poor medication adherence, as noted in countries without healthcare insurance coverage [24]. However, the behavior of RA patients with low SES in KOREA seemed different.

From another perspective, the prominent frequency of hospitalizations among patients with low income or low education offers insights into their biologics use behavior. It can be considered that patients with a low SES tend to prefer hospitalization over regular ambulatory care, potentially creating a behavioral pattern that impedes the adoption of biologic treatments requiring consistent outpatient visits. While hospitalization indicates an acute medical need, it can also represent a low-value pattern of healthcare utilization [25]. This preference for hospitalization over outpatient visits may be a result of insufficient awareness of the significance of regular outpatient visits, or the influence of social and workplace constraints. This suboptimal care pattern has negative implications for both healthcare cost and patient health [26]. Addressing this issue necessitates individual education and coordinated efforts within the social security framework. Policymakers should aim to provide healthier alternatives and reshape the healthcare environment accordingly.

The present study had several limitations. First, we did not examine disease outcomes of biologics treatment, which could provide valuable insights into the effectiveness of this treatment. Second, DAS 28 scores at study enrollment did not represent the time of biologics treatment initiation. Therefore, they were not included in the multiple regression model for risk factor analysis. Third, the biologics prescription was dependent on the physician, particularly rheumatologists, and might vary based on their characteristics, education level, decision-making processes, and adherence to guidelines [27]. However, physicians' characteristics were not investigated in the current cohort, thereby limiting our ability to assess the influence of these characteristics. Fourth, this study had a cross-sectional design, which inherently does not establish causality or address reverse causality. Nevertheless, this study has notable strengths and implications. First, it offers a national perspective on socioeconomic disparities in biologics use among Korean patients with RA. It highlights the crucial role of policymakers in evaluating cost-effectiveness by comparing the cost of hospitalization or check-ups to that of biologics and potentially revising the compensation framework for low SES patients so as to prioritize disease activity control. Second, the present study investigated the complex interplay of various factors, including SES, individually and simultaneously. This expands our understanding of the intricate relationships involved and identifies potential areas that need intervention.

In summary, using nationally representative data in a healthcare system with NHI coverage, this study examined the impact of SES on biologics use among RA patients in Korea. Low SES was associated with lower biologics use primarily because of low income and low education. To address the socioeconomic disparities observed in biologics use among RA patients, policy interventions are necessary. These interventions should be aimed at reducing low SES-related barriers, promoting disease activity control, and improving access to biologics for patients with low SES.

KEY MESSAGE

1. Low SES was associated with lower biologics use in RA patients.
2. Despite the higher disease activity, low SES patients use fewer biologics.
3. Comorbidities have limited influence on the biologics' utilization.
4. Biologics' use was not impacted by the level of insurance.
5. Despite favorable health-promoting behavior, low SES patients use fewer biologics
6. Policy interventions are needed to address socioeconomic disparities.

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