JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2023; 7: 284-292
https://doi.org/10.30621/jbachs.1102242
RESEARCH ARTICLE

WHAT FACTORS AFFECT TREATMENT EFFECTIVENESS IN RHEUMATOID ARTHRITIS: A MULTIDIMENSIONAL MEASUREMENT

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Received: 12.04.2022; **Accepted:** 20.06.2022; **Available Online Date:** 31.01.2023

Cite this article as: İlgün G, Şahin B. What factors affect treatment effectiveness in rheumatoid arthritis: A multidimensional measurement. J Basic Clin Health Sci 2023; 7: 284-292.

ABSTRACT

Purpose: The aim of the study was to examine the effects of socio-demographic characteristics, disease-related characteristics and health care use related-characteristics on the treatment effectiveness of rheumatoid arthritis patients, both separately and together.
Material and Methods: The sample of the study consisted of 440 rheumatoid arthritis patients for 99% confidence level, and this sample was reached based on the convenience sampling method. Patients who received at least one anti-TNF therapy were included in the study. Treatment effectiveness levels of rheumatoid arthritis patients were measured with a questionnaire. In the analysis of the study, four different regression models were established. In the first model, socio-demographic characteristics; in the second model, disease characteristics; in the third model, health care use characteristics: in the fourth model, the effect of all these variables on treatment effectiveness was examined.
Results: In the study, smoking status, age (socio-demographic characteristics), drug regimen complexity, comorbidity status, education about the disease, disease duration (disease characteristics), and a number of admissions (health care use characteristics), were found to have a significant effect on treatment effectiveness.
Conclusion: In the study, the factors affecting the treatment effectiveness were determined. Therefore, it is important to consider these factors revealed in this study in order to increase the treatment effectiveness in patients with rheumatoid arthritis.

Keywords: Anti-TNF therapy, rheumatoid arthritis, treatment effectiveness

INTRODUCTION

Increasing economic burden of chronic diseases together with demographic (age) and epidemiological (disease structure) changes is an important issue for policy makers (1). The fact that chronic diseases constitute a large part of the disease burden of countries and these diseases play an active role in the development of different diseases, cause disability, death, early retirement, decrease in work efficiency/productivity and increase in health expenditures force policy makers to take precautions against these diseases (2-4).

Rheumatoid arthritis, a chronic inflammatory joint disease, has been defined by the Center for Disease Control and Prevention in the USA as “Rheumatoid arthritis is an autoimmune and inflammatory disease, which means that your immune system attacks healthy cells in your body by mistake, causing

inflammation (painful swelling) in the affected parts of the body" (5). Since rheumatoid arthritis can cause serious damage to the articular cartilage or bones, the ability of patients who are not treated adequately and correctly to perform their daily activities is very low. Daily activities such as housework or walking can be painful for these patients (6-11). For this reason, in addition to the correct diagnosis of the disease, the correct and adequate treatment has a very important role in both improving the health outcomes of the patient and increasing the effectiveness/success of the treatment (12).

Treatment effectiveness is a two-dimensional concept: treatment response and treatment satisfaction. Treatment response encompasses pharmacologically based aspects, both treatment effectiveness and tolerability (side effects). Treatment satisfaction includes both the patient's and his/her relatives' subjective general satisfaction with the treatment. Evaluations of both treatment response and treatment satisfaction are made by patients (13). The high negative effects of rheumatoid arthritis on health outcomes and the high cost of treatments used in this disease both for the patient and the country necessitate the evaluation of the treatment effectiveness on these patients. In addition, measuring the treatment effectiveness of rheumatoid arthritis patients and determining the factors affecting the treatment effectiveness levels are an important factor in both improving health outcomes and reducing costs. Therefore, in this study, it was aimed to examine the effects of socio-demographic characteristics, disease-related characteristics, and health care use-related characteristics on the treatment effectiveness of rheumatoid arthritis patients.

MATERIAL AND METHODS

Population and Sample

The population of the study consists of 1306 rheumatoid arthritis patients who applied to the rheumatology outpatient clinic of a university hospital in 2018. Within the scope of the research, the formula used for the groups whose population is known was used in calculating the sample size. Accordingly, it was decided that the sample size that could represent the universe for the 99% confidence level was 440 rheumatoid arthritis patients. While deciding on the patients to be included in the sample of the research: in order for the groups to be homogeneous and comparable, attention was paid to the fact that the participants were using at least one biological agent (anti-TNF). In addition, individuals aged 18 and over were included in the study to ensure responsiveness regarding the scales used in the study. After calculating the sample size and determining the inclusion/exclusion criteria from the research, data were collected between May 2019 and January 2020 according to the convenience sampling method.

Data Collection

In the study, data on socio-demographic characteristics, disease-related characteristics, health service use and treatment effectiveness were collected with a questionnaire, which is the primary data source.

Care was taken to include the risk factors thought to be important for rheumatoid arthritis and the (14-17) features recommended in the literature while determining the questions regarding socio-demographic characteristics. From this point of view, patients were asked 8 questions to determine their socio-demographic characteristics such as age, gender and marital status.

Three questions that are thought to be important in rheumatoid arthritis in determining the characteristics of the disease (family history, disease duration and education about rheumatoid arthritis), medication regimen complexity and comorbidity are included. Drug regimen complexity was measured by the Medication Regimen Complexity Index (MRCI), developed by George et al. (18). The adaptation and validity of the index into Turkish was done by Okuyan et al. (19). The index consists of 3 parts, A, B and C, and there are 65 items in total in these 3 parts. Part A of the index includes 32 items on the dosage form of drugs, part B contains 23 items on the dose frequency of drugs, and part C 10 items on additional instructions for the use of drugs.

The Modified Rheumatic Diseases Comorbidity Index (mRDCI), developed by Michaud and Wolfe (20,21), validated by England et al. (22) and modified by Spaetgens et al. (23), was used to measure comorbidity, another important feature of the disease. The following formula was taken into account in calculating the index score.

mRDCI= 1 x Lung Disease / Asthma + [2 x (either Heart Attack or Another Heart Condition or Stroke) or 1 x Hypertension] + Fracture + Depression + Diabetes + Cancer + (Ulcer or Other Stomach Conditions) + 2 x Kidney Disease + (1 x BMI >30 or 2 x BMI >35)

According to the formula, patients' comorbidity scores range from 0 to 12, and high scores indicate high comorbidity.

Since it is expected that the use of health services will have an impact on the treatment effectiveness of rheumatoid arthritis, 6 questions to determine the characteristics of patients' use of health services (generally admitted hospital for rheumatoid arthritis, type of application to the hospital, application to the emergency department due to rheumatoid arthritis, using alternative medicine, and number of applications to hospital for rheumatoid arthritis) were asked.

In the study, the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General (FACIT-TS-G) scale developed by Peipert et al. (24) was used. The permission to use the Turkish version of the scale was obtained from the FACIT group. The scale consists of 8 questions and one dimension. In the scale, there are items to learn about the patients' recovery status, treatment-related side effects, satisfaction with the treatment, cooperation with the physician during the treatment process, recommending the treatment to others, and how they evaluate the treatment in general. The 3 questions in the scale were 0 (poor/quite bad) to 4 (excellent/quite good); 3 questions 0 (no, not at all) to 3 (yes, totally); 2 questions are scored between 0 (no) and 2 (yes). By adding the scores of the 8 questions in question, the total score for the scale is obtained. Therefore, the lowest treatment effectiveness score of the patients is 0, while the highest treatment effectiveness score is 25.

Ethical Declaration

Within the scope of the research, ethics committee approval was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee with the decision numbered GO 18/432-27 on 5 June 2018. The research is a cross-sectional study conducted in accordance with the Declaration of Helsinki. Before applying the questionnaire in the study, patients were informed about the research topic and informed consent was obtained from all patients.

Analysis

In the study, the socio-demographic, disease and health care use characteristics of the patients were examined with descriptive statistics suitable for the type of data. Then, the relative effects of patients' socio-demographic, disease, and health care use characteristics on treatment effectiveness were evaluated by multivariate linear regression analysis. For this purpose, 4 models were developed and the effects of socio-demographic characteristics in the 1st model, disease-related characteristics in the 2nd model, and the effects of the health services usage characteristics in the 3rd model on treatment effectiveness were examined. The effect of all these features on treatment effectiveness was investigated in the final model.

RESULTS

Table 1 shows the distribution of patients' socio-demographic, disease and health care use characteristics. According to this, 78% of the patients were female, 83% were married, 25% had a bachelor's degree or higher, 61.1% were unemployed, 43.2% were smokers and 57.7% were lived in Ankara. It was found that the mean age of the participants was 51.9 (±13.6) years and the mean income was 5182.2 (±2981.4) TL. When the characteristics of the participants about the disease are examined; It was determined that 55.2% of the patients did not receive any education about the disease and 64.1% did not have a family history. It was determined that the mean disease duration of the individuals participating in the study was 14.37 (±9) years, the mean of the drug regimen complexity index was 12.2 (±5.1) and the mean of the comorbidity index was 2.2 (±2.1). Finally, when the characteristics of the patients regarding the use of health services are examined, it is seen that 92.5% of the participants applied to Hacettepe University for the follow-up and treatment of rheumatoid arthritis, 74.5% of them had a special application method, and 78.9% of them went to the emergency room because of rheumatoid arthritis. it was determined that they did not apply and 78.9% of them did not use any of the alternative medicine methods. In addition, it was observed that patients applied to a health institution an average of 7.6 (±6.1) times in the last year.

Table 2 contains the results of the regression analysis to determine the factors affecting the treatment effectiveness. It was determined that all four models created for the purpose of the study were statistically significant ($p<0.001$) and there was no problem of multicollinearity and autocorrelation in the models.

In the first model, the effect of socio-demographic characteristics on treatment effectiveness was examined and it was found that education level,

Table 1. Socio-demographic, Disease and Health Service Use Characteristics of the Participants

Socio-demographic Characteristics (Model 1)			
Categorical Variables	***Categories***	***n***	***%***
Gender	Female	343	78.0
	Male	97	22.0
Marital Status	Married	365	83.0
	Single	75	17.0
Educational Status	Illiterate, literate and primary school	164	37.3
	Middle school and high school	166	37.7
	Bachelor's degree or higher	110	25.0
Working Status	Yes	171	38.9
	No	269	61.1
Smoking	No	186	42.3
	Yes	190	43.2
	Quit	64	14.5
Place of Residence	Ankara	254	57.7
	Outside Ankara	186	42.3
Continuous Variables		***Mean***	***SD***
Age (year)		51.9	13.6
Income (TL)		5182.2	2981.4
Disease Characteristics (Model 2)			
Categorical Variables	***Categories***	***n***	***%***
Education About Rheumatoid Arthritis	Yes	197	44.8
	No	243	55.2
Family History	Yes	158	35.9
	No	282	64.1
Continuous Variables		***Mean***	***SD***
Disease Duration (year)		14.4	9
Medication Regimen Complexity Index		12.2	5.1
Modified Rheumatic Diseases Comorbidity Index (0-12)		2.2	2.1
Health Services Usage Characteristics (Model 3)			
Categorical Variables	***Categories***	***n***	***%***
Generally Admitted Hospital for Rheumatoid Arthritis	University hospital	407	92.5
	Other hospitals	33	7.5
Type of Application to The Hospital	Normal polyclinic	112	25.5
	Private polyclinic	328	74.5
Application to the Emergency Department Due to Rheumatoid Arthritis (last 6 months)	Yes	93	21.1
	No	347	78.9
Using Alternative Medicine	Yes	93	21.1
	No	347	78.9
Continuous Variables		***Mean***	***SD***
Number of Applications to Hospital for Rheumatoid Arthritis (last year)		7.6	6.1

smoking status and age had a statistically significant effect on treatment effectiveness. Accordingly, it was found that the treatment effectiveness levels of individuals with a high education level and non-smokers were higher. In addition, it was determined that the treatment effectiveness decreased with increasing age.

In the second model, the effect of disease-related characteristics on treatment effectiveness was examined and it was statistically significant that all other variables, except family history, had a statistically significant effect on treatment effectiveness ($p<0.05$). Accordingly, it was determined that the level of treatment effectiveness decreased as the comorbidity index, drug regimen

complexity and disease duration increased. In addition, it was determined that the treatment effectiveness scores of people who received education about the disease were higher than those who did not receive education.

In the third model, the effect of health services usage characteristics on the treatment effectiveness was evaluated and it was determined that the status of admission to the emergency department and the number of admissions had a statistically significant effect on the treatment effectiveness ($p<0.05$). Accordingly, it was determined that the level of treatment effectiveness was higher in those who did not apply to the emergency department due to rheumatoid arthritis compared to those who applied. In addition, it was found that the level of treatment effectiveness decreased as the number of applied to any health institution increased.

In the final model, the effect of all the above-mentioned characteristics on treatment effectiveness was examined. Accordingly, smoking status, age (socio-demographic variables), drug regimen complexity, comorbidity status, education about the disease, duration of disease (variables related to the disease) and number of admissions (variable related to healthcare use) were found to affect treatment effectiveness. It was found that the treatment effectiveness levels of smokers were lower than those who did not smoke or quit, and those who did not receive education about the disease compared to those who received training. In addition, it was determined that the effectiveness of the treatment decreased as the complexity of the drug regimen, comorbidity value, duration of the disease and the total number of applications increased.

When the explanatory coefficients of the models are compared, ıt was found that the Model 1 explains 43.2%, the Model 2 explains 59.5%, the Model 3 explains 12.6%, and the Model 4 explains explain 64.8% of variation in treatment effectiveness.

DISCUSSION

The most important factor in the correct diagnosis and treatment is that the treatment applied improves the patient. For this, the patient must be diagnosed correctly, the prescribed drug must have good efficacy and the treatment must be effective. Therefore, after the correct diagnosis and prescription, physicians should focus on the treatment effectiveness. It is necessary to investigate how to increase the treatment effectiveness of patients in order to gain more benefits from the currently available therapeutic treatments (12). In this study, it was aimed to determine the factors affecting the treatment effectiveness levels of rheumatoid arthritis patients.

According to the multiple linear regression analysis in the fourth model, the treatment effectiveness levels of smokers were found to be lower compared to non-smokers and individuals who had quit smoking. Smoking is an important environmental risk factor for rheumatoid arthritis, as well as a prognostic risk factor that negatively affects the course of the disease. Therefore, it is thought that smoking plays a role in the more severe course of the disease and in obtaining the expected results from the treatments applied more slowly. Studies by Manfredsdottir et al. (25) and Carlens et al. (26) also emphasized that smoking is an important risk factor for rheumatoid arthritis. Similarly, studies by Abhishek et al. (27), Söderlin et al. (28) and Vittecoq et al. (29) reported that smoking may aggravate the progression of rheumatoid arthritis and reduce the effect of antirheumatic treatments.

The study findings reveal that age has a statistically significant effect on the treatment effectiveness and that the treatment effectiveness decreases with increasing age. It is thought that the increase in health problems with age, decrease in mobility and decrease in the cognitive and physical level required for self-care cause a decrease in the treatment effectiveness. The study by Smolen et al. (30) also found that younger patients were more likely to achieve remission when receiving combination etanercept and methotrexate induction therapy compared to older individuals. However, in the study conducted by Mu et al. (31), it was determined that there was no statistically significant difference between age and treatment success.

In this study, it was also determined that the complexity of the drug regimen had a negative effect on the treatment effectiveness, and the level of treatment effectiveness decreased as the complexity of the drug regimen increased. Increasing the number or frequency of drugs to be used by patients decreases the level of treatment adherence (32-38). Therefore, the level of effectiveness expected from the treatment of patients also decreases.

It has been found that comorbidity is another variable that has an effect on treatment effectiveness, and as the comorbidity index increases, treatment effectiveness decreases. It has been predicted that

Table 2. Factors Affecting Treatment Effectiveness

Variables/Models	Model 1		Model 2		Model 3		Model 4	
	Std. β	t	Std. β	t	Std. β	t	Std. β	t
Gender (Male)	-0.023	-0.594					-0.056	-1.782
Marital Status (Single)	0.011	0.261					0.052	1.535
Educational Status (Middle school and high school)	0.188	4.151***					0.052	1.399
Educational Status (Bachelor's degree or higher)	0.150	2.531*					0.017	0.357
Working Status (Yes)	-0.014	-0.293					-0.023	-0.616
Smoking (Yes)	-0.174	-4.441***					-0.102	-3.211**
Smoking (Quit)	-0.089	-2.093*					-0.061	-1.789
Place of Residence (Outside Ankara)	0.070	1.887					0.027	0.891
Age	-0.502	-10.354***					-0.159	-3.499**
Income	0.024	0.513					-0.001	-0.032
Medication Regimen Complexity Index			-0.395	-9.660***			-0.350	-8.581***
Modified Rheumatic Diseases Comorbidity Index			-0.283	-6.908***			-0.204	-4.790***
Education About Rheumatoid Arthritis (Yes)			0.180	5.432***			0.134	4.129***
Family History (Yes)			0.017	0.538			0.008	0.256
Disease Duration (year)			-0.132	-3.865***			-0.077	-2.209**
Generally Admitted Hospital for Rheumatoid Arthritis (Other hospitals)					0.050	1.108	-0.002	-0.052
Type of Application to The Hospital (Private polyclinic)					-0.039	-0.855	0.052	1.680
Application to the Emergency Department Due to Rheumatoid Arthritis (No)					0.193	4.120***	0.027	0.852
Number of Applications to Hospital					-0.222	-4.795***	-0.101	-3.184**
Using Alternative Medicine (Yes)					0.088	1.906	0.007	0.224
VIF	1.028-2.640		1.056-1.795		1.014-1.087		1.063-2.772	
Durbin-Watson	1.867		1.836		1.814		1.861	
F	32.605		127.352		12.468		38.638	
p	<0.001		<0.001		<0.001		<0.001	
R^2	**0.432**		**0.595**		**0.126**		**0.648**	

*p<0.05; **p<0.01; ***p<0.001

comorbidity may be associated with a decrease in the patient's ability to manage self-care, complicating treatment processes, increasing treatment-related side effects, complicating care coordination and follow-up, and decreasing the effectiveness or success of the treatment. In the study conducted by Krüger and Kneitz (39), it was emphasized that comorbidity may worsen the underlying rheumatic disease and may complicate or even prevent the implementation of the targeted therapy concept, thus reducing the success of treatment. In the study conducted by Curtis et al. (40), it was found that people with comorbidities had a lower response to the treatment given. Similarly, in the study conducted by Biggioggero et al. (41), it was observed that individuals with high comorbidity index had low treatment continuation and treatment response rates. In the study, it was determined that the state of being educated to manage rheumatoid arthritis also affects the effectiveness of the treatment, and the treatment effectiveness level of the individuals who did not receive the training was found to be lower. Since the increase in the level of knowledge about the disease will enable patients to be more careful, conscious and attentive about their health and treatment, the level of treatment effectiveness is expected to be higher in these patients. Hirano et al. (42) also stated that the health status of patients who were given education about the disease could improve between 15% and 30%.

It was found that the duration of the disease had a statistically significant effect on the effectiveness of the treatment, and the effectiveness of the treatment decreased as the duration of the disease increased. Considering the positive relationship between the duration of the disease and age, it is thought that the disease may have progressed more in the participants with a longer duration of the disease and therefore the effectiveness of the treatment may be lower. In addition, it has been predicted that prolonging the duration of the disease may reduce the effectiveness of the treatment, as it may cause patients to feel more financial and moral burden regarding their treatment. Similarly, in the study

conducted by Capelusnik and Aletaha (43), it was found that the duration of the disease was an effective factor on the success of the treatment. In the study conducted by Mu et al. (31), it was determined that the response levels to treatment in rheumatoid arthritis patients with a shorter treatment period were better than the patients with a longer treatment period. In the study conducted by Radner et al. (44), it was observed that the duration of the disease had a statistically significant effect on the response to treatment.

Finally, it was found that the number of annual applications to any health institution due to rheumatoid arthritis had a statistically significant effect on the treatment effectiveness. Accordingly, as the total number of applications increases, the treatment effectiveness decreases. It is thought that this situation may be caused by unscheduled (applications made outside of appointments) applications. When the average number of applications (7.6±6.1) and the average number of unplanned applications (4±5.8) were compared, it was found that the average number of unplanned applications was also quite high. Therefore, it was predicted that these unplanned applications may have a negative effect on the treatment effectiveness of the patients.

CONCLUSION

Based on the findings obtained from the study, it was determined that smoking, age, drug regimen complexity, comorbidity status, educational status, duration of rheumatoid arthritis and the total number of admissions had an effect on the treatment effectiveness. According to the research findings, in order to improve the treatment effectiveness of individuals who smoke, who are older, who have a complex drug regimen, who have comorbidities, who have a long disease duration, and who have a high number of admissions, it is necessary to take precautions regarding the treatment modalities of these patients, to increase their compliance with treatment, and to minimize treatment-related risks. and training patients to manage their diseases and treatments can be recommended.

* This study was produced from researcher Gülnur ilgün's doctoral thesis.

Acknowledgement: We would like to thank Umut Kalyoncu (PhD), Şaziye Şule Apraş Bilgen (PhD) and Levent Kılıç (PhD) who Hacettepe University Faculty of Medicine Department of Internal Medicine faculty members.

Author contribution: Gİ, BŞ: Conception, design, literature review. Gİ: Data collection, data processing, analysis, writing. BŞ: Critical review, editing.

Conflict of interests: No conflict of interest has been declared by the authors.

Ethical approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Hacettepe University (Ref. No: GO 18/432-27) in June 2018. All procedures were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding: No funding has been declared by the authors.

Peer-review: Externally peer-reviewed.

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