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Actual and Perceived Risk of Cardiovascular Disease among Sample of Iraqi Patients with Rheumatoid Arthritis

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Abstract **Background:** Independent of conventional risk factors, patients with rheumatoid arthritis (RA) have a significantly increased risk of cardiovascular disease (CVD). **Aims of the study:** To evaluate the actual and perceived 10-year CVD risk among Iraqi patients with RA as well as their level of knowledge about CVD risk. Patients and methods: This cross-sectional study included 100 of RA patients (85 females and 15 males) who visited Baghdad Teaching Hospital/Rheumatology Unit from January 2021 till July 2021. The Framingham Risk Score (FRS) was used to calculate the actual 10-year risk of CVD. The Heart Disease Fact-Rheumatoid Arthritis Questionnaire (HDFQ-RA) was used to assess the subjects' cardiovascular disease knowledge. **Results:** Among hundred Iraqi patients with RA, the median age was 51.23 ± 8.4 years. The findings of the study revealed that 23% had high risk for CVD and 27% & 50% had moderate and low risk respectively based on FRS calculator. The risk of CVD was significantly affected by the age of disease onset and seropositivity and steroid use (p value 0.001). When the perceived risk was compared to the actual risk of cardiovascular disease, there was a week agreement between them, only 31% had corresponding answers. **Conclusions:** The study showed an elevated risk of CVD in rheumatoid arthritis patients, as well as a gap between actual and perceived CVD risk.

Key Words rheumatoid arthritis, Iraq, cardiovascular disease risk, framingham risk score (FRS)

1. Introduction

It is generally known that individuals with RA have an increased risk of cardiovascular disease (CVD)-related morbidity and mortality [1]. It is a significant contributor to the growing mortality disparity between RA patients and the general population [2]. The increased CVD risk associated with RA is now obviously comparable to that of people with diabetes mellitus [3]. Studies have provided evidence indicating a significantly elevated risk of atherosclerosis and coronary calcification in patients with RA [4]–[6].

Moreover, individuals with RA are often less susceptible to experiencing angina symptoms, resulting in a considerable portion of their CVD going undetected or untreated. This lack of recognition or management of CVD among RA patients increases the potential for occurrences of sudden cardiac death [7]–[9].

A. Traditional and Rheumatoid Arthritis-Related Cardiovascular Risk Factors in Collaboration

The relationship between traditional risk factors and RA-related mechanisms is complicated and frequently bidirectional. For instance, oxidative stress characterizes systemic inflammation in RA and encourages insulin resistance, which in turn exacerbate the imbalance between ROS and antioxidants [10]–[14].

B. Treatments of Ra and Cardiovascular Disease Risk

1) Glucocorticoids

Given the adverse impacts on the cardiovascular system, such as hypertension, dyslipidemia, insulin resistance, and diabetes, the overall benefit of glucocorticoids in RA is controversial. On the other hand, glucocorticoids increase mobility and appear to have favorable effects on the lipid profile [15].

2) Non-Steroidal Anti-Inflammatory Drugs

Except for etoricoxib, which indicated a greater risk, users of NSAIDs generally had similar CVD risk [16]. COXIBs should not be administered to patients with known CV disease, according to the European guidance from the registration authorities (EMEA) [17].

3) Conventional Disease Modifying Anti Rheumatic Drugs (cDMARDs)

More evidence is pointing to the possibility that efficient anti-inflammatory therapy reduces the CVD risk in RA, and it appears that methotrexate reduces mortality and morbidity [18]–[20].

4) Biological and small molecule Disease Modifying Anti Rheumatic Drugs

When compared to cDMARDs, anti-TNF medicines had a decreased risk of CVD [21]. Tofacitnib has been attributed to a higher CVD risk and death, according to U S Food and Drug Administration (FDA) study of a large randomized safety clinical trial [22]. To compare the cardiovascular safety of various treatments for RA patients, further prospective trials are required [23].

5) Cardiovascular Disease Prevention and Management Among Those With Rheumatoid Arthritis

1) **Assessment of cardiovascular disease risk** Patients with rheumatoid arthritis cannot be appropriately categorized based on risk using conventional CVD risk models [24], [25]. At present, there are no RA-specific recommendations for CVD risk prediction from the ACR. Nonetheless, the European League Against Rheumatism (EULAR) recommends that in situations where national guidelines are unavailable, individuals with RA should undergo assessments for their 10-year CVD risk at least once every 5 years. Additionally, these assessments should be conducted following any alterations in medications. This recommendation emphasizes the importance of regularly monitoring and evaluating CVD risk in RA patients to ensure appropriate management and preventive measures that must be implemented [26].
2) **Management of traditional cardiovascular risk factors** The advantages of adopting a healthy lifestyle, getting regular exercise, and quitting smoking should be emphasized [24]. The recommendations for managing CVD risk in RA patients are very similar to those for the general population [26].
3) **Management of rheumatoid arthritis** According to current guidelines from the European League Against Rheumatism (EULAR), rheumatologists play a vital role in assessing and coordinating the management of CVD risk in patients with RA [27]. These guidelines prioritize achieving disease control rather than focusing solely on the specific class of medication chosen for treatment [28], [29].

2. Patients and Method

A. Study Design

From January 2021 to July 2021, a cross-sectional study was carried out in The Rheumatology Unit of Baghdad Teaching Hospital.

B. Patient Eligibility

In this study, 100 patients of either gender who were older than 40 years were enrolled. Patients who matched the 2010 American ACR/EULAR classification criteria for rheumatoid arthritis were eligible for enrollment. All trial participants were determined to be free of any prior CVD events, including myocardial infarction, stroke, transient ischemic attack, coronary artery disease/reperfusion therapy and peripheral arterial disease.

C. Clinical Evaluation and Measurements

1) **Sociodemographic data**
   - Age, gender, educational level, occupation, and smoking status.
   - Questions about lifestyle habits include those related to eating a balanced diet, which is described by the American Heart Association (AHA) as eating a variety of fruits and vegetables as well as grains and grains products. In addition to fish, poultry, lean meats, and low-fat or fat-free dairy products (Mediterranean diet). Being physically active is defined as engaging in at least 150 minutes per week of moderate-intensity aerobic activity, 75 minutes per week of vigorous aerobic activity, or a combination of both [28].
2) **Medical history** Including comorbidities (hypertension, DM, dyslipidemia and renal disease), current medications, and family history in first-degree relatives for CVD.
3) **Body Mass Index /BMI** The BMI of all patients were calculated using the formula: BMI=weight (kg)/height (m2) [29].
4) **Disease duration** It was calculated in respect to the date of the study.
5) **Disease features**
   - Using the Clinical Disease Activity Index (CDAI) score to assess the patients' disease activity [30].
   - Physical examination including (general, eye, cardiovascular, respiratory, and neurological examination, searching for extra-articular manifestations).
   - Rheumatoid Factor (RF) and Anti Citrullinated Peptide antibodies (ACPA) were collected from RA registry data of Rheumatology Consultant Clinic in our hospital.
6) **Perceived cardiovascular risk** "How likely is it that you will develop a CVD in the next 10 years? Is the likelihood low, moderate, high, or you don't know? This inquiry was used to evaluate people's perceptions of the risk of developing a CVD.
7) **Actual cardiovascular disease risk**
   - The risk was calculated by using Framingham risk score (FRS) [31].
   - Serum total cholesterol (TC) and serum high-density lipoprotein cholesterol (HDL) were mea-

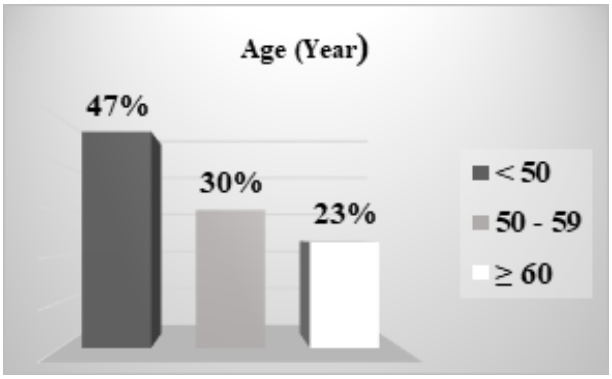

Figure 1: Distribution of study patients by age

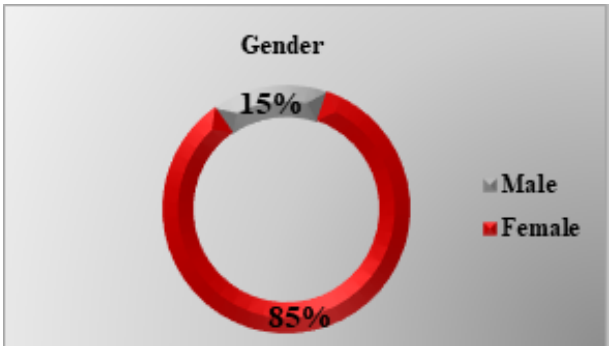

Figure 2: Distribution of study patients by gender Clinical characteristics

sured using spectrophotometric method.

- The risk is determined using (FRS) and multiplied by 1.5 in accordance with EULAR recommendations for management of CVD risk in RA patients [25].

8) **Cardiovascular disease knowledge** The subject's knowledge about CVD was measured with the Heart Disease Facts Questionnaire-Rheumatoid Arthritis (HDFQ-RA) (appendix). Those who had < 25 percentage correct answers were consider as poor knowledge, 25-74% and > 75% were considered as fair and good respectively. The questionnaires were translated into Arabic and validated.

D. Statistical Analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Analysis of Variance (ANOVA) (two tailed) was used to compare the continuous variables accordingly. Chi square test was used to assess the association between FRS and knowledge levels with certain information, while fisher exact test was used instead when the expected frequency was less than 5. A level of P – value less than 0.05 was deemed significant.

E. Patient Consent and Ethical Approval

A letter of ethical approval with the reference number (363) dated 25 January 2021 was obtained from the Iraqi Board for Medical Specializations. This paper has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

3. Results

A. Socio-demographic

The age of patients was ranging from 40 – 71 years with a mean of 51.23 ± 8.4 years. The proportion of females was much higher than males (85% versus 15%). The male to female ratio was 1:5.66 (Figure 1 and 2)

Variable	No. (n= 100)	Percentage (%)
Age of diagnosis (Year)		
<40	48	48.0
40 – 49	36	36.0
≥ 50	16	16.0
Duration of disease (Year)		
<10	53	53.0
10 – 19	33	33.0
≥ 20	14	14.0
Extra-articular disease		
Yes	36	36.0
No	64	64.0
Positive RF or ACPA antibody		
Yes	69	69.0
No	31	31.0
(CDAI)		
Remission	4	4.0
Low disease activity	48	48.0
Moderate disease activity	44	44.0
High disease activity	4	4.0
csDMARD		
Yes	91	91.0
No	9	9.0
Steroid		
Yes	48	48.0
No	52	52.0
Biological		
Yes	72	72.0
No	28	28.0
NSAIDs		
Yes	32	32.0
No	68	68.0

Table 1: Distribution of study patients by clinical characteristics

B. Clinical Characteristics

In this study, the most common age of diagnosis was < 40 years (48%); duration of disease was <10 years in 53%; Extra-articular disease was presented in 36%; and RF was positive in 69%. Regarding CDAI, 48% of cases showed low disease activity. The management included csDMARD in 91% of cases; steroid in 48%; NSAIDs in 32%; and biological in 72% (Table 1).

Variable	No. (n= 100)	Percentage (%)
Smoking status		
Current smoker	12	12.0
Non-smoker	88	88.0
BMI Level		
Normal	21	21.0
Overweight	44	44.0
Obese	35	35.0
Healthy diet		
Yes	59	59.0
No	41	41.0
Physical activity		
Inactive	85	85
Active	15	15
Hypertension		
Yes	30	30.0
No	70	70.0
Diabetes mellitus		
Yes	20	20.0
No	80	80.0
Dyslipidemia		
Yes	7	7.0
No	93	93.0
Statin		
Yes	3	3.0
No	97	97.0
Parental history of CVD		
Positive	36	36.0
Negative	64	64.0
Total cholesterol level		
High	10	10.0
Normal	90	90.0
HDL level		
Low	23	23.0
Normal	77	77.0
LDL level		
High	17	17.0
Normal	83	83.0

Table 2: Distribution of study patients by CVD risk factor

C. Cardiovascular Disease Risk Factors

In this study, 12% of patients were current smokers; 79% had high Body mass index; 41% were eating unhealthy diet; and 85% were physically inactive. We noticed that 30% of study patients were hypertensive; 20% were diabetics; 7% had dyslipidemia; and 36% had positive family history of CVD. Total cholesterol level was high in 10% of cases; LDL in 17%; and HDL was low in 23% (Table 2).

D. Framingham Risk Score (FRS) and Perceived Risk

Actual risk assessed by Framingham risk score (FRS) calculator, showed that half of study patients (50%) had low risk for CVD development, 27% moderate, and 23% had high risk. Regarding the perceived risk, only 3% of studied patients thought that they were in high risk level for CVD development, 10% moderate, 44% low risk, and 43% their risk level was not known (Table 3).

E. Comparison Between Actual and Perceived Risks

High risk was determined by FRS in 23 cases; only one of them was confirmed by patients' perception and 10 of them did not have any idea about the CVD risk. Low risk was determined by FRS in 50 cases; 26 of them were confirmed by patients' perception, and 21% had no idea about the risk. In conclusion, there was a weak agreement between actual and perceived risk, and this agreement was statistically significant (kappa= 0.169, P=0.049) (Table 4).

Variable	No. (n= 100)	Percentage (%)
FRS (actual risk)		
Low	50	50.0
Moderate	27	27.0
High	23	23.0
Perceived risk		
Low	44	44.0
Moderate	10	10.0
High	3	3.0
Don't know	43	43.0

Table 3: Distribution of study patients by actual and perceived risk

Perceived risk	Actual risk (FRS level)			Total	Kappa value	P-value
	Low	Moderate	High			
Low	26	11	7	44	0.169	0.049
Moderate	1	4	5	10		
High	2	0	1	3		
Total	29	15	13	57		

Table 4: Comparison between actual and perceived risks

The prevalence of high CVD risk was increasing significantly with advancing in age to reach the highest at age $\geq$ 60 years (47.8%, P= 0.001). Regarding gender, males had significantly higher prevalence of high CVD risk than females (33.3% versus 21.2%, P= 0.038) (Table 5).

Abbreviation: n: number. (%): percentage. P-value: probability value. P-value<0.05 was considered significant. CDAI: Clinical disease activity index. csDMARD: conventional synthetic disease modifying antirheumatic drugs. NSAIDs: non-steroidal anti-inflammatory drugs. RF: Rheumatoid Factor. ACPA: anti citrullinated peptide antibodies. FRS: Framingham Risk Score.

F. Knowledge About CVD Risk

The highest percentage of correct responses (97%) was to the question if keeping BP under control will reduce a person's chance of developing cardiovascular disease, while the highest proportion of incorrect responses (96%) were recorded when the patients asked if RA affects the balance of 'good' and 'bad' cholesterol in the blood in an undesirable way (Table 6).

G. Total Knowledge Score

Regarding the total score of patients about knowledge toward CVD risk, 25% of patients scored within good score level, while remaining 72% and 3% of them scored within fair and poor scores respectively as shown in the Figure 3.

It was obvious that there was a statistically significant association (P= 0.001) between knowledge toward CVD risk and each of educational level and occupation as 78.3% of participants with good score were highly educated. No signif-

Variable	Actual CVD risk level (FRS level)			Total (%) n= 100	P- Value	
	Low (%) n= 50	Moderate (%) n= 27	High (%) n= 23			P-value
Age of diagnosis (Year)						0.049
<40	30 (62.5)	9 (18.8)	9 (18.8)	48 (48.0)	0.001	
40 – 49	18 (50.0)	13 (36.1)	5 (13.9)	36 (36.0)		
≥ 50	2 (12.5)	5 (31.3)	9 (56.3)	16 (16.0)		
Duration of disease (Year)						
<10	29 (54.7)	13 (24.5)	11 (20.8)	53 (53.0)	0.84	
10 - 19	15 (45.5)	9 (27.3)	9 (27.3)	33 (33.0)		
≥ 20	6 (42.9)	5 (35.7)	3 (21.4)	14 (14.0)		
Extra-articular disease						
Yes	15 (41.7)	10 (27.8)	11 (30.6)	36 (36.0)	0.334	
No	35 (54.7)	17 (26.6)	12 (18.8)	64 (64.0)		
Positive RF or ACPA						
Yes	25 (36.2)	21 (30.4)	23 (33.3)	69 (69.0)	0.001	
No	25 (80.6)	6 (19.4)	0 (0)	31 (31.0)		
Clinical disease activity index (CDAI)						
Remission	3 (75.0)	0 (0)	1 (25.0)	4 (4.0)	0.062	
Low	27 (56.3)	10 (20.8)	11 (22.9)	48 (48.0)		
Moderate	19 (43.2)	17 (38.6)	8 (18.2)	44 (44.0)		
High	1 (25.0)	0 (0)	3 (75.0)	4 (4.0)		
csDMARD						
Yes	45 (49.5)	26 (28.6)	20 (22.0)	91 (91.0)	0.485	
No	5 (55.6)	1 (11.1)	3 (33.3)	9 (9.0)		
Steroid						
Yes	14 (29.2)	17 (35.4)	17 (35.4)	48 (48.0)	0.001	
No	36 (69.2)	10 (19.2)	6 (11.5)	52 (52.0)		
Biological						
Yes	36 (50.0)	19 (26.4)	17 (23.6)	72 (72.0)	0.962	
No	14 (50.0)	8 (28.6)	6 (21.4)	28 (28.0)		
NSAID						
Yes	17 (53.1)	11 (34.4)	4 (12.5)	32 (32.0)	0.192	
No	33 (48.5)	16 (23.5)	19 (27.9)	68 (68.0)		

Table 5: Association between actual risk and clinical characteristics

Knowledge Questions	Correct response no. (%)	Incorrect response no. (%)
General questions		
When someone has heart disease, they always know.	24 (24.0)	76 (76.0)
A person who smokes is more likely to develop stroke and heart disease.	91 (91.0)	9 (9.0)
Keeping BP under control will reduce a person's chance of developing cardiovascular disease.	97 (97.0)	3 (3.0)
A person with high cholesterol is more likely to develop heart disease.	79 (79.0)	21 (21.0)
If your good cholesterol (HDL) is high, you are more likely to develop heart disease.	48 (48.0)	52 (52.0)
A person's risk of acquiring heart disease can only be reduced by working out in a gym or taking fitness classes.	51 (51.0)	49 (49.0)
Eating fatty foods does not affect blood cholesterol levels.	50 (50.0)	50 (50.0)
Diabetes increases a person's risk of cardiovascular disease.	56 (56.0)	44 (44.0)
You are more prone to get heart disease if you have a family history of it.	71 (71.0)	29 (29.0)
A person's risk of developing heart disease increases with age.	93 (93.0)	7 (7.0)
RA related questions		
A person with RA can reduce their chance of heart disease by keeping their weight under control.	96 (96.0)	4 (4.0)
By giving up smoking, a person with rheumatoid arthritis can lower their risk of developing heart disease.	87 (87.0)	13 (13.0)
Exercise should not be done by those who have rheumatoid arthritis because it may harm their joints.	54 (54.0)	46 (46.0)
Patients with RA who take anti-inflammatory drugs such diclofenac or ibuprofen may be at an increased risk for heart disease.	47 (47.0)	53 (53.0)
Frequent rheumatoid arthritis flare-ups (or "flares") increase the risk of heart disease.	15 (15.0)	85 (85.0)
Rheumatoid arthritis affects the balance of 'good' and 'bad' cholesterol in the blood in an undesirable way.	4 (4.0)	96 (96.0)
A person with rheumatoid arthritis who uses steroids long-term or at high doses runs the risk of developing diabetes.	28 (28.0)	72 (72.0)

Table 6: The results of patients' response about knowledge questions

Figure 3: Total knowledge score level

icant associations ($P \geq 0.05$) were found between knowledge toward CVD risk and all other variables.

4. Discussion

It is a common belief that atherosclerosis is the major cause of mortality in RA patients. However, there are no sufficient published studies to date that comprehensively assess the knowledge about CVD risk or the actual risk among RA patients in Iraq. In the first part of this study, we assessed the actual CVD risk. Our findings reveled that 23% of the patients had high risk for CVD based on FRS calculator and 27% & 50% have moderate and low respectively. Similar study was done in Korea by Boo et al. [32]. Out of the subjects with RA, only 12% were classified as having a high risk for CVD, although they had close median age 52.61 ± 7.97. The reason behind this may be due to the difference in ethnicity, life style and the prevalence of traditional risk factors among these populations.

In this particular study, the risk for CVD was found to be higher in men (33.3% versus 21.2% in women, P= 0.038). Regarding the prevalence of traditional CVD risk factors, about 12% of studied patients were current smokers, 79% had high BMI, 41% were eating unhealthy diet and 85% physically inactive. So, we need strong effort to educate our patients about the importance of lifestyle modification to reduce the future CVD risk. About the other modifiable risk factors, we noticed that 30% of studied patients were hypertensive, 20% were diabetics. The total cholesterol level was high in only 10% of cases, and HDL was low in 23%. We also found that LDL and TC/HDL ratio were significantly lower in patients with low CVD risk level than in patients with moderate and high CVD risk level ($P < 0.05$). These results as compared to the result of the Korean study by Boo et al. [32] are approximately the same.

The study showed that 56.3 % of late disease onset had high risk (p value 0.001). All of the high-risk group had positive serology (p value 0.001) and this result reflect the importance of rheumatoid arthritis itself as a risk factor. Drugs may play role in CVD risk. In this study 48% of the studied patients were on steroid and there was an obvious association between steroid use and the actual risk of CVD (p value 0.001). Seventeen of 23 patients (73%) who categorized as high risk were on steroid. There are several studies that discussed the association between steroid use and CVD risk [16], [17]. Initiating glucocorticoids in steroid-naïve RA patients is associated with increased risk of CVD at daily doses $\geq$ 5mg as Ocon et al. said [33].

According to the 2019 ACC/AHA guidelines, individuals with chronic inflammatory disorders including RA with LDL-C 70 to 189 mg/dL and a 10-year atherosclerotic cardiovascular disease risk of over 5%, (low, border line), moderate or high-intensity statin therapy should be discussed (class IIA recommendation) [27]. If we applied these guidelines to our studied sample about 38% of them better to start statin, while unfortunately only 3% are currently on it. In a study by Chhibber et al. [34] they found that starting statins was linked to a 21% decreased risk of mortality in RA patients.

The last part of the current thesis was about assessing the level of CVD knowledge among the studied patients. This study showed that the response to questions related to smoking, high blood pressure and dyslipidemia and its association with CVD was good. These results are similar to the result in Boo et al. [32] and Michos et al. [35]. While, right responses to the questions about exercise and healthy life style were low as compared to the other two studies. It was evident, as we had expected, that there was a statistically significant association (P= 0.001) between good knowledge toward CVD risk and higher educational level. Only 15% of our patients think that their disease activity had an influence in the development of CVD. A possible reason is the lack of educational programs by healthcare providers.

5. Limitations

The current study had some limitations including:

1) It is a small-sample study conducted in a single center. Additional research with a larger sample size.
2) The Framingham Risk Score calculator (FRS) was utilized in this study to estimate the 10-years CVD risk due to the lack of a specific tool. It's crucial to remember, though, that evidence exists that suggests the FRS may significantly underestimate the real risk.

6. Conclusions

1) Patients with rheumatoid arthritis (RA) face a heightened risk for cardiovascular disease (CVD), making the implementation of measures to reduce this risk particularly challenging.
2) The study highlighted a lack of knowledge regarding the associations between rheumatoid arthritis (RA) and cardiovascular disease (CVD). Furthermore, there seem to be a discrepancy between RA patients' actual and perceived CVD risk, which may be partially attributed to the absence of adequate education programs on this matter.

Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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