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Cardiovascular disease risk evaluation impact in patients with rheumatoid arthritis

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ABSTRACT

Although rheumatoid arthritis (RA) results in a 50% increased risk of cardiovascular disease mortality, comparable to the risk associated with diabetes mellitus, a significant care gap remains in cardiovascular risk management for this high-risk population. A retrospective cohort study was conducted at a minority-serving institution to assess demographic, clinical, and laboratory data associated with referral to cardiology by rheumatology. The results showed that a minority (5%) of patients were referred to cardiology during an outpatient rheumatology encounter. Patients referred were more likely to be on antihypertensive medication and aspirin. Differences in traditional cardiovascular risk factors such as systolic blood pressure, LDL cholesterol, smoking history, and diabetes mellitus were not significantly associated with being referred. Patients with RA who were evaluated by cardiology were more likely to be started on cardiovascular risk-reducing medications such as antihypertensive, lipid-lowering, and aspirin therapy. This study highlights a care gap in the evaluation and referral of patients with RA and recognizes the improved preventive cardiovascular care received by patients evaluated by a cardiologist.

1. Introduction

The diagnosis of rheumatoid arthritis is associated with a 50% increase in cardiovascular disease-related mortality [1,2]. Multiple studies have shown that traditional risk factors for atherosclerotic cardiovascular disease (ASCVD) are predictive of and closely related to the progression of cardiovascular disease among patients with RA [3–6]. However, risk-enhancing factors alone do not account for the excess burden of cardiovascular disease among this patient population. Prior studies have observed that increased disease activity and inflammatory markers (i.e., C- reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) are associated with an increased risk of ASCVD [7–9]. Also, medications commonly prescribed for managing rheumatoid arthritis, such as glucocorticoids and targeted synthetic disease-modifying antirheumatic agents (DMARDs), have been associated with an increased risk of adverse cardiovascular events [10,11]. Recognizing the increased risk of cardiovascular disease in this patient population, the American College of Cardiology and American Heart Association (ACC/AHA) distinguishes RA as a risk-enhancing factor for ASCVD [12].

Despite the increased morbidity and mortality from cardiovascular disease among patients with RA, cardiovascular risk factors are often underdiagnosed and undertreated. A study reported that a majority of general practitioners did not identify RA as an independent risk factor for cardiovascular disease [13]. Cardiovascular risk assessment among this patient population also proves challenging as there have been mixed results in the validation of traditional risk calculators, and there are no formal guidelines that direct when the management of a patient's cardiovascular disease or risk should be escalated to a cardiologist trained in aggressive risk factor modification [14–17]. The European League Against Rheumatism (EULAR) task force recommends that patients with RA be assessed for their cardiovascular risk every five years and reassessment be considered with significant changes in antirheumatic medications [14], while the 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis does not specify how to screen and assess for cardiovascular disease risk [18].

To evaluate and address care gaps in cardiovascular disease risk

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management among patients with RA, an understanding of current referral practices and the impact of cardiology referral on the primary prevention of cardiovascular disease must be achieved. We aim to understand the characteristics of RA patients without a history of ASCVD referred to cardiology by rheumatology and determine changes in preventive cardiovascular disease management associated with an evaluation by cardiology.

2. Materials and methods

A retrospective cohort study was conducted at the University of Illinois Hospital and Health Sciences System (UI Health), defined by the U.S. Department of Education as a minority-serving institution [19]. Data were extracted from the electronic health record (EHR) for the study period from October 1, 2015, to October 1, 2020. The study was approved by the University of Illinois Chicago Institutional Review Board (UIC IRB #2021–0311).

Patients aged 40–75 with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) diagnosis of RA (M05-M06) and more than one outpatient rheumatology encounter during the study period were eligible for the study. Patients were excluded if they had ASCVD, defined using ICD-10 codes for ischemic heart disease, myocardial infarction, stroke, heart failure, angina, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or history of carotid intervention (Supplemental Table 1) [20].

First, to examine patient characteristics associated with ASCVD risk identification by rheumatology, we identified patients with a referral to cardiology by a rheumatologist. We limited the first analysis to patients referred to cardiology by a rheumatologist, as this specialty commonly sees the highest risk RA patients, especially given the use of JAK-inhibitors and glucocorticoids. Second, we identified RA patients evaluated by a cardiologist. Among these patients, we assessed changes in ASCVD risk management associated with an evaluation by cardiology, regardless of the referring specialty. Thus, we did not limit our scope to patients referred only by a rheumatologist to cardiology.

2.1. Variable definitions

Diabetes mellitus was defined by either an ICD-10 diagnosis of diabetes (E08) or a Hemoglobin A1c laboratory value greater than 6.4%. An absence of smoking history was assumed if a patient's smoking status was not reported in the EHR. Patients' zip code of residence as recorded in the EHR was used to determine the median annual household income based on United States Census Bureau data and approximate socioeconomic status (SES) [21].

Clinical and laboratory values were defined by the first value recorded during the study period that occurred either on or after the date of the initial rheumatology encounter. ASCVD risk-reducing medications were defined as either lipid-lowering medications, antihypertensive medications, or aspirin therapy. Patients were defined as being on a risk-reducing medication if prescribed or documented as being on a medication within three months of their first encounter with rheumatology during the study period. Patients were defined as being initiated on a medication if they were not on a given medication initially but were prescribed or documented as being on a medication within three months before their most recent outpatient encounter during the study period. For glucocorticoids and JAK-inhibitors, patients were defined as being on a medication if prescribed a given medication during the study period.

In the generalized linear models used to calculate odds ratios, continuous variables were converted to categorical variables for ease of interpretability. Definitions for elevated blood pressure were based on ACC and AHA definitions of Stage II Hypertension [22]. Body mass index was based on the standard definition of obesity. Elevated triglycerides and LDL-C were both based on risk-enhancing factors defined in the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [12]. Definitions of elevated ESR and CRP were guided by the 2010 Rheumatoid Arthritis Classification Criteria published by the American College of Rheumatology, and standard laboratory reference values used to define upper limits of normal [23].

2.2. Statistical analysis

All analyses were performed using R (version 4.1.2, R Foundation, Vienna, Austria). Characteristics of patients were summarized using the 'gtsummary' package in R with median and interquartile ranges for continuous variables and percentages for categorical variables [24]. Standard statistical tests of significance included the Welch Two Sample *t*-test, Pearson's Chi-squared test, and Fisher's exact test. Generalized linear models were used to calculate odds ratios in both univariable and multivariable models to assess the relationship between covariates and dependent variables. Odds ratios were further adjusted to account for time in the study of each patient.

3. Results

3.1. Cohort characteristics of patients with RA

Among 1062 patients with RA included in the study, the median age was 57 years, with 83% female, 41% non-Hispanic Black or African American, and 37% Hispanic. The median household income of the study population was $49,000. Patients were evaluated over a median period of 2.42 years. In the cohort, 22% of patients were currently smoking, and 7% had diabetes mellitus. A minority of patients were prescribed risk-modifying medicines for cardiovascular disease: 7% were prescribed lipid-lowering medication, 16% were prescribed antihypertensive medication, and 4% were prescribed aspirin. The use of glucocorticoids was common, with 61% of patients receiving a prescription during the study. More than 50% of patients did not have an associated lipid panel, 21% did not have a recorded blood pressure, and 22% did not have a recorded body mass index (Supplement; Table 4). Only 9% of patients had the necessary laboratory components to calculate their 10-year ASCVD risk using equation parameters reported in the 2013 ACC/AHA Cardiovascular Risk Assessment Guidelines [25].

3.2. Referral of RA patients to cardiology by rheumatology

72 (6%) patients were referred to cardiology during an outpatient rheumatology encounter. Patients who had cardiology referrals placed by rheumatology were more likely to be on antihypertensive medication (29% versus 15%; $P < 0.01$) and aspirin (12% versus 3%; $P < 0.01$) than those not referred to cardiology (Table 1). Significant differences were not detected for traditional ASCVD risk factors such as systolic blood pressure, LDL cholesterol, smoking history, and diabetes mellitus between those referred and not referred to cardiology. Other variables not associated with referral included body mass index, ESR, CRP, and the prescription of both glucocorticoids and JAK-inhibitors. In a multivariable analysis that adjusted for time in the study, the odds of being referred to cardiology remained significant for patients on antihypertensive medications (OR, 2.34; 95% CI, 1.22 to 4.32) and aspirin (OR, 3.88; 95% CI, 1.40 to 9.22) (Table 2). Elevated CRP was also associated with an increased odds of cardiology referral by rheumatology in adjusted multivariable analysis (OR, 2.71; 95% CI, 1.31 to 5.83).

3.3. ASCVD risk management of patients with RA by cardiology

We sought to determine how ASCVD risk factor management may differ when evaluated by a cardiologist. We identified all patients evaluated by cardiology and thus included patients who may have been referred to cardiology by a specialty different from rheumatology. Among 1062 patients with RA, 171 (16%) patients were evaluated by cardiology (Supplement; Table 1). Patients assessed by cardiology had

Table 1
Characteristics of patients referred to cardiology.

Characteristic	N	Overall, $N = 1062$[1]	Not referred to cardiology, $N = 1011$[1]	Referred to cardiology, $N = 51$[1]	p-value[2]
Age	1062	57 (49 – 64)	56 (49 – 63)	59 (50 – 66)	0.15
Gender	1062				0.94
Female		879 (83)	837 (83)	42 (82)	
Male		183 (17)	174 (17)	9 (18)	
Race	1062				0.35
Other		36 (3.4)	36 (3.6)	0 (0)	
Asian		25 (2.4)	24 (2.4)	1 (2.0)	
Black or African American		432 (41)	405 (40)	27 (53)	
Hispanic		388 (37)	371 (37)	17 (33)	
White		181 (17)	175 (17)	6 (12)	
Income	1055	49 (39 – 69)	50 (39 – 69)	49 (37 – 62)	0.38
Time in study	1062	2.42 (1.17 – 3.82)	2.39 (1.12 – 3.80)	2.98 (2.12 – 4.10)	0.002**
Systolic blood pressure	842	132 (120 – 143)	132 (120 – 143)	134 (119 – 151)	0.33
Diastolic blood pressure	842	75 (67 – 83)	75 (67 – 83)	76 (66 – 82)	0.90
Body mass index	827	30 (26 – 36)	30 (26 – 36)	28 (24 – 32)	0.33
Total cholesterol	209	182 (156 – 211)	181 (156 – 211)	191 (156 – 212)	0.51
LDL	203	103 (78 – 127)	102 (80 – 128)	117 (76 – 126)	0.70
HDL	209	51 (44 – 62)	51 (44 – 62)	52 (42 – 62)	0.70
Triglycerides	205	107 (76 – 166)	107 (76 – 161)	103 (74 – 210)	0.49
ESR	607	20 (11 – 38)	20 (11 – 38)	20 (10 – 44)	0.43
CRP	564	3 (1 – 8)	3 (1 – 8)	3 (1 – 7)	0.66
Current smoker	1062	232 (22)	220 (22)	12 (24)	0.77
Diabetes mellitus	1062	70 (6.6)	65 (6.4)	5 (9.8)	0.38
On lipid-lowering medication	1062	69 (6.5)	65 (6.4)	4 (7.8)	0.57
On antihypertensive medication	1062	169 (16)	154 (15)	15 (29)	0.007**
On aspirin	1062	38 (3.6)	32 (3.2)	6 (12)	0.008**
On diabetes medication	1062	45 (4.2)	42 (4.2)	3 (5.9)	0.47
On glucocorticoid	1062	643 (61)	609 (60)	34 (67)	0.36

Patients with ≥1 total glucocorticoid prescriptions during the study were classified as on glucocorticoid.
[1] Median (IQR); n (%).
[2] Welch Two Sample *t*-test; Pearson's Chi-squared test; Fisher's exact test; *$p<0.05$; ***$p<0.001$.
** $p<0.01$;.

similar characteristics to those referred to cardiology by rheumatology. In a multivariable analysis that adjusted for time in the study, patients evaluated by cardiology had a greater likelihood of being initiated on ASCVD risk-reducing medications, including lipid-lowering medication (OR, 4.10; 95% CI, 2.07 to 7.95), antihypertensive medication (OR, 3.08; 95% CI, 1.77 to 5.24), and aspirin (OR, 4.27; 95% CI, 1.60 to 11.1) compared to those not seen by cardiology (Table 3).

4. Discussion

Patients with RA are at significantly increased risk of ASCVD morbidity and mortality and thus benefit from dedicated cardiovascular risk evaluation. Despite this increased risk, a minor proportion of patients with RA (6%) were referred to cardiology following evaluation by rheumatology. Additionally, only 9% of patients had all the necessary information within their chart to calculate their 10-year ASCVD risk 2013 ACC/AHA Cardiovascular Risk Assessment Guidelines. Once seen by cardiology, patients were significantly more likely to be started on ASCVD risk-reducing medications.

The risk of ASCVD imparted by rheumatoid arthritis is comparable to diabetes mellitus [2]. Although diabetes mellitus has multiple guidelines that address ASCVD risk prediction and mitigation, rheumatoid arthritis has few guidelines that do the same [12,26,27]. The guidelines developed for patients with diabetes mellitus provide concrete recommendations, including blood pressure targets and the appropriate use of statin therapies. Comparatively, no guidelines for ASCVD prevention in rheumatoid arthritis provide disease-specific recommendations, which may explain the low rate of lipid-lowering and antihypertensive medication use within this cohort. This assumption is based on prior studies that have shown improvements in the management and treatment of a given disease following the dissemination of guidelines [28–31].

Without a computed ASCVD risk, the identification of patients to refer for cardiovascular disease prevention becomes a difficult task. Although the concept of a preventive cardiology practice and its role within the medical landscape has been highlighted previously, discussion regarding referral practices is scant within the literature [32,33]. Given the low percentage of patients referred to cardiology by a rheumatologist, this study highlights the need to engage specialties working closely with RA patients to improve referral rates for this high-risk population to benefit from enhanced preventive cardiovascular care.

To improve referral patterns, our study sought to understand the characteristics of RA patients referred by rheumatology to cardiology for primary prevention. Although patients on antihypertensive and aspirin therapy were more likely to be referred to cardiology, other traditional risk factors commonly known to significantly affect the risk of ASCVD, such as blood pressure, smoking history, cholesterol, and diabetes mellitus, were not significantly associated with referral. In addition to traditional risk factors, laboratory tests related to increased inflammation in rheumatoid arthritis, such as ESR, were also not significantly associated. These findings suggest a gap in the clinical care management of patients with RA, as known risk factors for ASCVD did not result in a statistically significant referral pattern.

Rheumatoid arthritis medications such as glucocorticoids and JAK-inhibitors were also not associated with an increased likelihood of referral. The lack of appropriate referral of patients on these medications is of particular concern given glucocorticoids' known risk of hypertension, diabetes mellitus, and dyslipidemia [10]. These risk factors can lead to significant morbidity and mortality, with a large meta-analysis showing a 1.47 relative risk of cardiovascular events in patients taking corticosteroids [11]. In addition to glucocorticoids, JAK-inhibitors have shown safety signals in prospective studies. Specifically, the ORAL Surveillance trial demonstrated an increased risk of major adverse cardiovascular events (MACE) in patients treated with tocilizumab compared to a TNF-inhibitor, raising concerns about the detrimental cardiovascular effects of JAK-inhibitors [34]. As glucocorticoids and JAK-inhibitors impact the risk of cardiovascular disease, these results identify the importance of changing current preventive cardiovascular disease management in patients with rheumatoid arthritis.

Table 2
Likelihood of referral based on patient characteristics.

Characteristic	Unadjusted OR[1]	95% CI[1]	p-value	Adjusted for time in study OR[1]	95% CI[1]	p-value[2]
Age	1.02	0.99 to 1.06	0.14	1.02	0.99 to 1.06	0.16
Income tercile						
Bottom	—	—		—	—	
Top	0.62	0.29 to 1.28	0.21	0.63	0.29 to 1.32	0.23
Time in study	1.31	1.07 to 1.61	0.008			
Elevated systolic blood pressure	1.70	0.95 to 3.03	0.071	1.63	0.90 to 2.91	0.10
Elevated diastolic blood pressure	0.66	0.20 to 1.68	0.44	0.62	0.18 to 1.57	0.37
Elevated body mass index	0.68	0.38 to 1.21	0.20	0.66	0.37 to 1.18	0.17
Elevated LDL	1.01	0.15 to 4.02	>0.99	1.04	0.15 to 4.15	0.96
Elevated triglycerides	2.18	0.93 to 4.92	0.063	2.14	0.91 to 4.87	0.073
Elevated ESR	1.00	0.54 to 1.82	>0.99	0.96	0.52 to 1.76	0.89
Elevated CRP	1.87	0.86 to 4.70	0.14	3.20	1.35 to 8.50	0.012*
Current smoker	1.11	0.55 to 2.09	0.77	0.95	0.46 to 1.80	0.87
Diabetes mellitus	1.58	0.53 to 3.77	0.35	1.55	0.52 to 3.70	0.37
On lipid-lowering medication	1.24	0.37 to 3.16	0.69	1.31	0.38 to 3.36	0.62
On antihypertensive medication	2.32	1.21 to 4.26	0.008	2.34	1.22 to 4.32	0.008**
On aspirin	4.08	1.48 to 9.63	0.003	3.88	1.40 to 9.22	0.004**
On diabetes medication	1.44	0.34 to 4.15	0.55	1.46	0.34 to 4.22	0.54
On glucocorticoid	1.85	0.99 to 3.33	0.045	1.79	0.96 to 3.23	0.060

Patients with ≥1 total glucocorticoid prescriptions during the study were classified as on glucocorticoid. ORs with confidence interval > 100 not shown. Elevated systolic blood pressure defined as ≥140 mmHg; elevated diastolic blood pressure defined as ≥90 mmHg; elevated body mass index defined as ≥30 kg/m2; elevated LDL defined as ≥160 mg/dL; elevated ESR defined as ≥20 mm/hr; and elevated CRP defined as ≥0.9 mg/dL.

[1] OR = Odds Ratio, CI = Confidence Interval.

[2] Welch Two Sample *t*-test; Pearson's Chi-squared test; Fisher's exact test; ***$p<0.001$.

* $p<0.05$;.

** $p<0.01$;.

Once referred to cardiology, RA patients seen by a cardiologist received improved preventive cardiovascular disease care. The screening rate for ASCVD was improved with evaluation by cardiology as those seen had a significantly increased likelihood of having a reported lipid profile. Furthermore, patients with RA whom a cardiologist evaluated were more likely to be appropriately initiated on ASCVD risk-reducing therapies such as lipid-lowering medications, antihypertensives, and aspirin. In such a high-risk population, these medications likely provide significant risk-modifying benefits.

There are limitations to this study. First, the results of this study may have limited generalizability as the study was conducted at a single academic medical center. However, this academic institution was unique in its designation as a minority-serving institution [19]. As this was a retrospective EHR-based study, there were missing variables, such as blood pressure, lipid panels, ESR, and CRP. Additionally, variables such as the DAS-28 (or Disease Activity Score) would have furthered our understanding of individual ASCVD risk for each patient in the study. Although these variables were missing, this lack of information provided insight into the suboptimal rate patients with RA had necessary lab tests, such as lipid panels. Patients without lab tests such as lipid panels can be assumed not to have their 10-year ASCVD risk score calculated. Third, given our study's retrospective nature, we were limited in evaluating changes in anthropometric values during the study period. Prospective studies could examine the impact of co-management of cardiovascular disease risk with cardiology and rheumatology and identify changes in anthropometric variables such as blood pressure, weight, and cholesterol. Lastly, due to the limited sample size of patients seen by cardiology who had also been referred by rheumatology, we could not complete a meaningful subgroup analysis of patients referred by rheumatology and subsequently seen by cardiology; a multicenter study would likely provide the statistical power to perform such analysis.

The results of this study inform the need to improve the identification of patients with increased ASCVD risk and clinical care pathways for ASCVD risk co-management for specialized patients.

Given the high prevalence of cardiovascular disease risk within this patient population, formal guidelines are required to address the appropriate referral of RA patients to cardiology. We propose to incorporate early referral to cardiology for this patient population, as aggressive ASCVD risk stratification is imperative for patients with RA. A dedicated preventive cardiology clinic to care for these patients with focused ASCVD risk screening and continued monitoring can facilitate risk reduction to help reduce cardiovascular events in this high-risk population.

Author contributions

AA, YJK, and NTN significantly contributed to the study design. AA acquired and analyzed the data. AA, YJK, and NTN drafted the initial manuscript. All authors were involved in data interpretation, manuscript revision, and approval of the final version submitted for publication.

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Table 3
Likelihood of initiation of risk-reducing medications in patients evaluated by cardiology.

Characteristic	Unadjusted N	OR[1]	95% CI[1]	p-value	Adjusted for time in study OR[1]	95% CI[1]	p-value[2]
Lipid-lowering medication initiated	1062	3.90	1.98 to 7.49	<0.001	4.10	2.07 to 7.95	<0.001***
Antihypertensive medication initiated	1062	3.06	1.77 to 5.19	<0.001	3.08	1.77 to 5.24	<0.001***
Aspirin initiated	1062	4.32	1.63 to 11.1	0.002	4.27	1.60 to 11.1	0.003**

[1] OR = Odds Ratio, CI = Confidence Interval.

[2] Pearson's Chi-squared test; *$p<0.05$;.

** $p<0.01$;.

*** $p<0.001$.

Declaration of Competing Interest

All authors declare that no competing financial interests exist.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2022.100380.

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