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Comorbidity burden and the role of hydroxychloroquine in venous thromboembolism risk among rheumatoid arthritis patients: a retrospective case-control study

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ABSTRACT

Aims: Patients with rheumatoid arthritis (RA) are at increased risk for venous thromboembolism (VTE). This study aims to identify clinical characteristics and treatment-related factors associated with VTE in RA patients.

Methods: A retrospective analysis of 363 RA patients was conducted, including 34 RA patients with documented VTE. Demographics, comorbidities, and treatment data were compared between patients with and without VTE. Age-and sex-matched subgroup analysis and multivariate logistic regression were used to identify independent predictors of VTE.

Results: The mean age of RA patients with VTE was 66.8 (11.5) and 30 (88.2) were female. VTE was significantly associated with older age, hypertension, hyperlipidemia, and higher Charlson Comorbidity Index (CCI). In the multivariate model, higher CCI was independently associated with VTE (OR 2.84, 95% CI: 1.46–3.80, p<0.001). Hydroxychloroquine use was negatively associated with VTE (OR 0.34, 95% CI: 0.10–0.86, p=0.049). Other DMARDs and glucocorticoids did not show independent associations.

Conclusion: A high comorbidity burden significantly increases VTE risk in RA patients and HCQ use was associated with lower odds of VTE. These findings highlight the importance of individualized comorbidity management and suggest a potential role for hydroxychloroquine in thrombosis prevention in RA.

Keywords: Rheumatoid arthritis, venous thromboembolism, Charlson Comorbidity Index, hydroxychloroquine

INTRODUCTION

The incidence and prevalence of venous thromboembolism (VTE) has increased in rheumatoid arthritis (RA) due to increased chronic inflammation, older age, comorbidities, and RA-specific medications.[1-3] Epidemiological studies have found that the risk of developing VTE is 2.23 times higher than in age-gender- and comorbidity-matched control groups in patients with RA.[4] Following the approval of tofacitinib for the treatment of RA, it has been demonstrated that these treatments increase the risk of VTE and cardiovascular events.[5,6] However, real-world studies have not found a statistically significant difference in VTE incidence between patients treated with tumor necrosis factor alpha (TNF-α) inhibitors or tofacitinib.[7,8] Although studies exist on the demographic and clinical characteristics of RA patients with VTE, studies on the frequency of comorbid conditions and use of comorbidity indices are lacking. In our study, we aimed to examine the clinical and demographic characteristics of RA patients with and without VTE and to detail the factors associated with thrombosis.

METHODS

Ethics

The study has been approved by the Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 05.10.2021, Decision No: 2021/16-31). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Selection and Exclusion

This study was a retrospective single centre study. Patients with RA who were treated at the Rheumatology Outpatient

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Clinics of Hacettepe University Hospitals between January to December 2021 were included in the study according to International Classification of Diseases (ICD)-10 diagnosis code. Two experienced rheumatologists reviewed the patients' medical histories, laboratory parameters, and radiographs from the hospital's electronic system, and patients with a confirmed diagnosis of RA were included in this study. Patients with RA who had a history of VTE (deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE)) more than one year prior to their RA diagnosis, unconfirmed RA diagnosis, patients with incomplete medical records were excluded from the study.

Venous Thrombosis and Rheumatoid Artritis

To detect the history of VTE in RA patients; medical history, extremity venous doppler ultrasonography for the diagnosis of DVT and chest computed tomography (CT) for the diagnosis of PTE were scanned and analyzed.

Collected Data of Patients and Control Groups

We systematically reviewed the demographic and clinical characteristics, comorbid diseases/indices, laboratory parameters from the hospital's electronic medical records database. Treatments were recorded as ever and two types of drug used to treat RA: conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, and biological disease-modifying anti-rheumatic drugs (bDMARDs), such as TNF-α and non-TNF agents, including baricitinib, tofacitinib, abatacept and rituximab were documented. We used the Charlson Comorbidity Index (CCI) to calculate the comorbidity burden.[9] We selected age-and sex-matched patients from the cohort of RA patients without VTE to serve as the "control group" (**Figure**). We compared the demographic, differences in treatment choices and clinical characteristics of RA patients with VTE with those of the control group.

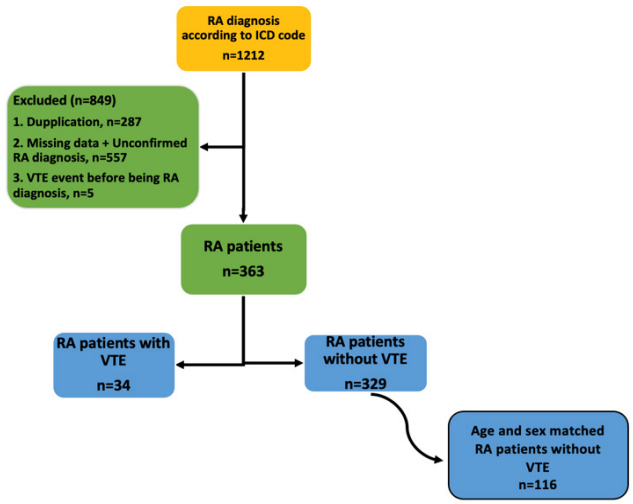

Figure. Selection of study groups

Statistical Analysis

This study utilised IBM SPSS Statistics for Windows, Version 26.0. (SPSS Inc., Chicago, IL, USA) for all statistical methods. Visual (histogram and normality plots) and analytical methods (Kolmogorov–Smirnov) were used to determine whether the data were normally distributed. For descriptive analysis, we used mean (standard deviation) and median interquartile range (IQR). We then assessed factors associated with the VTE using univariate analysis ($p<0.20$) and entered these into logistic regression by backward LR to determine independent predictors of VTE. $p<0.05$ was accepted for statistical significance.

RESULTS

Patient Characretistics

A total of 363 patients with RA confirmed diagnosis were included in the study, of whom 39 (9.4%) had a documented history of VTE. Five (12.8%) of them had VTE event before being diagnosed with RA were excluded and 34 RA patients with VTE were included in the analysis. Of the VTE patients, 16 (47%) had DVT, 16 (47%) had PTE and two (5.8%) had both. Of these patients, nine (56%) had DVT in the right lower extremity, five (8.9%) had DVT in the left lower extremity, two (1.2%) had DVT in both lower extremities, and one (6.2%) had DVT in the left upper extremity. The median time between RA diagnosis and VTE was 10.1 (1.2-50.7) years. The mean age was significantly higher in RA patients with VTE compared to those without VTE (66.8±11.5 vs. 60.6±14.9 years, $p=0.012$). Female predominance was observed in both groups, but the proportion was significantly higher in the VTE group (88.2% vs. 71.5%, $p=0.032$).

Table 1 compares RA patients with VTE to control RA patients. The prevalence of hypertension (79.4% vs. 52.7%, $p=0.005$) and hyperlipidemia (73.5% vs. 40.5%, $p=0.01$) remained significantly higher in the VTE group. The median CCI was significantly higher in patients with VTE (4.48 [1.59] vs. 3.5 [1.3], $p<0.001$), and higher proportion of patients with VTE had CCI scores ≥5 (41.2% vs. 20.7%, $p=0.016$). Rates of malignancy, coronary artery disease, and other comorbidities did not differ significantly. Glucocorticoid (96.9% vs. 62%, $p=0.02$), and methotrexate (73.5% vs. 48.2%, $p<0.001$) use was more frequent among patients with VTE. Conversely, hydroxychloroquine use was lower in the VTE group (50% vs. 80.9%, $p=0.001$). Other treatment modalities were comparable.

We examined the parameters associated with the presence of VTE by comparing them to control groups. In the univariate analysis, the following parameters had p-values less than 0.2: hypertension, hyperlipidemia, presence of malignancy, methotrexate use, hydroxychloroquine use, glucocorticoid use, and mean CCI score (**Table 2**). The factors associated with VTE in multivariate analysis are demonstrated in **Table 2**. Higher CCI score was significantly associated with VTE (OR: 2.84, 95% CI: 1.46–3.80, $p<0.001$), indicating that increased comorbidity burden strongly predicted thrombotic events. Hydroxychloroquine use was negatively associated with VTE occurrence (OR: 0.34, 95% CI: 0.10–0.86, $p=0.049$), suggesting a potential protective effect. In contrast, glucocorticoid use (OR: 0.32, $p=0.19$) and methotrexate use (OR: 0.89, $p=0.16$) were not independently associated with VTE risk after adjustment. Among cardiovascular comorbidities, both hypertension (OR: 3.6, 95% CI: 0.98–13.2, $p=0.051$) and

Table 1. Comparison of RA patients with venous thromboembolism and control RA patients

Demographic and clinical findings	Age and sex-matched RA patients without VTE n=116	RA patients with VTE n=34	p-value
Age, mean (SD)	64.4 (13.2)	66.8 (11.5)	0.28
Gender, female, n (%)	89 (76.7)	29 (85.2)	0.18
Age at the RA diagnosis, mean (SD)	49.9 (11.5)	48.3 (12.9)	0.84
Smoking history, (ever) n (%)	36 (55.4)	10/27 (37)	0.08
RF and/or ACPA positivity, n (%)	85 (78)	28 (82.4)	0.38
RF positivity, n (%)	76 (65.5)	24 (70.6)	0.37
ACPA positivity, n (%)	49 (57)	16/32 (50)	0.31
ANA positivity, n (%)	47 (57.3)	19/29 (65.5)	0.29
Comorbidities, n (%)			
Hypertension	48 (52.7)	27 (79.4)	0.005
Diabetes mellitus	21 (22.8)	6 (17.6)	0.35
Coronary artery disease	12 (12.8)	8 (23.5)	0.11
Hyperlipidemia	47 (40.5)	25 (73.5)	0.01
Thyroid diseases	18 (31.7)	12 (35.3)	0.34
Presence of malignancy	8 (6.8)	6 (17.6)	0.08
Chronic obstructive pulmonary disease	14 (15.2)	4 (12.1)	0.35
Interstitial lung disease	11 (9.4)	5 (14.7)	0.46
CCI, mean (IOR)	3.5 (1.3)	4.48 (1.59)	<0.001
CCI, subgroups, n (%) 1-2 3-4 ≥5	 34 (29.3) 58 (50) 24 (20.7)	 2 (5.9) 18 (52.9) 14 (41.2)	 0.003 0.51 0.016
Interstitial lung disease	10 (25)	5 (14.7)	0.45
Medications, n (%)			
Glucocorticoids	72 (62)	31 (96.9)	0.02
Methotrexate	56 (48.2)	25 (73.5)	<0.001
Sulfasalazine	41 (35.3)	16 (47.5)	0.07
Leflunomide	49 (42.2)	19 (55.8)	0.06
Hydroxychloroquine	93 (80.9)	17 (50)	0.001
Tumor necrosis factor inhibitors	27 (23.2)	5 (14.7)	0.27
Rituximab	14 (14.1)	7 (20.5)	0.22
Abatacept	2 (1.9)	1 (2.9)	0.14
JAK-inhibitors	5 (4.9)	1 (2.9)	0.61

RA: Rheumatoid arthritis, ANA: Antinuclear antibody, CCI: Charlson Comorbidity Index, SD: Standard deviation, IQR; Interquartile range, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibodies, JAK: Janus kinase, VTE: Venous thromboembolism

hyperlipidemia (OR: 2.7, 95% CI: 0.88–8.6, p=0.08) showed strong trends toward increased VTE risk, though the findings were not found to be statistically significant within the multivariate model (**Table 2**).

Table 2. Predictive factors associated with VTE in RA patients

Parameters	Univariate		Multivariate	
	OR (CI)	p	OR (CI)	p
CCI, mean (SD)	3.25 (1.6-4.32)	<0.001	2.84 (1.46-3.80)	<0.001
Glucocorticoid use	0.44 (0.1-1.4)	0.06		
Methotrexate use	2.3 (0.92-7.8)	0.08		
Hydroxychloroquine use	0.26 (0.11-0.95)	0.001	0.34 (0.1-0.86)	0.049
Hyperlipidemia	1.9 (0.9-7.86)	0.09		
Hypertension	2.9 (1.4-11.6)	0.02	3.6 (0.98-13.2)	0.051

VTE: Venous thromboembolism, RA: Rheumatoid arthritis, SD: Standard deviation, CCI: Charlson Comorbidity Index, CI: Confidence interval, OR: Odds ratio

DISCUSSION

In this study, our results demonstrate that RA patients with VTE were significantly older and more likely to be female. Hypertension and hyperlipidemia were consistently more prevalent in RA patients with VTE. These findings align with existing literature indicating that conventional cardiovascular risk factors are major contributors to thrombotic events in autoimmune disease populations.

RA patients have a higher prevalence of multimorbidity compared to the age- and sex-matched general population.[10,11] Due to the lack of a standard index to scale multimorbidity in RA patients, the studies used general comorbidity indexes (Multimorbidity Weighted Index, Rheumatic Disease Comorbidity Index (RDCI), and CCI).[9,11-14] Our noteworthy finding was the association between higher comorbidity burden as measured by the CCI and the occurrence of VTE. Both univariate and multivariate analyses confirmed that increasing CCI was an independent predictor of VTE (OR: 2.84, p<0.001), highlighting the cumulative effect of multiple chronic conditions in predisposing RA patients to thrombotic complications. A recent study examining the relationship between risk factors for VTE in RA patients revealed that the mean CCI is elevated in RA patients compared to non-RA patients.[15] Özen et al.[16] also used the RDCI to determine the burden of comorbidity in their study and they highlighted that RDCI was associated with an increased risk of VTE, with an OR of 1.20 (95% CI 1.14-1.31). Consistent with our results, multimorbidity may be associated with an increased risk of VTE in RA patients. This supports the importance of considering global health status, not just RA disease activity, when evaluating VTE risk.

In our multivariate analysis, hydroxychloroquine use was inversely associated with VTE risk (OR: 0.34, p=0.049). A large real-world cohort study of RA patients showed that treatment with methotrexate led to a two-fold increased risk of VTE compared to hydroxychloroquine.[17] Studies have shown that the antithrombotic effect of hydroxychloroquine is associated with a reduced risk of thrombosis in systemic lupus erythematosus (SLE) patients.[18] A case-control study conducted in both SLE and RA patients showed that use of HCQ is associated with a decrease in the overall risk of cardiovascular events and a decrease in the development of VTE.[19] Previous studies have shown that hydroxychloroquine may have a protective effect against comorbid diseases, such as liver fibrosis. Moreover, a recently published study showed that HCQ might protect against comorbid diseases such as liver fibrosis in patients with RA.[20-22] Jung et al.[23] documented factors associated with thrombovascular events (arterial and venous thrombosis) in their study of 482 SLE patients. In

multivariate analysis, they found that older age was associated with an increased risk of VTE (OR 1.04, 95% CI 1.01–1.07), whereas antimalarial use was associated with a decreased risk of thromboembolic events. In a study of SLE patients by Akhavan et al.,[24] hydroxychloroquine use was associated with less damage in the first three years. In our study, the combined use of HCQ in RA patients was associated with a reduced risk of VTE 0.34 (0.1-0.86) (OR: 0.34, 95 CI: 0.1-0.86), consistent with the results of previous studies. While observational, this result underscores the possible thrombo-preventive benefits of hydroxychloroquine beyond its immunomodulatory role and suggests its continued use may be advantageous in high-risk RA patients. Contrary to expectations, glucocorticoid use was not independently associated with VTE risk in the multivariate model. While glucocorticoids have previously been linked to thromboembolic events due to their metabolic and vascular side effects, the widespread use of these agents across both groups in our cohort may have limited the detection of a distinct association.

Limitations

The present study has several limitations. The limited number of patients with VTE (n=34) has a detrimental effect on the statistical power of the multivariate model. Recent studies have shown a strong association between disease activity index and hospitalization duration and risk of VTE in patients with RA.[25,26] Due to retrospective design of our study, data on disease activity, functional indices, and their effects on VTE are lacking. Furthermore, there is a paucity of data regarding important parameters of VTE etiology, including prolonged hospitalization history, body-mass index, hereditary thrombophilia, and all anti-phospholipid autoantibody laboratory evaluations. The surgical history of RA patients was missing, and the temporal relationship between surgical history and VTE was unknown in our study. As a result, the relationship between these factors and VTE development could not be studied.

CONCLUSION

As a result, this study highlights that VTE in patients with RA is associated with older age, hypertension, hyperlipidaemia, and a higher burden of comorbidities. Multivariate analysis revealed that a higher CCI was independently associated with a higher risk of VTE, while the use of hydroxychloroquine was associated with a reduced risk. It is imperative that prospective studies are conducted in order to corroborate these associations and to provide a scientific basis for the development of preventive strategies for patients who are at high risk.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study has been approved by the Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 05.10.2021, Decision No: 2021/16-31).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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