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ORIGINAL RESEARCH ARTICLE

Soluble interleukin-33 receptor (sST-2): a novel marker for assessing cardiovascular risk in rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease, and it significantly increases the risk of cardiovascular disease and death. The evaluation of cardiovascular risk (CVR) is crucial in these patients, but it may be underestimated using the current criteria, as they do not include nontraditional CVR factors. Soluble ST-2, which is the circulating form of the IL-33 receptor, has been identified as a biomarker for cardiovascular and rheumatic diseases. In this study, we examined the role of sST-2 in assessing CVR in RA.
Methods: Monocentric, retrospective, observational trial. Inclusion of RA patients on variable DMARD therapy. Analysis of RA disease using established scores (DAS 28, VAS, HFQ), clinical findings (number of swollen and painful joints), and laboratory investigation. Documentation of numerous CVR variables. Quantification of soluble sST-2 by ELISA.
Results: In total, 129 individuals were included. Soluble sST-2 did neither correlate nor was associated with any variable of RA disease activity. In contrast, significant associations were identified between sST-2 and a number of established CVR markers.
Conclusions: The data indicates a novel role for sST-2 in CVR prediction in RA.

Keywords: RA, sST-2, Cardiovascular risk, Prediction

Introduction

Rheumatoid arthritis (RA) is the most common entity within inflammatory rheumatic diseases, with a prevalence of approximately 1% in Central Europe and the United States (1,2). It is characterized by chronic synovial inflammation of autoimmune origin, leading to recurrent joint inflammation with a typical pattern of involvement. If left untreated, RA typically causes irreversible joint and bone damage, potentially resulting in disability for those affected.

In addition to its detrimental effects on joints, tendons, and bones, RA has also been identified as substantial risk factor for cardiovascular morbidity and mortality (3). The risk increases significantly due to the proatherogenic effects of systemic inflammation (4), as well as the hemodynamic and metabolic effects of medications used to control disease activity and progression (5). The influence of drug therapy should not be underestimated. NSAIDs and glucocorticoids have potentially strong proatherogenic effects (6,7). The observation of an increased risk of atherosclerosis in systemic inflammatory conditions was not only made in the case of RA; rather, it is likely to be an almost unspecific phenomenon of chronic inflammatory conditions of autoimmune origin. The development of an EULAR guideline addressing cardiovascular risk (CVR) management in not only RA but also other inflammatory joint disorders is not without rationale (8). Finally, traditional CVR factors accumulate in RA in the same way as in individuals without RA. In general, assessing CVR requires considering various variables, including the severity of arterial hypertension, glucose metabolism, end-organ damage, and cardiovascular sequelae. The ”2018 ESC/ESH Guidelines for the management of arterial hypertension“ (9), for example, provides a summary of relevant recommendations. However, these and other strategies used for evaluating CVR may not effectively identify the risk in patients with RA or other immune-mediated inflammatory disorders. The incorporation of CVR biomarkers has been suggested as a promising strategy in this regard (10–12).

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The cytokine Interleukin-33 (IL-33) belongs to the Interleukin-1 family (13). In RA and other autoimmune diseases, it is believed to play a crucial role in facilitating interactions between macrophages, mast cells, and other cell types (14). Its receptor, ST-2 has been identified on cell membranes and in the extracellular fluid, the latter being defined as soluble ST-2 (sST-2) (15). The circulating IL-33 receptor isoform has been evaluated as a biomarker in rheumatic (16,17) and cardiovascular diseases (18–20). In a 2022 published study by Erfurt and colleagues (21), sST-2 was identified as a predictor of in-hospital survival in patients with acute kidney injury.

The aim of this study was to analyze the role of soluble ST-2 (sST-2) in assessing CVR and disease activity in patients with RA.

Methods

Design

Monocentric, retrospective, observational trial. The study was formally approved by the ethics committee of the Brandenburg Medical School (E-01-20200316). All participants provided written consent by signing a consent form.

Patients

All patients were recruited from the rheumatology outpatient clinic of the Health Center of the Brandenburg University Hospital (Brandenburg Medical School). Inclusion criteria were: diagnosis of RA according to the 'ACR/EULAR 2010 rheumatoid arthritis classification criteria' (22). Additional inclusion criteria were as follows: individuals aged between 18 and 90 years, of any gender, with newly initiated or established disease receiving treatment with one or more conventional or biologic disease-modifying anti-rheumatic drugs, and variable daily prednisolone doses adjusted based on disease activity. Exclusion criteria consisted of uncontrolled psychiatric disorders, presence of additional autoimmune-mediated diseases, uncontrolled infectious diseases such as HIV, hepatitis B or C, and tuberculosis, uncontrolled drug or alcohol addiction, and pregnancy. The following patient characteristics were collected: nationality, height, weight, concurrent diseases, medications, smoking status, and family history of rheumatoid arthritis. Disease activity was assessed using the DAS28-CRP score. Remission, low, moderate, and high disease activity were defined by scores of <2.6, 2.6 to 3.2, 3.2 to 5.1, and >5.1, respectively. Additional tools for measuring disease activity included the visual analog scale (VAS), which ranges from 0 (no pain) to 10 (maximum pain imaginable), as well as the assessment of swollen and painful joints, and the Hannover Functional Questionnaire (HFQ) (23). The following therapy-related data were collected: current DMARD therapy (active substance and dosage), NSAID intake (active substance, dosage, and frequency of intake), and daily prednisolone dosage in mg. The assessment of CVR was conducted by capturing the following morbidities and laboratory parameters: arterial hypertension, diabetes mellitus including HbA1C (%), past and current smoking, total cholesterol (mmol/l), LDL (mmol/l), HDL (mmol/l), and Lp(a) (nmol/l). Various additional laboratory parameters were measured, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) titers, CRP levels (mg/l), complete blood count, serum creatinine (micromol/l), sodium, potassium, AST (U/l), ALT (U/l), (U/l), and proteinuria (defined as Urine Proteine Creatinine-Ratio – UPCR – of >0.3 g/g in Spot Urine).

Quantification of serum soluble Interleukin-33 receptor

Quantification of serum soluble Interleukin-33 receptor (sST-2) was performed using an ELISA method as described in detail by Erfurt and colleagues (21). The commercially available kit used was the Human ST2/IL-33R Quantikine ELISA Kit (DST 200, R&D).

Statistics

Initially, categorical data were analyzed by the Chi-Squared test. Non-categorical data were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were compared using the t-test for two groups or the Mann-Whitney test for more than two groups. Non-normally distributed data were compared using ANOVA for two groups or the Kruskal-Wallis test for more than two groups. Correlation analyses were conducted using the Pearson correlation coefficient. Statistical significance was defined as a p-value below 0.05. Results were reported as percentages or as median with interquartile range (IQR), or as mean with standard error of the mean (SEM). All statistical analyses were conducted using the WIZARD application for the MacOS (version 2.0.14, developed by Evan Miller).

Results

Patients

A total of 129 patients were included in the study, with 87 (67.4%) being females and 42 (32.6%) being males. The average age of all individuals was 62.3 ± 12 years. The average height was 1.67 ± 0.09 meters, and the mean weight was 81.4 ± 17.2 kilograms. Rheumatoid factor (RF) and/or ACPA were detected in 73.6% of the patients. The mean DAS 28 at inclusion was 3.6 ± 1.5. The following disease-modifying anti-rheumatic drugs (DMARDs) were used: methotrexate (MTX) alone in 27.1% of cases, MTX in combination with either leflunomide, sulfasalazine, or biologics in 27.1% of cases, a MTX-free regimen in 16.3% of cases, and no DMARD at all in 29.5% of cases. In 26.4% of cases, patients were included before initiating any DMARD therapy. Table 1 summarizes all baseline characteristics, including morbidities, medication, and the results of CVR assessment.

sST-2 and RA disease activity and management

The serum levels of sST-2 did not show a significant correlation with the DAS 28 (p = 0.63). Additionally, there was no significant correlation observed between sST-2 levels and the HFQ (p = 0.19). The ratings on the visual analog scale were assigned to one of six categories (VAS 0≤ and <1, 1≤ and <3, 3≤ and <4, 4≤ and <5, 5≤ and <7, 7≤ and <10). Similar sST-2 concentrations were found in all categories (p = 0.067). Also, there were no correlations between sST-2 and the numbers of swollen or painful small or large joints, respectively (p-values: swollen small – 0.31, painful small – 0.66, swollen

TABLE 1 - Baseline characteristics of all included patients (abbreviations: SD – standard deviation; m – metres; kg – kilograms; DMARD – Disease Modifying Anti-Rheumatic Drugs; VAS – Visual Analogue Scale; HFQ – Hannover Functional Questionnaire; NSAID – Non-Steroidal Anti-Inflammatory Drugs)

Variable	Result
gender	females 87, males 42
age (years ± SD)	62.3 ± 12
height (mean m ± SD)	1.76 ± 0.09
weight (mean kg ± SD)	81.4 ± 17.2
DAS 28 (mean ± SD)	3.6 ± 1.5
VAS (mean ± SD)	4.1 ± 2.5
HFQ (mean % ± SD)	73.6 ± 23.2
DMARD therapy (substance in n)	
no DMARD	4
early disease, untreated	34
MTX alone	35
MTX + other	21
other	
seropositivity (%)	73.6
C-reactive protein (mean mg/l ± SD)	5.7 ± 9.7
Erythrocyte Sedimentation Rate (ESR) in hour 1 (mean mm ± SD)	20.5 ± 15.5
serum creatinine (mean micromol/l ± SD)	72.4 ±1 6.5
total cholesterol (mean mmol/l ± SD)	5.4 ± 1.1
LDL (mean mmol/l ± SD)	3.1 ± 0.9
HbA1C (mean % ± SD)	5.7 ± 0.7
NT-proBNP (mean pg/mL ± SD)	188.7 ± 410
proteinuria (n)	57
regular NSAID intake (n)	33
arterial hypertension (%)	65.9
diabetes mellitus (%)	15.5
coronary artery disease (CAD) (%)	9.3
family history of CAD (%)	26.4
smoking (%)	32
stress (%)	34.9
regular exercise (%)	41.1
regular alcohol consumption (%)	40.5
pulmonary disease (%)	12.4
osteoporosis (%)	16.3
history of neoplasia (%)	6.2
ESR (mean mm in hour 1 ± SD)	19.3 ± 15.9
Framingham score (mean ± SD)	9.4 ± 8.1

large – 0.45, painful large – 0.26). No significant differences were found between the 5 DMARD treatment groups (p = 0.4). If systemic glucocorticoids were used (n = 118), patients were assigned to one of three dosage categories: 0≤ and <2.5 mg daily, 2.5≤ and <5 mg daily, and 5≤ and <20 mg daily. There was once again no significant difference observed in serum sST-2 levels between these categories (p = 0.35). Patients regularly taking NSAIDs did not show different sST-2 concentrations compared to individuals without regular use of NSAIDs (p = 0.28). RF and/or ACPA positive patients did not differ in sST-2 levels compared to seronegative subjects (p = 0.47). Finally, serum sST-2 did not correlate with either C-reactive protein (p = 0.21) or the erythrocyte sedimentation rate in hour 1 (p = 0.13). Table 2 shows all variables and the p-values in detail.

TABLE 2 - sST-2 and RA disease activity (abbreviations: DMARD – Disease Modifying Anti-Rheumatic Drugs; VAS – Visual Analogue Scale; HFQ – Hannover Functional Questionnaire; NSAID – Non-Steroidal Anti-Inflammatory Drugs)

Correlation analysis		
Variable	**p-value**	
DAS 28	0.63	
HFQ	0.19	
number of swollen small joints	0.31	
number of painful small joints	0.66	
number of swollen large joints	0.45	
number of painful large joints	0.26	
C-reactive protein	0.21	
ESR (hour 1)	0.13	
Categorical analysis		
Variable	**Results**	**p-value**
VAS		
0≤ and <1	20,920 ± 2,745 pg/mL	
1≤ and <3	17,816 ± 1,433 pg/mL	
3≤ and <4	14,154 ± 2,191 pg/mL	0.067
4≤ and <5	15,347 ± 3,449 pg/mL	
5≤ and <7	16,560 ± 1,128 pg/mL	
7≤ and <10	18,637 ± 2,065 pg/mL	
DMARD therapy		
no DMARD	12,933 ± 3,981 pg/mL	
early disease, untreated	18,835 ± 1,591 pg/mL	0.4
MTX alone	15,937 ± 915 pg/mL	
MTX + other	15,706 ± 1,274 pg/mL	
other	19,531 ± 2,788 pg/mL	
systemic glucocorticoid therapy		
0≤ and <2.5 mg daily	15,522 ± 1,216 pg/mL	0.35
2.5≤ and <5 mg daily	16,423 ± 1,675 pg/mL	
5≤ and <20 mg daily	18,227 ± 1,136 pg/mL	
regular NSAID intake	yes: 15,939 ± 1,510 pg/mL; no: 17,206 ± 841 pg/mL	0.28
Seropositivity	positive: 16,802 ± 876 pg/mL; negative: 18,045 ± 1,562 pg/mL	0.47

sST-2 and CVR in RA

The analysis of serum sST-2 in relation to various surrogate markers of increased CVR (CVR) revealed numerous significant findings in RA patients. Initially, significantly lower serum levels were observed in individuals with low CVR compared to those with moderate or high CVR according to the Framingham score (low: 14,837 ± 846 pg/mL; moderate: 19,034 ± 1,303 pg/mL; high: 21,685 ± 3,106 pg/mL; p = 0.009). Soluble ST-2 was also found to have a positive correlation with the Framingham score (p < 0.001). It was higher in males than females (19,550 ± 1,308 pg/mL versus 15,961 ± 919 pg/mL; p=0.007) and positively correlated with age (p = 0.004). Patients who reported regular stress showed lower concentrations compared to those without stress (14,908 ± 1,055 pg/mL versus 18,558 ± 1,023 pg/mL; p = 0.02). Regular physical activity was also associated with lower levels (14,578 ± 945 pg/mL versus 18,909 ± 1,075 pg/mL; p = 0.005). A negative family history of CAD and the presence of CAD in the patients themselves were associated with higher sST-2 (18,432 ± 973 pg/mL versus 13,625 ± 1,005 pg/mL; p = 0.004 and 22,824 ± 2,367 pg/mL versus 16,546 ± 790 pg/mL; p = 0.006). The intake of statins (20,067 ± 1,616 pg/mL versus 16,278 ± 852 pg/mL; p = 0.009), aspirin (20,328 ± 1,925 pg/mL versus 16,508 ± 823 pg/mL; p = 0.02), and antidiabetic medications (24,982 ± 3,712 pg/mL versus 16,250 ± 703 pg/mL; p = 0.01) were all associated with higher levels of sST-2, respectively. Diabetic individuals also showed higher sST-2 than non-diabetics (24,551 ± 2,493 pg/mL versus 15,768 ± 712 pg/mL; p < 0.001). Positive correlations were identified between sST-2 and NT-proBNP (p < 0.001), serum creatinine (p < 0.001), HbA1C (p < 0.001), ALT (p = 0.02), and gGT (p = 0.001). Finally, negative correlations were found between the marker and total cholesterol (p = 0.009) and LDL (p = 0.005). Table 3 and Figure 1 show all analyzed variables and the significant findings in detail.

TABLE 3 - sST-2 and CVR variables in RA – significant findings (LDL – low density lipoproteins; ALT – alanine aminotransferase; gGT – gamma glutamyltransferase)

Correlation analysis		
Variable	**p-value**	
Age	0.004, r = 0.24	
Framingham score	<0.001, r = 0.31	
serum creatinine	<0.001, r = 0.35	
HbA1C	<0.001, r = 0.34	
NT-proBNP	<0.001, r = 0.37	
total cholesterol	0.009, r = -0.22	
LDL	0.005, r = -0.24	
ALT	0.02, r = 0.19	
gGT	<0.001, r = 0.28	
Categorical analysis		
Variable	**Results**	**p-value**
gender	females: 15,961 ± 919 pg/mL; males: 19,550 ± 1,308 pg/mL	0.007
CVR		
low	14,837 ± 846 pg/mL	0.009
moderate	19,034 ± 1,303 pg/mL	
high	21,685 ± 3,106 pg/mL	
stress	stress: 14,908 ± 1,055 pg/mL; no stress: 18,558 ± 1,023 pg/mL	0.02
regular physical activity	physical activity: 14,578 ± 945 pg/mL; no physical activity: 18,909 ± 1,075 pg/mL	0.005
family history of CAD	family history: 13,625 ± 1,005 pg/mL; no family history: 18,432 ± 973 pg/mL	0.004
CAD	CAD: 22,824 ± 2,367 pg/mL; no CAD: 16,546 ± 790 pg/mL	0.006
aspirin	aspirin: 20,328 ± 1,925 pg/mL; no aspirin: 16,508 ± 823 pg/mL	0.02
statins	statins: 20,067 ± 1,616 pg/mL; no statins: 16,278 ± 852 pg/mL	0.009
antidiabetic medication	antidiabetic medication: 24,982 ± 3,712 pg/mL; no antidiabetic medication: 16,250 ± 703 pg/mL	0.01
diabetes mellitus	diabetes mellitus: 24,551 ± 2,493 pg/mL; no diabetes mellitus: 15,768 ± 712 pg/mL	<0.001

Discussion

Our study reveals numerous associations between sST-2 and anamnestic, clinical, and laboratory surrogate markers of increased CVR in individuals with seropositive and seronegative rheumatoid arthritis under DMARD therapy. Most variables that were characterized by differences in sST-2 concentration indicate higher levels in the presence of a proatherogenic surrogate marker: male gender, older age, lack of physical activity, diabetes mellitus, including HbA1C, NT-proBNP, coronary heart disease, and finally the Framingham score itself. However, the intake of aspirin, statins, or antidiabetic drugs were also associated with higher sST-2 levels. It is important to consider that direct pharmacological impacts on sST-2 homeostasis cannot be definitively excluded. Finally, the marker correlated inversely with a positive family history of cardiovascular diseases, specifically coronary heart disease, and with total cholesterol and LDL. The latter could be explained by the fact that despite the increased CVR, patients with active Rheumatoid Arthritis (RA) have paradoxically reduced lipid levels (24-26). In the past 10-15 years, it has become increasingly evident how much rheumatoid arthritis (RA) contributes to both cardiovascular morbidity and the associated risk of death (3,7,27). The increase in risk is the combined result of the inflammatory activity of the underlying disease itself, as well as the almost routine proatherogenic substance groups such as glucocorticoids and NSAIDs (5,10). The quantification of CVR is of utmost clinical and prognostic significance in rheumatoid arthritis (RA). According to the 2015/2016 updated EULAR recommendations for CVR management in patients with RA and other inflammatory joint disorders, CVR assessment should be performed at least every 5 years based on national guidelines (8). Considering the possibility of underestimating

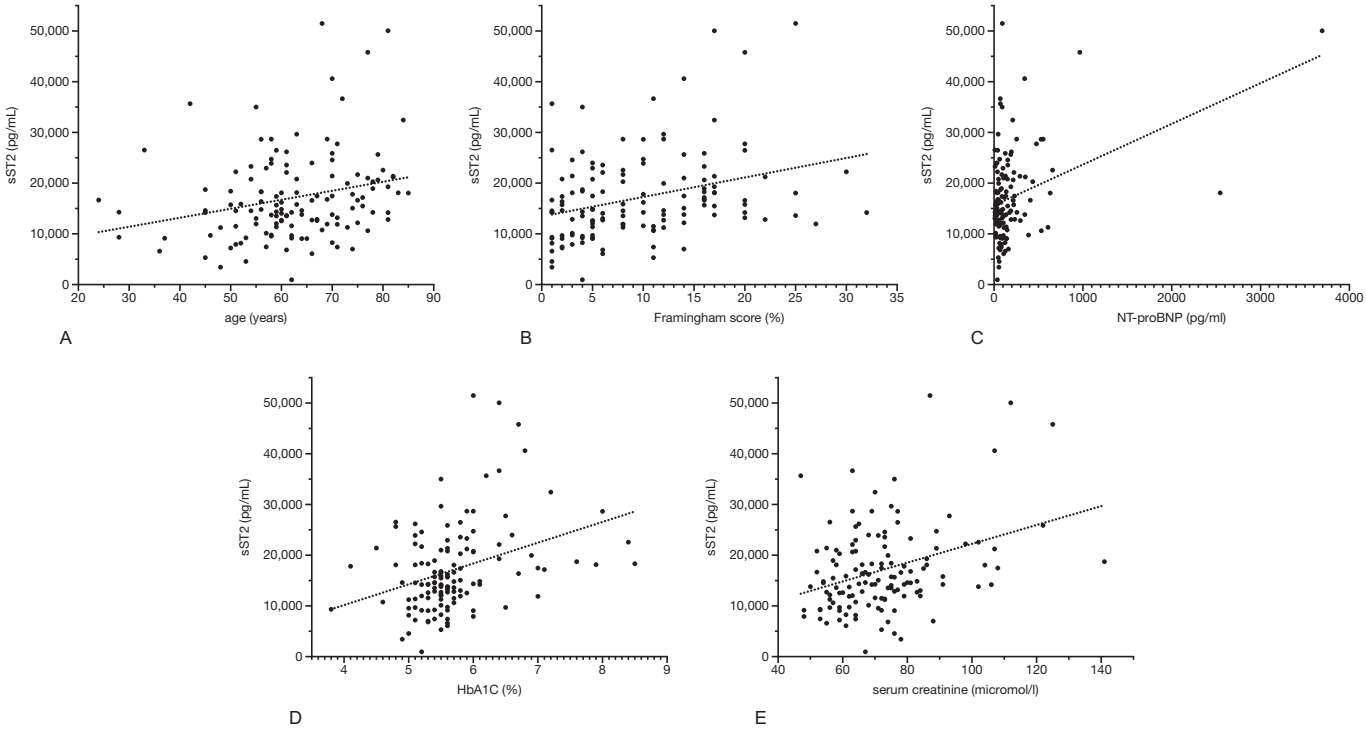

FIGURE 1 - Positive correlations between sST-2 and selected CVR variables (for p-values see text and Table 3).

the CVR in RA patients using prediction models for the general population, they concluded to an adaptation by adding a 1.5 multiplication factor for the calculated CVR. The same approach is recommended by the 2021 ESC guidelines on cardiovascular disease prevention in clinical practice (28).

In this regard, according to the guidelines of the European Society of Cardiology (ESC) (9), CVR stratification must take into account five categories: the severity of potential arterial hypertension, the presence of a diabetic metabolic condition, additional CVR factors, end-organ damage, and cardiovascular sequelae or comorbidities. The specifications do not take into account the potential additive increase in risk due to the presence of a proatherogenic inflammatory disorder or the regular use of substances such as glucocorticoids or leflunomide (29). They also do not consider the influence of antiatherogenic agents like methotrexate (30). It has been shown that chronic inflammatory diseases increase the risk of vascular calcification, not only in the case of RA. Individuals with Spondyloarthritis are also affected by this issue (31). Patients with chronic inflammatory rheumatic diseases may evade the CVR stratification system published by the ESC. This potential gap in the detection of a higher CVR could potentially be reduced in the future through the addition of biomarkers, such as sST-2.

Popsecu et al. (10) recently summarized relevant studies on this topic. They also discussed markers whose activities correlate with CVR in RA, such as anti-β2GPI IgA (positive) or miR-425-5p (negative). Curtis and colleagues (11) published a promising approach for biomarker-based CVR prediction in rheumatoid arthritis (RA). Since 2010, the determination of a so-called MBDA score has been offered in the USA, and health insurance companies cover the costs when indicated correctly. The MBDA score, primarily established for assessing RA activity, is calculated based on the quantification of 12 RA-associated biomarkers (such as IL-6, TNF-R1, EGF, and others). In the cited study, the CVR predictive potential of the score was analyzed using a Cox proportional hazards regression model. The model tested the predictive probability of different risk constellations, such as “age and gender” or “age, gender, and smoking.” The MBDA score itself was also considered as a constellation. In total, 30,751 RA patients with a cumulative count of 904 cardiovascular events were included. Ultimately, the MBDA score showed a hazard ratio of 2.89 for cardiovascular events in the following three years. With the increasing prevalence of artificial intelligence algorithms, diagnostic and therapeutic approaches in medicine are expected to undergo fundamental changes also. Al-Maini et al. (12) recently discussed the incorporation of genomic-based biomarkers (GBBM) and non-invasive radiomic-based biomarkers (RBBM) into CVR assessment in RA. They proposed the integration of GBBM and RBBM into the “AtheroEdge model” (AtheroPoint, CA, USA), a deep learning algorithm for CVR risk prediction in RA.

Without doubt, additive biomarkers are gaining recognition in determining which RA patients are particularly at high CVR. sST-2 is the circulating isoform of the IL-33 receptor. In 2011, Hong and colleagues (17) published data on sST-2 in RA, which revealed elevated serum levels of this marker in patients compared to healthy controls. Two additional studies have measured sST-2 levels in adult Still’s disease (32) and Sjögren syndrome (33), both of which found elevated levels of the marker in affected patients. In addition

to inflammatory rheumatic diseases, serum sST-2 has also been studied in cardiovascular disorders, including coronary artery disease, arterial hypertension, arrhythmias, and other conditions (18). A study conducted by our group has identified sST-2 as a novel predictor of survival in patients experiencing newly onset acute kidney injury (21). Therefore, sST-2 is suitable for identifying uncontrolled inflammatory and non-inflammatory disorders. However, it cannot be used as a universal "danger signal" in rheumatic diseases, as it does not provide a comprehensive assessment of RA disease activity on its own.

Limitations

One limitation is the low prevalence of coronary artery disease (CAD) (9.3%) or known CAD risk factors such as diabetes mellitus (15.5%) in the study cohort. Therefore, we cannot conclusively decide whether sST-2 is an even more potent CVR predictor in RA than in individuals without RA. To further enhance the understanding of sST-2 in assessing CVR, it would be beneficial to include larger numbers of RA patients with and without CAD. Another limitation is the lack of comprehensive follow-up data. On one hand, the marker was not found to correlate or be associated with variables of RA disease activity. However, analyzing the serum dynamics of sST-2 over time could potentially provide valuable information for assessing RA activity and for predicting DMARD response.

Conclusions

In RA, sST-2 may be proposed as promising marker of increased CVR and additional studies must clarify its exact role in the identification of those individuals that potentially escape traditional CVR risk profiling but may benefit from additional sST-2 analysis.

Declarations

Author contributions

Inga Claus collected blood samples and clinical data from all included patients. Meike Hoffmeister conducted ELISA analyses. Constantin Remus assisted in patient recruitment and data collection. Werner Dammermann aided in data analysis. Ourania Gioti prepared tables. Oliver Ritter aided in data analysis and figure preparation. Daniel Patschan analyzed data, prepared figures, and assisted in writing. Susann Patschan designed the study, analyzed data, and wrote the article. All authors approved the final version of the article.

Disclosures

Conflict of interest: The authors declare that they have no conflicts of interest.

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Data availability statement: All data will be provided by the corresponding author upon reasonable request.

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