Comparison of cardiovascular risk burden in patients with psoriatic arthritis, ANCA-associated vasculitis and systemic lupus erythematosus

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Abstract

Background

Cardiovascular risk factors and diseases represent the comorbidities with the highest prevalence in rheumatic diseases. Still, actual cardiovascular risk burden is often underestimated in current risk prediction models

Methods

To assess and compare traditional and nontraditional cardiovascular risk burden in patients with different rheumatic diseases, we analyzed demographical, clinical, laboratory, and non-invasive imaging data on patients with psoriatic arthritis in comparison with a cohort of ANCA-associated vasculitis and systemic lupus erythematosus in a cross-sectional design. Overall, we analyzed 138 patients.

Results

Data analysis revealed significant differences in traditional and nontraditional markers for cardiovascular disease risk as well as disparities in diastolic (6.67 % in PsA vs. 36% in AAV; OR 0.12 [0.03; 0.42], $p < 0.05$) and systolic left ventricular function (1.11% in PsA vs. 13.04% in SLE; OR 0.07 [0.005; 0.54], $p < 0.05$), whereas odds ratios for cardiovascular events did not differ significantly.

Conclusion

Our findings suggest that cardiovascular risk prediction algorithms should consider disease-specific disparities, which includes non-traditional cardiovascular risk burden, arguing for a patient-oriented risk assessment and consequently accurate risk stratification.

Introduction

A variety of patients with rheumatic diseases (RMD) have a substantially increased risk for cardiovascular diseases (CVD) and attributable mortality [1]. The COMORD study [2] has just recently pointed out the high prevalence of cardiovascular risk factors and CVD as the most frequent comorbidities in RMD.

In their 2015/16 update on recommendations for CVD risk management in RMD, the European League Against Rheumatism (EULAR) [3] suggests implementing the Systematic Coronary Risk Evaluation (SCORE) algorithm for estimating the 10-year risk for cardiovascular events. However, the authors acknowledge that the SCORE risk prediction model might underestimate CVD risk in RMD. As the algorithm is adapted to the general population, it consequently considers traditional cardiovascular risk

factors such as gender, smoking, age, dyslipidemia, and hypertension, while disregarding nontraditional and specifically disease-related risk factors. In patients with rheumatoid arthritis, the EULAR guidelines recommend a correction of the SCORE result by a 1.5 multiplication factor. However, no recommendations were given to adjust for the risk in other RMD.

A considerable amount of research has focused on pathophysiological parallels between RMD and atherosclerosis [4], investigating, in particular, their synergistic role in CVD genesis. Interestingly, there is a growing body of research on the contribution of nontraditional risk factors in this field. These include most notably disease-related factors such as disease-activity, disease duration, exposure to inflammation [5], and comedication, in particular steroid exposure. In 2020, Pujades-Rodriguez et al. concluded that even a low dose steroid exposure below 5 mg was associated with an increased CVD risk [6].

Numerous studies have also investigated the predictive role of inflammatory markers such as c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) in CVD and cardiovascular event occurrence [7]. Likewise, uric acid is a long-running topic of debate as a predictor in CVD risk. In fact, uric-acid lowering therapeutics have recently been considered in risk reduction strategies [8].

As the undetected atherosclerosis contributes to this underestimation of CVD risk in RMD, several authors demand more attentiveness to diagnostic imaging [9]. In this regard, the carotid intima-media thickness (cIMT) was described as a surrogate measure of atherosclerosis and that provides predictive value in cardiovascular risk assessment [10].

Overall, current research appears to support the notion that present prediction models tend to underrate the actual risk for CVD and cardiovascular events in RMD.

Our study is the first to identify and systematically compare cardiovascular risk profiles between different RMD. We incorporated nontraditional parameters in clinical assessment, imaging, and laboratory diagnostics with evidence-based predictive value for CVD risk to investigate disparities in profiles of patients with psoriatic arthritis (PsA), ANCA-associated vasculitis (AAV), and systemic lupus erythematosus (SLE). To date, no study has looked specifically at the key disparities between these three patient groups.

The aim of this analysis is twofold. The first is to compare comprehensive profiles of traditional and nontraditional CVD risk burden in all three patient cohorts and offer a rationale for a focused and individualized CVD risk assessment. Second, in examining the contribution of traditional and nontraditional risk factors, this study seeks to further examine the role of nontraditional risk factors in CVD risk assessment in RMD and provide possible adjustments for future risk-stratification models.

Materials And Methods

Patient recruitment

This study was conducted in the University Hospital Frankfurt Goethe University. Included patients were individuals with diagnosis of PsA, AAV, and SLE.

Demographics, laboratory parameters, non-invasive imaging results as well as clinical and disease-related markers for traditional and nontraditional cardiovascular risk were obtained at enrollment.

Study design

In this single-center observational study, we used a cross-sectional design to compare disease-specific traditional and nontraditional cardiovascular risk burden between cohorts of PsA, AAV, and SLE patients. The PsA cohort was considered as the reference group.

Comorbidities and assessment of traditional CVD risk

ST-elevation MI (STEMI) or non-ST elevation MI (NSTEMI) were summarized as myocardial infarction. Measurement of the carotid intima-media thickness (cIMT) was assessed by longitudinal B-mode ultrasound. Left ventricular ejection fraction (LV-EF) and diastolic function, were obtained by either cardiac MRI or transthoracic echocardiogram. Impaired left ventricular function was defined as a LV-EF $\leq$ 50%. In this study, left ventricular diastolic dysfunction is referred to as diastolic dysfunction. Overweight was defined as a BMI > 25 kg/m^2.

For calculating the 10 year risk for a fatal or non-fatal cardiovascular events, we used the SCORE2 risk prediction algorithm [11]. The SCORE2 model was implemented based on region-specific recommendations. For patients younger than 40 years, we calculated risk at 40-44 years. Risk for patients older than 69 years was recalibrated accordingly to patients between 65 and 69 years.

Assessment of non-traditional CVD risk

We used the disease activity score in 28 joints based on C-reactive protein [12] and patient global assessment to assess disease activity in patients with PsA.

Stratification of disease activity in individuals with AAV was performed with the Birmingham Vasculitis Activity Score version 3 (BVASv3) [13] and with SLEDAI-2K [14] in individuals with SLE, respectively.

The duration of the disease was calculated in months from the date on which the diagnosis was made. Furthermore, patients were considered as under current steroid exposure if the steroid intake lasted more than 4 weeks.

Statistical analysis

To compare continuous parameters of traditional and nontraditional risk burden, a mixed model analysis with a Geisser-greenhouse correction and Dunnett's post-hoc test was carried out. Categorical variables were summarized as counts and percentages and were compared using Chi-square analysis. Continuous variables indicating traditional CVD risk burden were age, body mass index (BMI), cholesterol, LDL, triglycerides, non-HDL, smoking exposure. Continuous variable in non-traditional CVD risk were disease

activity, disease duration, laboratory diagnostics (CRP, ESR, glomerular filtration rate (GFR), uric acid, fibrinogen, homocysteine, HbA1c, NT-proBNP) and imaging parameters. Categorical variables in cardiovascular outcome were coronary disease, left ventricular impairment, diastolic dysfunction, peripheral artery disease, myocardial infarction, and stroke.

Odds ratios for cardiovascular consequences were obtained using the Baptista Pike method. Results were considered significant at a p-level < 0.05. Mean and standard deviation (SD) were used to report continuous variables, odds ratios (OR), and corresponding 95%-confidence intervals (95%-CI) were calculated to describe probabilities for CVD as well as fatal and nonfatal cardiovascular events. Data analysis was conducted using in Graphpad prism and Microsoft Excel.

Results

Comparison of traditional risk burden in PsA vs. AAV and PsA vs. SLE

In total, we analyzed 138 patients (90 PsA, 25 AAV, and 23 SLE). Seventeen patients with granulomatosis with polyangiitis (GPA), five with eosinophilic GPA, and three with microscopic polyangiitis.

Table 1 shows a comparison of baseline characteristics of traditional CVD risk factors for PsA vs. AAV and PsA vs. SLE, respectively. The presented dataset includes demographical, clinical, and laboratory parameters.

Table 1
Comparison of traditional risk burden in PsA vs. AAV and PsA vs. SLE.

	PsA (n=90)	**AAV (n=25)**	**PsA vs. AAV**	**SLE (n=23)**	**PsA vs. SLE**
	Mean ± SD	*Mean ± SD*	*p-value*	*Mean ± SD*	*p-value*
Age (years)	56.32 ±12.9	57.0 ±18.92	0.961	47.43 ±12.79	0.042*
BMI (kg/m^2)	27.86 ±4.68	25.9 ±4.69	0.194	26.92 ±5.33	0.709
Cholesterol (mg/dl)	207.74 ± 47.07	207.6±38.2	>0.99	193.21 ± 48.75	0.639
LDL (mg/dl)	126.03 ± 41.4	122.84 ± 32.54	0.866	117.10 ± 38.24	0.692
Triglycerides (mg/dl)	158.12 ± 94.8	116.20 ± 57.82	0.044*	126.43 ± 62.33	0.211
Non-HDL (mg/dl)	147.72 ± 45.3	135.67 ± 37.97	0.466	131.13 ± 42.78	0.49
Smoking exposure (pack years)	8.76 ± 20.44	8.5 ± 9.17	0.997	4.22 ± 8.64	0.186
	Prevalence % (n)	*Prevalence % (n)*	*p-value*	*Prevalence % (n)*	*p-value*
Male	46.67 (42)	28.00 (7)	0.113	4.55 (2)	0.0006*
Hypertension	44.44 (40)	32.0 (8)	0.359	21.74 (5)	0.057
Current/ former smoker	48.98 (44)	24 (6)	0.039*	30.43 (7)	0.158
Type 1/2 Diabetes mellitus	14.44 (13)	4 (1)	0.297	0 (0)	0.066
Dyslipidemia	15.56 (14)	12 (3)	>0.999	17.39 (4)	0.759
SCORE2 (low risk)[1]	34.44 (31)	20 (5)	0.224	56.52 (13)	0.059
SCORE2 (medium risk)[2]	50 (45)	68 (17)	0.12	43.48 (10)	0.644
SCORE2 (high risk)[3]	15.56 (14)	12 (3)	>0.999	0 (0)	0.069

	PsA (n=90)	AAV (n=25)	PsA vs. AAV	SLE (n=23)	PsA vs. SLE
Values are mean ± standard deviation (SD) or percentages (counts). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; SCORE2 indicates Systematic Coronary Risk Evaluation 2 predicting 10 years (yrs) risk for fatal or non-fatal cardiovascular events [1] 10 yrs risk is <2.5% [2] 10 yrs risk in < 50 yrs old patients is 2.5- 7.5 %; in 50-59 yrs old patients is 2.5- 10% [3] 10 yrs risk in < 50 yrs old patients is > 7.5%; in 50-59 yrs old patients is >10%. *Indicates significance at p-level < 0.05.					

As shown, PsA patients had the highest prevalence of current and former smokers (88%), which was significantly over the AAV cohort (24%), while total smoke exposure did not differ at a significant level (8.76 ± 20.44 vs. 8.5 ± 19.17 packyears, p> 0.05). Furthermore, mean triglyceride levels were higher in PsA (56.32 ± 12.94 mg/dl) compared with levels in AAV patients (116.20 ± 57.82 mg/dl).

Subjects in the SLE cohort had a mean age of 47.43 ± 12.79 years and were significantly younger than individuals from the PsA cohort (56.32 ± 12.94 years). Furthermore, the SLE cohort had the lowest proportion of male patients (46.67% in PsA vs. 28% in SLE, p< 0.05) included. Measurement of further lipid mediators showed comparable results.

Estimating the 10-year risk for cardiovascular events with the SCORE2 algorithm, revealed no significant difference between the three cohorts.

Comparison of nontraditional risk burden in PsA vs. AAV and PsA vs. SLE

Table 2 shows a comparison of laboratory, clinical and non-invasive image parameters capturing nontraditional risk burden.

Table 2
Comparison of nontraditional risk burden in PsA vs. AAV and PsA vs. SLE.

	PsA (n=90)	AAV (n=25)	PsA vs. AAV	SLE (n=23)	PsA vs. SLE
	Mean ± SD	*Mean ± SD*	*p-value*	*Mean ± SD*	*p-value*
Disease activity	DAS28-CRP: 2.20 ± 0.74	BVASv3 persistent: 2.08 ±1.52 BVASv3 new: 1.0 ± 3.08	-	2.73± 2.41	-
Disease duration (months)	181.53 ± 143.71	118.69 ± 85.38	0.033*	213.30 ± 192.51	0.694
CRP (mg/dl)	0.375 ± 0.43	0.56 ± 1.08	0.597	0.35 ± 0.38	0.974
ESR (mm/h)	17.84 ± 17.32	20.16 ± 19.91	0.841	21.34 ± 22.44	0.724
GFR (ml/min/ 1.73)	100.03 ± 80.32	74.74 ± 31.38	0.0003*	86.77 ± 22.28	0.083
Uric acid (mg/dl)	5.38 ± 1.27	5.20 ± 1.50	0.851	4.78 ± 1.48	0.206
Fibrinogen (mg/dl)	320.01 ± 62.33	337.64 ± 97.91	0.620	286.08 ± 91.61	0.209
Homocysteine (µmol/l)	14.16 ± 4.33	15.43 ± 7.90	0.656	15.60 ± 5.95	0.616
HbA1c (%)	5.79 ± 0.73	5.66 ± 0.62	0.626	5.48 ± 0.31	0.045*
NT-proBNP (pg/ml)	104.24 ± 272.26	237.51 ± 255.96	0.172	298.27 ± 664.58	0.423
cIMT right (mm)	0.56 ± 0.182	0.47 ± 0.16	0.793	0.47 ± 0.21	0.140
cIMT left (mm)	0.55 ± 0.15	0.51 ± 0.21	0.333	0.45 ± 0.17	0.374
	Prevalence % (n)	*Prevalence % (n)*	*p-value*	*Prevalence % (n)*	*p-value*
Current steroid exposure	13.33 (12)	72 (18)	<0.0001*	47.83 (11)	0.0007*

	PsA (n=90)	AAV (n=25)	PsA vs. AAV	SLE (n=23)	PsA vs. SLE

Values are mean ± standard deviation (SD) or percentages (counts). BVAS stands for Birmingham Vasculitis Activity Score; DAS, disease activity score. CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate ESR; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin A1c; NT-proBNP, N-terminal pro-brain natriuretic peptide; cIMT, carotid intima-media thickness.

*Indicates significance at p-level < 0.05.

Despite a comparable mean age as AAV patients (56.32 ±12.94 vs. 57.0 ± 18.92 years), PsA subjects had a significantly longer disease duration of 181.53 ± 143.71 vs. 118.69 ± 85.38 months (p< 0.05) in AAV subjects. Furthermore, GFR, representing renal function, was lowest in the AAV cohort (100.03 ± 80.32) and differed significantly from GFR in the PsA cohort (74.74 ± 31.38 ml/min/ 1.73, p< 0.05).

HbA1c reports the average blood-glucose exposure during the previous three months. HbA1c levels were significantly elevated in PsA (5.79± 0.73%) compared with SLE (5.48 ± 0.31%) subjects.

The SLE cohort on the other hand, had the highest prevalence of patients on steroid exposure, with a proportion of 47.83% vs. 13.33% in the PsA cohort (p<0.05).

Mean DAS28-score in PsA patients indicated remission (DAS28-CRP < 2.6) [15], while mean disease activity scores in AAV (BVAS3 persistent: 2.08/new:1) [16] and SLE (SLEDAI-2K: 2.7) indicated a low to moderate disease activity in the majority of individuals

[17]. ESR and CRP as clinical and serological markers of inflammation did not differ significantly between the groups but mean CRP levels were above the normal range only in the AAV group.

Disparities in cardiovascular diseases and cardiovascular events

Table 3 presents prevalence and odds ratios of CVD and cardiovascular events.

Table 3
Disparities in cardiovascular diseases and cardiovascular events.

	PsA (n=90)	AAV (n=25)	PsA vs. AAV	SLE (n=23)	PsA vs. SLE
	Prevalence % (n)	*Prevalence % (n)*	OR [95% CI]	*Prevalence % (n)*	OR [95% CI]
Coronary disease	6.25 (5)	3.81 (4)	0.35 [0.09; 1.23]	4.35 (1)	1.467 [0.178;17.99]
LV-EF impairment	1.11 (1)	4 (1)	0.26 [0.01; 5.32]	13.04 (3)	0.07 [0.005; 0.54] *
Diastolic dysfunction	6.67 (6)	36 (9)	0.12 [0.03; 0.42] *	8.7 (2)	0.75 [0.169;3.874]
Peripheral artery disease	1.11 (1)	4.0 (1)	0.26 [0.01;5.32]	0 (0)	Infinit [0.028; Infinit]
Myocardial infarction	1.11 (1)	0 (0)	Infinit [0.03; Infinit]	4.35 (1)	0.247 [0.012;4.897]
Stroke	2.22 (2)	4 (1)	Infinit [0.11; Infinit]	0 (0)	Infinit [0.117; Infinit]

OR indicates odds ratio; CI, confidence interval.

*Indicates significance at p-level < 0.05.

Diastolic dysfunction was most frequent in patients with AAV (36%) compared to PsA (6.67%), whereas significantly more SLE patients had a left ventricular impairment (13.04%) compared to PsA patients (1.11%). Concerning diastolic impairment, SLE patients had a comparable prevalence (8.7%) compared with PsA. Furthermore, subjects in the AAV group had a similar ratio of left ventricular dysfunction (4%).

The prevalence and odds ratios for coronary disease, peripheral artery disease, myocardial infarction, or stroke, were not significantly different in PsA vs. AAV or PsA vs. SLE subjects, respectively.

Discussion

Cardiovascular morbidity and mortality are elevated across all RMD. Algorithms for risk prediction are leaned on recommendations for the general population. Thus, current risk scores mostly neglect disease-related factors. In fact, preventive recommendations largely focus on lipid-lowering agents [18], often disregarding the role of disease-specific medication. Although several studies have pointed out the impact of nontraditional risk factors on RMD, to date no research group has looked at comparative disease-specific disparities in this regard.

To our knowledge, this is the first study to highlight commonalities and differences in cardiovascular risk profiles of patients with PsA, AAV, and SLE, offering a rationale with not only theoretical but also foremost practical relevance for a disease-specific CVD risk stratification.

In this cross-sectional observational study, we compared disparities in risk burden between cohorts of PsA (n=90), AAV (n=25), and SLE (n=23) patients.

Our data analysis revealed a significantly higher proportion of traditional risk factors in PsA subjects, whereas nontraditional cardiovascular risk markers were more often in the SLE and AAV cohorts. Nonetheless, implementing the SCORE2 algorithm did not reveal significant differences in risk stratification. Still, the younger mean age and the higher prevalence of females in the SLE cohort contributed to overall better outcomes in the SCORE2 results (Table 2). Considering that the disease duration might serve as a surrogate marker for the inflammatory exposure, it should be emphasized that SLE subjects had the longest disease duration of all. CRP and ESR levels, however, did not differ notably between the disease groups.

Interestingly, while odds ratios for cardiovascular events were comparable between PsA, AAV and SLE patients, there were differences in left ventricular function. AAV subjects had a substantially increased odds ratio for diastolic dysfunction, whereas SLE subjects had an elevated odds ratio for systolic dysfunction compared to PsA. However, consideration of traditional risk factors alone, could not predict these differences.

Overall, our findings in PsA are consistent with previous results showing increased prevalence and incidence of traditional cardiovascular risk factors [19]. Nonetheless, data on nontraditional factors are limited although its contribution to CVD risk burden is acknowledged in various studies [20].

Together, the presented findings confirm that current algorithms for risk prediction fail to capture the complexity of underlying pathological mechanisms in RMD-related CVD risk.

Pointing out disease-specific disparities in CVD risk profiles may help us to understand pathophysiological processes leading to these differences and consequently provide the groundwork for future therapeutic strategies.

As a lack of time is a crucial factor in patient care and risk-assessment [21], our study also contributes to a more targeted and thus less time-consuming approach.

Limitations of this study include the cross-sectional study design, which prevents further investigation of causality and thus limits predictive conclusions.

Moreover, the findings regarding the higher proportion of diastolic dysfunction in the AAV group should be interpreted with caution as this might be due to elevated prevalence in patients with impaired renal function. Overall, limitations in representative value due to small sample sizes and thereupon limitations in regional and socioeconomic variability have to be considered.

As a side note, the mean BMI was over 25 kg/m^2 across all patient groups. Although no significant differences were detected between PsA, AAV and SLE, a low-grade inflammation due to overweight has to be taken into consideration [22].

Conclusions

Although presenting considerably less traditional cardiovascular risk factors, significantly more patients with AAV and SLE showed impaired cardiac function compared to PsA subjects. Other cardiovascular outcomes were statistically comparable. In conclusion, our preliminary findings shall raise awareness of the limited prognostic value of current predictive algorithms and emphasize the importance of a multivariable model for an accurate CVD risk estimation in RMD. Consideration of nontraditional risk factors goes hand in hand with improved risk discrimination and consequently contributes to individualized preventive strategies. Future studies will have to clarify how this translates into a better understanding of disease-specific mechanisms underlying cardiovascular disease pathology.

Abbreviations

AAV	ANCA-associated vasculitis
cIMT	Carotid intima-media thickness
CRP	C-reactive protein
CVD	Cardiovascular disease
ESR	Erythrocyte sedimentation rate
GFR	Glomerular filtration rate
HDL	High density lipoprotein
LDL	Low density lipoprotein
OR	Odds ratio
PsA	Psoriatic arthritis
RMD	Rheumatic diseases
SCORE	Coronary Risk Evaluation
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
SLE	Systemic lupus erythematosus

Declarations

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Availability of data and materials

Not applicable.

Ethical Approval and Consent to participate

This study was approved by the ethical committee of the University Hospital Frankfurt (study code: TMP-0208-2019-22). All participants were adult patients (age ³ 18 years). Eligible participants were asked to read and sign a consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests

Authors' contributions

FB and HLB designed the study and contributed to the interpretation of the data. MK contributed to the patient recruitment and management of the electronic database. SMP carried out the data collection, analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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